ORIGINAL RESEARCH

Association of Systemic Arterial Properties With Right Ventricular Morphology: The Multi-Ethnic Study of Atherosclerosis (MESA)-Right Ventricle Study

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***Background*—**Systemic arterial stiffness is recognized as a major contributor to development of left ventricular dysfunction and failure; however, the relationship of systemic arterial properties and the right ventricle (RV) is unknown.

***Methods and Results*—**The associations between systemic arterial measures (total arterial compliance [TAC], systemic vascular resistance [SVR], and aortic augmentation index [AI]) and RV morphology (mass, end-systolic [RVESV] and end-diastolic volume [RVEDV], and ejection fraction [RVEF]) were examined using data from the Multi-Ethnic Study of Atherosclerosis. All analyses were adjusted for anthropometric, demographic, and clinical variables and the corresponding left ventricular parameter. A total of 3842 subjects without clinical cardiovascular disease were included with a mean age of 61 years, 48% male, 39% non-Hispanic white, 25% Chinese-American, 23% Hispanic, and 13% black. RV measures were within normal range for age and sex. A 1-mL/mm Hg decrease in TAC was associated with 3.9-mL smaller RVESV, 7.6-mL smaller RVEDV, and 2.4-g lower RV mass. A 5-Wood-unit increase in SVR was associated with 0.6-mL decrease in RVESV, 1.7-mL decrease in RVEDV, and 0.4-g decrease in RV mass. A 1% increase in AI was associated with 0.2-mL decrease in RVEDV. We found significant effect modification by age, sex, and race for some of these relationships, with males, whites, and younger individuals having greater decreases in RV volumes and mass.

***Conclusions*—**Markers of increased systemic arterial load were associated with smaller RV volumes and lower RV mass in a population of adults without clinical cardiovascular disease. **(*J Am Heart Assoc*. 2016;5:e004162 doi: 10.1161/JAHA.116.004162)**

Key Words: arterial stiffness • artery • magnetic resonance imaging • right ventricle • ventricle

There is growing recognition of the importance of the right ventricle (RV) in common diseases of the left ventricle (LV), such as heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction.[1,2] A major contributor to the development of HFpEF and associated LV diastolic dysfunction is increased systemic vascular stiffness.[3] The relationship between systemic vascular stiffness and RV morphology and function has not been well studied. Increased vascular stiffness can have adverse mechanical and cellular consequences. First, increased vascular stiffness imposes greater afterload on the LV, which leads to its eventual remodeling and dysfunction and subsequent increased afterload on the RV.[4,5] Both the LV and RV demonstrate similar subendocardial fibrosis in HFpEF even before the presence of overt RV dysfunction.[6] Second, the systemic vascular endothelial layer is exposed to altered hemodynamic forces in the setting of increased stiffness, leading to endothelial dysfunction and release of a cascade of inflammatory markers.[7–9] Third, systemic vascular function could serve as an indicator of pulmonary vascular health.[10–13]

In light of its demonstrated paracrine and endocrine effects, systemic vascular pathobiology offers a compelling potential driver of RV dysfunction in disease states, such as

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HFpEF. Identification of an association between RV morphology and systemic vascular function in healthy individuals or in a preclinical state would enlighten the mechanism to HFpEF and RV dysfunction. Whereas it is presumed that impact of the systemic vasculature on the RV is mediated through effects on the LV, the systemic vasculature could potentially influence the RV through circulating mediators in the coronary blood supply. Exploring an association between systemic arterial properties and RV morphology in a healthy state is an important first step in understanding subclinical changes in the RV.

Using baseline data from the well-characterized Multi-Ethnic Study of Atherosclerosis (MESA), we examined the cross-sectional association between different pulsatile and resistive measures of the systemic vasculature (total arterial compliance [TAC], aortic augmentation index [AI], and systemic vascular resistance [SVR]) and RV morphology as assessed by cardiac magnetic resonance imaging (CMR) in individuals without clinical cardiovascular disease. We hypothesized that lower TAC, higher SVR, and higher AI (consistent with increased vascular stiffness) would be associated with greater RV mass, larger RV end-systolic volume (RVESV) and end-diastolic volumes (RVEDV) and lower RV ejection fraction (RVEF).

Methods

Subjects

The MESA study is a multicenter, prospective cohort of 6814 men and women aged 45 to 84 years free from clinical cardiovascular disease with the purpose of investigating the prevalence, correlates, and progression of subclinical cardiovascular disease in a racially and ethnically diverse population. All participants were recruited between 2000 and 2002 from 6 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. The MESA-Right Ventricle Study is an ancillary study that selected 4634 of the CMR scans performed at the baseline examination without regard to age, sex, or race and completed the assessment of RV morphology in 4204, which were available and interpretable. The study protocols were approved by the institutional review boards of all participating centers, and all study participants signed informed consent.

Demographic and Clinical Variables

The details of the baseline study visit have been previously described.[14] Race and ethnicity were self-reported. Height and weight were measured and blood pressure was measured 3 times in the seated position after a 5-minute rest using the Dinamap model PRO 100 automated oscillometric device (Critikon, Tampa, FL). Medical history, smoking status, and medication use were obtained by standard questionnaires. Fasting blood samples were collected for the determination of study participants' lipid profile. Physical activity was assessed using the MESA Typical Week Physical Activity Survey, adapted from the Cross-Cultural Activity Participation Study.[15]

Cardiac MRI Measures

The CMR protocol has been previously described, and methods of interpretation of LV and RV parameters have been previously reported.[16–18] Images were performed with 1.5 Tesla magnets with a 4-element phased-array surface coil positioned anteriorly and posteriorly and electrocardiogram gating. CMR images were transmitted to Johns Hopkins University in Baltimore, Maryland, and image analysis was done on Windows workstations with QMASS software (version 4.2; Medis medical imaging systems, Leiden, the Netherlands). The endocardial and epicardial borders of the RV were traced manually on the short-axis cine images at the end-systolic and end-diastolic phases. The outflow tract was included in the RV volume, and RVEDV and RVESV were calculated using Simpson's rule by summation of areas on each slice multiplied by the sum of the slice thickness and image gap. RV mass was determined at the end-diastole phase as the difference between the end-diastolic epicardial and endocardial volumes multiplied by the specific gravity of the myocardium (1.05 g/cm^3). RVEF was calculated by dividing the difference of RVESV and RVEDV by RVEDV. The intra- and inter-reader intraclass correlation coefficients from random, blinded rereads of 229 scans were 0.94 for RV mass and from 230 scans were 0.99 for RVEDV and 0.89 for RVEF.[18]

Measures of Arterial Load

The systemic vasculature has both pulsatile and resistive components.[19] Parameters of pulsatile load include TAC[20,21] and AI,[22,23] which encompass vascular elastance and the wave reflection physiology. The SVR quantifies the resistive load.[24,25] Radial tonometry data were recorded for 30 seconds using the HDI/PulseWave-CR2000 tonometry device (Hypertension Diagnostics, Eagan, MN), and the data were digitized at 200 Hz for offline processing. Analysis of waveforms was performed using custom-designed software written in MatLab (The MathWorks, Inc., Natick, MA). TAC was calculated as the ratio of LV stroke volume obtained from CMR to central pulse pressure determined from arterial tonometry. AI was determined from pulse-wave analysis whereby a generalized transfer function was applied to the

radial pressure waveform to obtain a central pressure waveform.[22] After identification of the first and second systolic peaks from the arterial waveforms, AI was computed as the ratio of the second systolic peak to the first systolic peak multiplied by 100. SVR was calculated as the ratio of the mean arterial pressure measured at time of CMR to LV cardiac output determined from CMR. Noninvasive determinations of cardiac output, stroke volume, and arterial compliance by CMR have good agreement with invasive determinations of these measurements.[26–28]

Statistical Analysis

Continuous variables were summarized as means±SDs or medians and interquartile ranges, as appropriate. Categorical variables were summarized as counts and percentages. Univariate analyses were performed to assess the association between each of the independent variables (TAC, AI, and SVR) and the dependent RV measures (RV mass, RVESV, RVEDV, and RVEF). Multivariate linear regression models were created by including variables based on a priori clinical knowledge of covariates thought to be associated with RV structure and function and/or affect systemic vascular function, including age, sex, race/ethnicity (white, Chinese-American, black, and Hispanic), height, weight, heart rate, smoking status (never, former, or current), level of education (less than high school, high school, more than high school but less than college, or college or higher), presence of hypertension, presence of diabetes mellitus, urinary albumin-to-creatinine ratio, total cholesterol, high-density lipoprotein cholesterol, current diuretic use, physical activity (metabolic equivalent of task [MET]-min/week), and the corresponding LV parameter (LV mass, LV volumes, and ejection fraction). Because we are interested in the associations between arterial properties and RV measures, we chose not to adjust for blood pressure, which is dependent on flow and arterial properties. Adding blood pressure to our models would have rendered the arterial properties surrogates for flow. We also performed additional analyses to evaluate the potential confounding of the associations between the systemic vascular measures and the RV measures by lung volumes and different parameterizations of body size. Multivariate analyses were repeated with additional adjustment for forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) from spirometry performed on a subset of the study population for a different ancillary study (MESA-Lung; n=2584). Additional models used the logarithm of the RV measures (RV mass, RVESV, RVEDV, and RVEF) as the dependent variables with adjustment for log (height), log (weight), and the logarithm of the corresponding LV parameter (LV mass for RV mass, LV volumes for RV volumes, and LV ejection fraction for RVEF). We also created a model with RV mass-to-volume ratio, defined as the ratio of RV mass to RVEDV, as the dependent variable. Based on previous knowledge of effect modification by certain variables,[5,29] interactions between each of the independent variables of vascular function and age (as a continuous variable), sex, race/ethnicity, and hypertension were assessed separately in the multivariate models and retained if the *P* value for the interaction was <0.05 determined from the *F* test. All analyses were performed in R software (version 3.2.1; R Foundation for Statistical Computing; Vienna, Austria).

Results

Of the 6814 participants in the MESA study cohort, 5098 subjects underwent CMR, of which 5004 scans were interpretable for LV measures. The MESA-RV Study randomly selected 4634 cardiac MRI scans for interpretation of RV parameters, of which 4204 of 4424 reviewed were available and interpretable for RV morphology and function. Of those, 3842 participants had complete data for our primary outcomes and main predictors and were included in the analysis (Figure).

Table 1 shows that the study sample (n=3842) was similar to those excluded (n=2972) in terms of demographics,

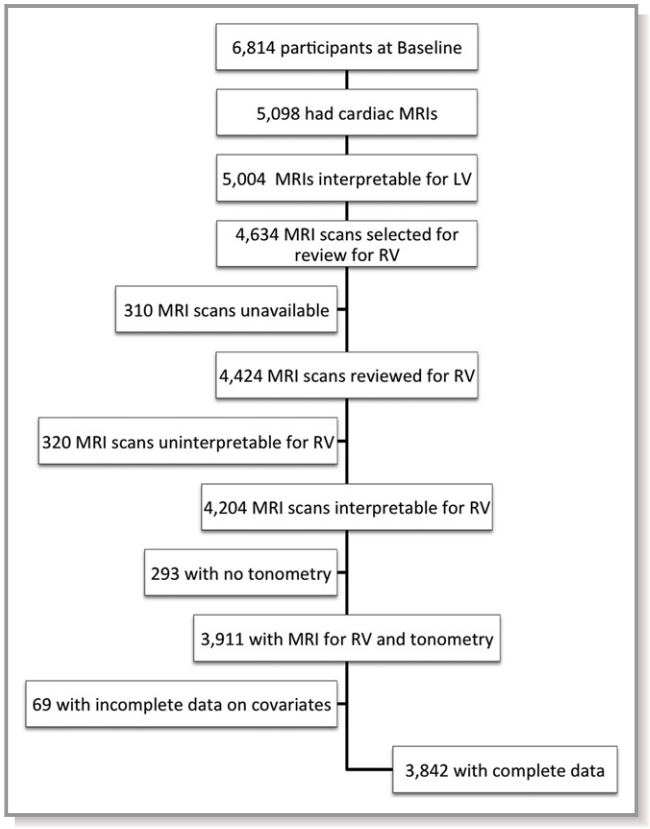

Figure. Study population. LV indicates left ventricle; MRI, magnetic resonance imaging; RV, right ventricle.

Table 1. Baseline Characteristics of Study Subjects

	All (n=6814)	Study Sample (n=3842)	Excluded (n=2972)
Age, y	62±10	61±10	63±10
Males, n (%)	3213 (47)	1845 (48)	1368 (46)
Race/ethnicity, n (%)			
White	2622 (38)	1492 (39)	1130 (38)
Chinese-American	1892 (28)	979 (25)	913 (31)
Black	804 (12)	496 (13)	308 (10)
Hispanic	1496 (22)	875 (23)	621 (21)
Height, cm	166.4±10	166.4±10.0	166.3±10.1
Weight, kg	78.6±17	77.3±16.2	80.3±18.6
Body mass index, kg/m^2	28.3±5.5	27.8±5.0	29.0±6.0
Education level, n (%)			
<High school	1225 (18)	637 (17)	588 (20)
High school	1236 (18)	713 (18)	523 (18)
>High school, <college	1109 (16)	607 (16)	502 (17)
≥College	3221 (47)	1885 (49)	1336 (45)
Diabetes mellitus, n (%)	859 (13)	452 (12)	407 (14)
Hypertension, n (%)	3058 (45)	1643 (43)	1415 (48)
Total cholesterol, mg/dL	194±36	194±35	194±37
HDL cholesterol, mg/dL	51±15	51±15	51±15
Urine albumin/creatinine, mg/g	5.4 [3.30–11]	5.2 [3.3–10.1]	5.6 [3.4–12.5]
Smoking status, n (%)			
Never	3418 (50)	1995 (52)	1423 (48)
Former	2487 (37)	1375 (36)	1112 (38)
Current	887 (13)	472 (12)	415 (14)
Physical activity, MET-min/week			
Moderate and vigorous PA	4020 [1980–7500]	4140 [2055–7738]	3848 [1860–7200]
Total intentional exercise	825 [105–2021]	840 [210–2076]	760 [35–1972]
Heart rate, beats/min	63±10	63±9	64±10
Total arterial compliance, mL/mm Hg	—	1.6±0.5	—
Systemic vascular resistance, Wood units	—	20.5±4.7	—
Aortic augmentation index, %	—	15.0±2.4	—
RV mass, g	—	21.1±4.4	—
RVESV, mL	—	37.5±14.2	—
RVEDV, mL	—	124.5±30.8	—
RVEF, %	—	70.4±6.5	—

Results presented as mean±SD or median [interquartile range]. HDL indicates high-density lipoprotein; MET, metabolic equivalent of task; RV, right ventricular; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; PA, physical activity.

anthropometrics, and comorbidities. Mean age of the study sample was 61±10 years with 48% male, 39% non-Hispanic white, 25% Chinese-American, 23% Hispanic, and 13% black participants. A diagnosis of hypertension was present in 43% and a diagnosis of diabetes mellitus in 12%.

Mean RV mass in the study sample was 21.1±4.4 g, mean RVESV was 37.5±14.2 mL, mean RVEDV was 124.5±30.8 mL, and mean RVEF was 70.4±6.5%. Mean TAC of the study sample was 1.6±0.5 mL/mm Hg, mean SVR was 20.5±4.7 Wood units, and mean AI was 15.0±2.4% (Table 1).

Table 2. Models for the Association of Systemic Vascular Measures With the RV Mass and Ejection Fraction (n=3842)

	RV Mass Models						RVEF Models					
	Unadjusted			Adjusted*			Unadjusted			Adjusted*		
	β	SE (β)	*P* Value	β	SE (β)	*P* Value	β	SE (β)	*P* Value	β	SE (β)	*P* Value
TAC per 1 mL/mm Hg	4.8	0.1	<0.001	2.4	0.1	<0.001	−1.5	0.2	<0.001	0.1	0.2	0.61
SVR per 5 Wood units	−1.8	0.1	<0.001	−0.4	0.08	<0.001	1.0	0.1	<0.001	0.3	0.1	0.06
AI per 1%	−0.3	0.03	<0.001	−0.03	0.02	0.23	0.3	0.04	<0.001	−0.007	0.04	0.87

AI indicates aortic augmentation index; RV, right ventricular; RVEF, right ventricular ejection fraction; SVR systemic vascular resistance; TAC, total arterial compliance.
*Adjusted for age (years), sex (males/females), race/ethnicity (white, Chinese-American, black, and Hispanic), height (cm), weight (kg), heart rate (beats/min), smoking status (never, former, or current), level of education (<high school, high school, >high school but <college, or ≥college), presence of hypertension (yes/no), presence of diabetes mellitus (yes/no), urinary albumin-to-creatinine ratio, total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), current diuretic use (yes/no), physical activity (metabolic equivalent of task per minute per week), and the corresponding left ventricle (LV) parameter (LV mass for RV mass model, LVEF for RVEF model).

Total Arterial Compliance

In univariate analysis, lower TAC was associated with smaller RVESV and RVEDV, lower RV mass, and greater RVEF (Tables 2 and 3). After adjusting for anthropometric and clinical covariates as well as the corresponding LV parameter, lower TAC remained associated with smaller RVESV and RVEDV and lower RV mass, but not with RVEF. A 1-mL/mm Hg decrease in TAC was associated with a 3.9-mL decrease in RVESV, a 7.6-mL decrease in RVEDV, and a 2.4-g decrease in RV mass ($P<0.001$ for all). However, lower TAC was associated with higher RV mass-to-volume ratio, indicating a more concentric relative RV geometry (Table 4).

We found effect modification by age for TAC with RV mass and volumes (Table 5), with younger individuals having greater decreases in RV volumes and mass than older individuals with decrease in TAC (*P* for interaction 0.02, 0.006, and 0.002 for RV mass, RVESV, and RVEDV, respectively). Sex also had an effect on the association of TAC with RV volumes (Table 5), with males having larger decreases in RVEDV and RVESV as compared to females with decreases in TAC (*P* for interaction <0.001 and 0.002 for RVESV and RVEDV, respectively).

Systemic Vascular Resistance

Higher SVR was associated with smaller RVESV and RVEDV, lower RV mass, and higher RVEF on univariate analysis (Tables 2 and 3). After multivariate adjustment, SVR remained significantly associated with RVESV and RVEDV and RV mass (Table 3). A 5-Wood-unit increase in SVR was associated with a 4.9-mL smaller RVESV, a 12.3-mL smaller RVEDV, and a 1.8-g smaller RV mass. SVR was not associated with the RV mass-to-volume ratio (Table 4).

We found significant effect modification by race and age for SVR with RV mass and volumes (Table 6), with younger individuals having greater decrease in RV mass and volumes (*P* for interaction <0.001, 0.006, and 0.002 for RV mass, RVESV, and RVEDV, respectively). Race/ethnicity had a significant effect on the association of SVR with RV mass (Table 6), with white individuals having a greater decrease in RV mass as compared to Chinese-Americans,

Table 3. Models for the Association of Systemic Vascular Measures With the RV Volumes (n=3842)

	RVESV Models						RVEDV Models					
	Unadjusted			Adjusted*			Unadjusted			Adjusted*		
	β	SE (β)	*P* Value	β	SE (β)	*P* Value	β	SE (β)	*P* Value	β	SE (β)	*P* Value
TAC per 1 mL/mm Hg	13.2	0.4	<0.001	3.9	0.4	<0.001	37.5	0.8	<0.001	7.6	0.7	<0.001
SVR per 5 Wood units	−4.9	0.2	<0.001	−0.6	0.2	0.01	−12.3	0.5	<0.001	−1.7	0.4	<0.001
AI per 1%	−1.0	0.1	<0.001	−0.06	0.07	0.41	−2.3	0.2	<0.001	−0.2	0.1	0.05

AI indicates aortic augmentation index; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; SVR, systemic vascular resistance; TAC, total arterial compliance.
*Adjusted for age (years), sex (males/females), race/ethnicity (white, Chinese-American, black, and Hispanic), height (cm), weight (kg), heart rate (beats/min), smoking status (never, former, or current), level of education (<high school, high school, >high school but <college, or ≥college or higher), presence of hypertension (yes/no), presence of diabetes mellitus (yes/no), urinary albumin-to-creatinine ratio, total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), current diuretic use (yes/no), physical activity (metabolic equivalent of task per minute per week), and the corresponding left ventricle (LV) parameter (LVESV for RVESV model, LVEDV for RVEDV model).

Table 4. Model for the Association of Systemic Vascular Measures With the RV Mass-to-Volume Ratio (n=3842)

	RV Mass-to-Volume Ratio					
	Unadjusted			Adjusted*		
	β	SE (β)	*P* Value	β	SE (β)	*P* Value
TAC per 1 mL/mm Hg	−0.01	0.0006	<0.001	−0.007	0.0008	<0.001
SVR per 5 Wood units	0.01	0.002	<0.001	−0.002	0.002	0.46
AI per 1%	0.0005	0.0001	<0.001	0.0003	0.0001	0.82

AI indicates aortic augmentation index; RV, right ventricular; SVR, systemic vascular resistance; TAC, total arterial compliance.
*Adjusted for age (years), sex (males/females), race/ethnicity (white, Chinese-American, black, and Hispanic), height (cm), weight (kg), heart rate (beats/min), smoking status (never, former, or current), level of education (<high school, high school, >high school but <college, or ≥college or higher), presence of hypertension (yes/no), presence of diabetes mellitus (yes/no), urinary albumin-to-creatinine ratio, total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), current diuretic use (yes/no), physical activity (metabolic equivalent of task per minute per week), and the corresponding left ventricle (LV) parameter (LV wall-to-cavity index).

blacks, and Hispanics (*P* for interaction, 0.03). We also found effect modification by sex for SVR with RV volumes (Table 6), with males having a larger decrease in RVESV and RVEDV as compared to females (*P* for interaction <0.001 for both RVESV and RVEDV).

Table 5. Effect Modification for TAC for the RV Measures

	β	SE (β)	*P* Value	*P* for Interaction
RV mass				
TAC (at 51 years of age) per 1 mL/mm Hg	2.6	0.1	<0.001	0.02
TAC (at 71 years of age) per 1 mL/mm Hg	2.1	0.2	<0.001	
RVESV				
TAC (at 51 years of age) per 1 mL/mm Hg	4.6	0.5	<0.001	0.006
TAC (at 71 years of age) per 1 mL/mm Hg	2.9	0.5	<0.001	
TAC (female) per 1 mL/mm Hg	2.5	0.6	<0.001	<0.001
TAC (male) per 1 mL/mm Hg	4.7	0.5	<0.001	
RVEDV				
TAC (at 51 years of age) per 1 mL/mm Hg	8.9	0.8	<0.001	0.002
TAC (at 71 years of age) per 1 mL/mm Hg	5.8	1.0	<0.001	
TAC (female) per 1 mL/mm Hg	5.6	1.0	<0.001	0.002
TAC (male) per 1 mL/mm Hg	8.9	0.8	<0.001	

Models adjusted for age (years), sex (males/females), race/ethnicity (white, Chinese-American, black, and Hispanic), height (cm), weight (kg), heart rate (beats/min), smoking status (never, former, or current), level of education (<high school, high school, >high school but <college, or ≥college or higher), presence of hypertension (yes/no), presence of diabetes mellitus (yes/no), urinary albumin-to-creatinine ratio, total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), current diuretic use (yes/no), physical activity (metabolic equivalent of task per minute per week), and the corresponding left ventricle (LV) parameter (LV mass for RV mass model, LVESV for RVESV model, and LVEDV for RVEDV model). Data for nonsignificant interactions with age, sex, race/ethnicity, and hypertension not shown. RV indicates right ventricular; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; TAC, total arterial compliance.

Aortic Augmentation Index

Higher AI was associated with smaller RVESV and RVEDV, RV mass, and greater RVEF on univariate analysis; however, after multivariate adjustment, AI remained significantly associated only with RVEDV. The magnitude of the association was very small, whereby a 1% increase in AI was associated with a 0.2-mL smaller RVEDV (Tables 2 and 3).

We found significant effect modification by age and sex for AI with RVEDV (Table 7). Younger individuals had a greater decrease in RVEDV as compared to older individuals (*P* for interaction=0.008). Males had a greater decrease in RVEDV as compared females (*P* for interaction <0.001).

Sensitivity Analyses

The observed associations between the different vascular measures and RV parameters were consistent in the log-log models (data not shown). The results did not significantly change after additional adjustment for spirometric measures (Tables 8 through 10).

Discussion

This is the first large study to examine the association between systemic vascular measures and the RV. In a US multiethnic cohort of individuals without clinical cardiovascular disease, lower arterial compliance (ie, greater arterial stiffness) was associated with smaller RV volumes and mass and a greater RV mass-to-volume ratio. We also found that higher SVR was associated with smaller RV volumes and mass. Higher AI was associated with smaller RVEDV and lower RVEF. These associations were independent of a number of confounders, including anthropometric relationships, demographic and

Table 6. Effect Modification for SVR for the RV Measures

	β	SE (β)	*P* Value	*P* for Interaction
RV mass				
SVR (white) per 5 WU	−0.6	0.1	<0.001	0.03
SVR (Chinese-American) per 5 WU	−0.4	0.1	0.005	
SVR (black) per 5 WU	−0.3	0.1	0.02	
SVR (Hispanic) per 5 WU	−0.3	0.1	0.02	
SVR (at 51 years of age) per 5 WU	−0.8	0.1	<0.001	<0.001
SVR (at 71 years of age) per 5 WU	−0.3	0.08	<0.001	
RVESV				
SVR (at 51 years of age) per 5 WU	−1.3	0.3	<0.001	0.006
SVR (at 71 years of age) per 5 WU	−0.4	0.3	0.13	
SVR (female) per 5 WU	−0.02	0.3	0.93	<0.001
SVR (male) per 5 WU	−1.8	0.3	<0.001	
RVEDV				
SVR (at 51 years of age) per 5 WU	−2.9	0.6	<0.001	0.002
SVR (at 71 years of age) per 5 WU	−1.3	0.4	0.002	
SVR (female) per 5 WU	−0.9	0.4	0.03	<0.001
SVR (male) per 5 WU	−3.3	0.5	<0.001	

Models adjusted for age (years), sex (males/females), race/ethnicity (white, Chinese-American, black, and Hispanic), height (cm), weight (kg), heart rate (beats/min), smoking status (never, former, or current), level of education (<high school, high school, >high school but <college, or ≥college or higher), presence of hypertension (yes/no), presence of diabetes mellitus (yes/no), urinary albumin-to-creatinine ratio, total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), current diuretic use (yes/no), physical activity (metabolic equivalent of task per minute per week), and the corresponding LV parameter (LV mass for RV mass model, LVESV for RVESV model, and LVEDV for RVEDV model). Data for nonsignificant interactions with age, sex, race/ethnicity, and hypertension not shown. RV indicates right ventricular; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; SVR, systemic vascular resistance; WU, Wood units.

Table 7. Effect Modification for AI for the RV Measures

	β	SE (β)	*P* Value	*P* for Interaction
RVEDV				
AI (female) per 1%	0.02	0.1	0.90	<0.001
AI (male) per 1%	−0.8	0.2	<0.001	
AI (at 51 years of age) per 1%	−0.5	0.2	0.001	0.008
AI (at 71 years of age) per 1%	−0.003	0.1	0.99	

Models adjusted for age (years), sex (males/females), race/ethnicity (white, Chinese-American, black, and Hispanic), height (cm), weight (kg), heart rate (beats/min), smoking status (never, former, or current), level of education (<high school, high school, >high school but <college, or ≥college or higher), presence of hypertension (yes/no), presence of diabetes mellitus (yes/no), urinary albumin-to-creatinine ratio, total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), current diuretic use (yes/no), physical activity (metabolic equivalent of task per minute per week), and the corresponding left ventricle (LV) parameter (LVESV for RVESV model). Data for nonsignificant interactions with age, sex, race/ethnicity, and hypertension not shown. AI indicates aortic augmentation index; RV, right ventricular; RVEDV, right ventricular end-diastolic volume.

clinical variables, as well as the corresponding LV parameters. These findings indicate that systemic arterial characteristics are associated with RV morphology. The representation of men, women, and minorities in the MESA cohort also provided a unique opportunity to examine heterogeneity of effects by sex and race/ethnicity.

The hemodynamic load is a predictor of LV workload at rest and during exercise.[30] However, using a single vascular parameter, such as TAC or SVR, underestimates LV workload because of the complexity of the LV-vascular coupling relationship, hence the need for multiple indices that reflect the pulsatile and resistive load of the arterial system.[31] With growing evidence of similar pathophysiological processes affecting the pulmonary and systemic vascular systems,[6] we hypothesized that increased systemic arterial load (lower TAC, higher SVR, and higher AI) would be associated with greater RV mass, larger RV volumes, and lower RVEF. The results of our study, namely, that increased vascular stiffness markers were generally associated with *smaller RV volumes and lower RV mass*, were contrary to our original hypotheses, which was based on observations of the response of RV in the setting of HFpEF.[4,5,32] It is notable that previous investigations in MESA-RV have similarly revealed relationships between smaller RV size and aging, risk of incident dyspnea, emphysema/chronic obstructive pulmonary disease, and inflammatory biomarkers.[33–38] Our findings serve as a caution to extrapolating information from disease states to preclinical stages of disease given that the consistency between inflammatory biomarkers and vascular stiffness and decreased RV size imply distinct pathophysiological processes in individuals without clinical cardiovascular disease.

TAC, as estimated by the ratio of stroke volume to arterial pulse pressure, is a surrogate measure of pulsatile arterial load.[20,21] TAC decreases as vascular stiffness increases and is largely dependent on the properties of large- and medium-sized conduit arteries.[20,21] Lower TAC (more vascular stiffness) has been previously shown to be associated with lower LV mass and higher LV wall-to-cavity volume ratio in MESA.[19] We found a similar association between TAC and RV mass and RV volumes, although this association was disproportionate for the RV given that it persisted despite adjustment for the respective LV measures. In our study, women had smaller decreases in RV volumes with decrements in TAC, suggesting a stronger effect of vascular stiffness on RV volumes in men. We also

Table 8. Baseline Characteristics of Study Subjects in the Sensitivity Analysis Cohort

	Study Sample (n=3842)	Sensitivity Analysis (n=2584)	Excluded (n=1258)
Age, y	61±10	61±10	63±10
Males, n (%)	1845 (48)	1281 (50)	564 (45)
Race/ethnicity, %			
White	1492 (39)	920 (35)	572 (45)
Chinese-American	979 (25)	460 (18)	36 (3)
Black	496 (13)	614 (24)	365 (29)
Hispanic	875 (23)	590 (23)	285 (23)
Height, cm	166.4±10.0	166.6±10.0	166.1±9.9
Weight, kg	77.3±16.2	76.5±16.1	78.9±16.2
Body mass index, kg/m^2	27.8±5.0	27.5±4.8	28.5±5.2
Education level, n (%)			
<High school	637 (17)	414 (16)	223 (18)
High school	713 (18)	473 (18)	240 (19)
>High school, <college	607 (16)	409 (16)	198 (16)
≥College	1885 (49)	1288 (50)	597 (47)
Diabetes mellitus, n (%)	452 (12)	267 (10)	185 (15)
Hypertension, n (%)	1643 (43)	1042 (40)	601 (48)
Total cholesterol, mg/dL	194±35	194±35	195±35
HDL cholesterol, mg/dL	51±15	51±15	51±15
Urine albumin/creatinine, mg/g	5.2 [3.3–10.1]	5.0 [3.2–9.8]	5.5 [3.5–10.9]
Smoking status, n (%)			
Never	1995 (52)	1401 (54)	594 (47)
Former	1375 (36)	898 (35)	477 (38)
Current	472 (12)	285 (11)	187 (15)
Physical activity, MET-minutes/week			
Moderate and vigorous physical activity	4140 [2055–7738]	4121 [2055–7770]	4189 [2057–7642]
Total intentional exercise	840 [210–2076]	840 [210–2100]	840 [123–1993]
Heart rate, bpm	63±9	63±9	63±10
RV mass, g	21.1±4.4	21.0±4.3	20.7±4.6
RVESV, mL	37.5±14.2	37.8±14.4	36.9±13.9
RVEDV, mL	124.5±30.8	125.3±30.9	122.9±30.6
RVEF, %	70.4±6.5	70.3±6.4	70.4±6.5
Forced expiratory volume in 1 second, L	—	2.4±0.7	—
Forced vital capacity, L	—	3.2±1.0	—
FEV1/FVC ratio, %	—	75±8	—

FEV1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; HDL, high-density lipoprotein; MET, metabolic equivalent of task; RV, right ventricular; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume.

found a stronger relationship between vascular stiffness and RV morphology in younger than in older individuals.

Higher SVR was also associated with lower RV mass and smaller RV volumes. SVR has been previously shown to affect LV wall-to-cavity ratio or remodeling, with higher SVR leading to concentric geometry of the LV.[19] We found that with increases in SVR, whites had the greatest decrease in RV mass as compared to Chinese-Americans, blacks, and Hispanics. Racial and ethnic differences in RV mass have been previously reported,[18,39] and our study findings suggest

Table 9. Multivariate Regression Models for RV Mass and RVEF in Sensitivity Analysis With Spirometry (n=2584)

	RV Mass Model			RVEF Model		
	β	SE (β)	*P* Value	β	SE (β)	*P* Value
TAC per 1 mL/mm Hg	2.3	0.1	<0.001	0.2	0.3	0.59
SVR per 5 Wood units	−0.4	0.1	<0.001	0.5	0.2	0.01
AI per 1%	−0.009	0.03	0.74	−0.02	0.05	0.72

Model adjusted for age (years), sex (males/females), race/ethnicity (white, Chinese-American, black, and Hispanic), height (cm), weight (kg), heart rate (beats/min), smoking status (never, former, or current), level of education (<high school, high school, >high school but <college, or ≥college), presence of hypertension (yes/no), presence of diabetes mellitus (yes/no), urinary albumin-to-creatinine ratio, total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), current diuretic use (yes/no), physical activity (metabolic equivalent of task per minute per week), forced expiratory volume in 1 second (L), forced vital capacity (L), and the corresponding left ventricle (LV) parameter (LV mass for RV mass model, LVEF for RVEF model). AI indicates aortic augmentation index; RV, right ventricular; RVEF, right ventricular ejection fraction; SVR, systemic vascular resistance; TAC, total arterial compliance.

a differential racial-ethnic response of RV mass to changes in SVR. Younger individuals had a greater decrease in RV mass and volumes with an increase in SVR in our study. This is likely related to the fact that in young individuals, the SVR largely determines blood pressure and arterial load with less contribution from large vessel compliance.[40] We also found that males had a greater decrease in RV volumes as compared to females. Whereas prepubertal women are known to have higher vascular resistance as compared to their male counterparts, postpubertal women have lower vascular resistance until menopause.[41,42] The changing vascular resistance properties in women with aging likely attenuate the effect of SVR on RV volumes as compared to men.

Table 10. Multivariate Regression Models for RV Volumes in Sensitivity Analysis With Spirometry (n=2584)

	RVESV Model			RVEDV Model		
	β	SE (β)	*P* Value	β	SE (β)	*P* Value
TAC per 1 mL/mm Hg	3.3	0.5	<0.001	5.9	0.9	<0.001
SVR per 5 Wood units	−1.0	0.3	0.002	−2.2	0.5	<0.001
AI per 1%	−0.03	0.09	0.73	−0.1	0.1	0.45

Model adjusted for age (years), sex (males/females), race/ethnicity (white, Chinese-American, black, and Hispanic), height (cm), weight (kg), heart rate (beats/min), smoking status (never, former, or current), level of education (<high school, high school, >high school but <college, or ≥college), presence of hypertension (yes/no), presence of diabetes mellitus (yes/no), urinary albumin-to-creatinine ratio, total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), current diuretic use (yes/no), physical activity (metabolic equivalent of task per minute per week), forced expiratory volume in 1 second (L), forced vital capacity (L), and the corresponding left ventricle (LV) parameter (LVESV for RVESV model, LVEDV for RVEDV model). AI indicates aortic augmentation index; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; SVR, systemic vascular resistance; TAC, total arterial compliance.

The timing and site of arterial wave reflection affects LV afterload.[31,43] Given that AI is derived from the properties of the arterial waveforms, it not only reflects changes in arterial stiffness, but also reflects the complex interaction between the LV and arterial load.[44] AI is increased with isometric exercise and in hypertensive patients and is highly correlated with LV mass.[30] We found no association between AI and RV mass after multivariate adjustment; however, higher AI was associated with smaller RVEDV.

The vascular endothelium is involved in the production and release of several vasoactive and inflammatory mediators.[45] Systemic vascular stiffness induces enhanced oxidative stress, which, in turn, activates the interleukin-6 (IL-6) signaling pathway in both adventitial and endothelial layers of the vasculature.[46–48] IL-6 and its downstream product, C-reactive protein (CRP), are known inflammatory cytokines that are well-established independent predictors of cardiovascular disease and all-cause mortality.[49–52] In the MESA-RV cohort, higher levels of IL-6 and CRP have been shown to be associated with lower RV mass and smaller RV volumes.[34] IL-6, and its signaling pathways through glycoprotein 130, mediate the interface between the cardiomyocyte's compensatory remodeling and apoptosis in response to injury, which could explain the reduction in RV size.[52,53] Collectively, these findings imply that systemic arterial health could affect the RV through vasoactive mediators by a direct effect through the coronary flow and microvasculature. However, it is also possible that the systemic vasculature affects the RV through effects on the LV. Increased vascular stiffness and LV dysfunction may lead to decreased RV coronary perfusion and myocardial ischemia, which may explain smaller RV volumes.[54]

Our study has several limitations. One limitation is the observational cross-sectional design, which does not permit inferences regarding the directionality of the relationship between RV morphology and systemic vascular stiffness and therefore causation. Although it is difficult to conceive that decreases in RV size would increase systemic vascular stiffness, this is still possible. Arterial load was determined by brachial blood pressure measurements and radial tonometry, which have some limitations compared to carotid tonometry or invasive measurements. There is a possibility of measurement error of the various vascular properties (TAC, SVR, and AI); however, we expect such error to be nondifferential with respect to the RV measures, biasing to the null. We adjusted our models for several demographic, socioeconomic, and clinical variables that could affect the association between the systemic vascular measures and the RV measures; however, the possibility of residual confounding

remains. We did not adjust *P* values to account for multiple testing of different outcomes; however, the findings appear consistent among the different vascular and RV parameters.

Conclusion

The study is the first multiethnic, population-based study cohort with data on several measures of systemic vascular health and RV size and function in subjects free of cardiovascular disease. This broad representation of men and women and minorities provided a unique opportunity to examine the effects of sex and race on the relationship between these vascular measures and the RV in a generalizable way. Systemic vascular load metrics are significantly associated with RV mass and volumes in a population free of cardiovascular disease. These findings persisted after adjustment for potential confounders and have important clinical implications of the systemic vasculature affecting the morphology of the RV. Whether therapeutic modification of the systemic vascular stiffness could impact RV morphology and patient outcomes remains to be determined.

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Disclosures

None.

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