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MINI-FOCUS ISSUE: LEFT VENTRICULAR FUNCTION AND REMODELING

Race-Related Differences in Left Ventricular Structural and Functional Remodeling in Response to Increased Afterload

The ARIC Study

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate racial differences in arterial elastance (Ea), which reflects the arterial afterload faced by the left ventricle, and its associations with cardiac structure and function. The hypothesis under study was that the left ventricle in blacks displays heightened afterload sensitivity compared with whites.

BACKGROUND Chronic increasing in arterial afterload may be an important trigger for left ventricular (LV) remodeling and dysfunction that lead to heart failure. Racial differences in the predisposition to heart failure are well described, but the underlying mechanisms remain unclear.

METHODS In total, 5,727 community-based, older ARIC (Atherosclerosis Risk In Community) study participants (22% black) who underwent echocardiography between 2011 and 2013 were studied.

RESULTS Blacks were younger (mean age 75 ± 5 years vs. 76 ± 5 years), were more frequently female (66% vs. 57%), and had higher prevalence rates of obesity (46% vs. 31%), hypertension (94% vs. 80%), and diabetes mellitus (47% vs. 34%) than whites. Adjusting for these baseline differences, Ea was higher among blacks (1.96 ± 0.01 mm Hg/ml vs. 1.80 ± 0.01 mm Hg/ml). In blacks, Ea was associated with greater LV remodeling (LV mass index, $\beta = 3.21 \pm 0.55$ g/m^2, $p < 0.001$) and higher LV filling pressures (E/e′ ratio, $\beta = 0.42 \pm 0.11$, $p < 0.001$). These relationships were not observed in whites (LV mass, $\beta = 0.16 \pm 0.32$ g/m^2, $p = 0.61$, p for interaction <0.001; E/e′ ratio, $\beta = -0.32 \pm 0.06$, $p < 0.001$, p for interaction <0.001).

CONCLUSIONS These community-based data suggest that black Americans display heightened afterload sensitivity as a stimulus for LV structural and functional remodeling, which may contribute to their greater risk for heart failure compared with white Americans. (J Am Coll Cardiol HF 2017;5:157–65) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BP = blood pressure

BSA = body surface area

Ea = arterial elastance

Ees = end-systolic elastance

HF = heart failure

LA = left atrial

LV = left ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

SV = stroke volume

Black Americans have the highest incidence of heart failure (HF) among racial groups in the United States. Although this has been in part attributed to race-related differences in socioeconomic status and prevalence of hypertension and diabetes (1-3), reasons for the higher incidence of HF among blacks are largely unexplained. For instance, racial differences in the incidence of HF could result from differences in the incidence of coronary artery disease, but blacks still have higher incidence of HF after excluding cases preceded by a myocardial infarction (1).

The development of HF has been linked to abnormalities in ventricular-arterial coupling, which is represented by the ratio between arterial and ventricular elastance (4). Arterial elastance (Ea) is a lumped parameter that incorporates mean and pulsatile components of the systemic vascular properties and reflects the total arterial afterload (5). High arterial afterload may be a trigger for changes in left ventricular (LV) structure and function, which are predecessors of clinical HF (6-9). Arterial afterload appears to be higher among blacks than whites, as a result of racial differences in arterial stiffness and intravascular volume (10-12). In parallel, LV hypertrophy is more common among blacks with hypertension (13). However, it is uncertain whether this is out of proportion to arterial afterload.

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Therefore, we assessed the racial differences in Ea and its associations with cardiac structure and function in a large biracial community-based study of an older population, among whom these differences are expected to be more noticeable as a consequence of the long-term cardiac effects of arterial afterload.

METHODS

STUDY POPULATION. The ARIC (Atherosclerosis Risk In Communities) study is an ongoing, prospective observational study. The original cohort recruited 15,792 subjects 45 to 64 years of age in 4 communities in the United States (Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland) between 1987 and 1989. After baseline evaluation, the participants underwent 4 subsequent follow-up visits. At the time of visit 5, between 2011 and 2013, 10,740 participants were alive, 6,538 attended, and 6,118 underwent echocardiography. Population characteristics, sampling, design, procedures, and detailed study rationale have been previously published (14).

Race was self-reported using a questionnaire. Hypertension was defined as systolic blood pressure (BP) (average between second and third measures) ≥140 mm Hg, diastolic BP (average between second and third measures) ≥90 mm Hg, or use of antihypertensive medication at any of the ARIC visits. Diabetes mellitus was defined as present if a participant self-reported a physician diagnosis of diabetes, was taking medication for diabetes, had a fasting blood glucose level ≥126 mg/dl, or had a nonfasting blood glucose level ≥200 mg/dl at any of the ARIC visits. Prevalent HF at visit 5 was defined as an adjudicated HF hospitalization since 2005, HF hospitalization with International Classification of Diseases-9th Revision, code 428x before 2005, or self-report of HF or treatment for HF with subsequent confirmation of self-report by treating physician (15).

From the 6,118 participants, we excluded subjects with moderate or severe aortic valve disease (stenosis or insufficiency, n = 78), atrial fibrillation at the time of echocardiography (n = 267), those whose race was neither white nor black (n = 6), and those with missing Ea (n = 40), resulting in 5,727 subjects for the present analysis. The Institutional Review Board of each center approved the study protocol, and all participants provided written informed consent.

ECHOCARDIOGRAPHY. All studies were obtained using a dedicated Philips iE33 ultrasound system (Philips Medical Systems, Andover, Massachusetts) by trained sonographers according to a dedicated echocardiographic protocol (16). All measurements were performed according to American Society of

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TABLE 1 Participant Characteristics According to Race

	Blacks (n = 1,286)	Whites (n = 4,441)	p Value
Age, yrs	75.0 ± 4.9	76.1 ± 5.1	<0.001
Women	854 (66)	2,523 (57)	<0.001
Height, cm	165 ± 9	165 ± 10	0.96
Weight, kg	83 ± 18	77 ± 17	<0.001
Body mass index, kg/m^2	30 ± 7	28 ± 5	<0.001
Body surface area, m^2	1.90 ± 0.21	1.84 ± 0.22	<0.001
Hypertension	1,209 (94)	3,545 (80)	<0.001
Antihypertensive medication use	1,117 (87)	3,127 (71)	<0.001
Diabetes mellitus	607 (47)	1,521 (34)	<0.001
Current smokers	86 (7)	249 (6)	0.21
CHD	117 (9)	680 (16)	<0.001
Heart failure	73 (6)	160 (4)	<0.001
Systolic BP, mm Hg	135 ± 19	129 ± 17	<0.001
Diastolic BP, mm Hg	70 ± 11	65 ± 10	<0.001
Pulse pressure, mm Hg	65 ± 16	64 ± 14	0.07
Heart rate, beats/min	64 ± 11	62 ± 10	<0.001

Values are mean ± SD or n (%).
BP = blood pressure; CHD = coronary heart disease.

Echocardiography guidelines in a dedicated echocardiography core laboratory (17). Details about the design and protocol of the ARIC visit 5 echocardiographic study, including reproducibility data, have been previously published (16).

LV dimensions and wall thickness were obtained from the parasternal long-axis view according to the recommendations of the American Society of Echocardiography (18). LV mass was determined by the linear method, and all measurements were indexed to body surface area (BSA) when appropriate. LV mass was also indexed to height$^{2.7}$, which may have some advantages over indexing to BSA in obese patients (19). LV hypertrophy was defined as LV mass index (LV mass/BSA) >115 g/m^2 in men and >95 g/m^2 in women (18). LV outflow tract (LVOT) diameter was obtained from the parasternal long-axis view and stroke volume (SV) was calculated as the product of LVOT area and the LVOT velocity-time integral.

We assessed LV diastolic function using pulsed-wave Doppler of mitral inflow (E and A velocities and E/A ratio) and peak septal and lateral mitral annular relaxation tissue Doppler velocities (e′). Left atrial (LA) volume was measured by the method of disks using apical 4- and 2-chamber views at an end-systolic frame preceding mitral valve opening and indexed to BSA (LA volume index).

ASSESSMENT OF ARTERIAL FUNCTION AND VENTRICULAR-ARTERIAL COUPLING. Ea was calculated as end-systolic pressure divided by SV (20). Using the brachial BP measurement at the time of echocardiographic examination, end-systolic pressure was estimated as 0.9 × systolic BP (7-9,20,21). We also estimated the steady and pulsatile components of arterial load (22). Systemic vascular resistance index was estimated as mean arterial pressure multiplied by 80 and divided by cardiac index and total arterial compliance as the ratio between SV and pulse pressure (23,24). Carotid-femoral pulse-wave velocity was measured using a ColinVP-1000 plus system (Omron, Komaki, Japan) (25).

LV end-systolic elastance (Ees) was determined using the single-beat method (21) using left ventricular ejection fraction (LVEF), brachial BP, SV, pre-ejection period, and total ejection period. The latter 2 measurements were obtained from pulsed-wave Doppler of LVOT flow. To correct for the effects of chronic LV remodeling, we normalized Ees for the ratio of LV mass to volume, as previously described (26).

LV SYSTOLIC FUNCTION. LV volumes and the LVEF were assessed using the modified Simpson rule. Speckle-tracking analysis was performed using TomTec Cardiac Performance Analysis package (TomTec, Unterschleissheim, Germany). Global longitudinal strain was obtained from apical 4- and 2-chamber views. Peak systolic mitral annular velocity (s′) was also obtained using tissue Doppler imaging.

EUROPEAN ANCESTRY AMONG BLACKS. Proportion of European ancestry was estimated in black participants using genotyping methods in the ARIC study, described previously (27). Briefly, genotyping was performed on stored deoxyribonucleic acid from visit 1 using the Illumina BeadLab platform at the Center for Inherited Disease Research (Johns Hopkins University, Baltimore, Maryland) (28). Blind duplicate genotypes were performed as part of a quality control program and had a mismatch rate of 0.1%. Samples were eliminated from the analysis because of low call, sex mismatch, duplicity, excess of heterozygous genotypes, or estimated proportion of European ancestry higher than 0.85. ANCESTRYMAP software was used to estimate the proportion of European ancestry for each individual. We classified black participants as below or above median European ancestry.

STATISTICAL ANALYSIS. We compared clinical differences between black and white participants using unpaired Student *t* tests or chi-square tests, as appropriate. We compared measures of cardiac structure and function between race groups, adjusting for potential confounders, including age, sex, body mass index, use of antihypertensive

TABLE 2 Differences in Cardiac Function and Structure Between Blacks and Whites Adjusted for Clinical Covariates

	Unadjusted			Adjusted*		
	Black (n = 1,286)	White (n = 4,441)	p Value	Black (n = 1,257)	White (n = 4,233)	p Value
Cardiac structure						
EDVI, ml/m^2	44.2 ± 0.3	43.9 ± 0.2	0.44	45.2 ± 0.3	43.8 ± 0.2	<0.001
LV mass/BSA, g/m^2	78.1 ± 0.6	79.6 ± 0.3	0.023	77.7 ± 0.5	79.6 ± 0.3	0.003
LV mass/height$^{2.7}$, g/m$^{2.7}$	38.3 ± 0.3	37.8 ± 0.2	0.15	36.9 ± 0.3	38.2 ± 0.1	<0.001
LV mass/EDV, mg/ml	1.82 ± 0.01	1.87 ± 0.01	0.001	1.76 ± 0.01	1.88 ± 0.01	<0.001
LV hypertrophy	12%	10%	0.079	10%	10%	0.88
LA volume index, ml/m^2	25.9 ± 0.2	25.4 ± 0.1	0.034	26.1 ± 0.2	25.3 ± 0.1	0.001
Systolic function						
Ejection fraction, %	64.7 ± 0.2	65.6 ± 0.1	<0.001	64.5 ± 0.2	65.7 ± 0.1	<0.001
Peak longitudinal strain	−17.52 ± 0.07	−18.14 ± 0.04	<0.001	−17.60 ± 0.07	−18.11 ± 0.04	<0.001
s′, cm/s	6.77 ± 0.04	7.03 ± 0.02	<0.001	6.76 ± 0.04	7.05 ± 0.02	<0.001
Stroke volume, ml	65.0 ± 0.4	67.4 ± 0.2	<0.001	64.8 ± 0.4	67.5 ± 0.2	<0.001
Cardiac output, l/min	4.35 ± 0.03	4.36 ± 0.02	0.67	4.22 ± 0.03	4.40 ± 0.02	<0.001
Diastolic function						
E-wave, cm/s	65.5 ± 0.5	66.6 ± 0.3	0.072	64.9 ± 0.5	66.7 ± 0.3	0.003
A-wave, cm/s	82.6 ± 0.5	79.8 ± 0.3	<0.001	80.6 ± 0.5	80.3 ± 0.3	0.61
Deceleration time, ms	199 ± 1	208 ± 1	<0.001	200 ± 1	208 ± 1	<0.001
E/A ratio	0.82 ± 0.008	0.87 ± 0.004	<0.001	0.84 ± 0.008	0.87 ± 0.004	0.001
e′, cm/s	6.17 ± 0.04	6.28 ± 0.02	0.022	6.24 ± 0.04	6.28 ± 0.02	0.44
E/e′ ratio	11.5 ± 0.1	11.3 ± 0.1	0.20	11.27 ± 0.11	11.34 ± 0.06	0.65
Arterial function and ventricular-arterial coupling						
Ea, mm Hg/ml	1.95 ± 0.01	1.81 ± 0.01	<0.001	1.96 ± 0.01	1.80 ± 0.01	<0.001
SVRI, dyne · s · cm^{-5} · m^2	3,378 ± 24	3,064 ± 13	<0.001	3,410 ± 24	3,056 ± 13	<0.001
TAC, ml/mm Hg	1.05 ± 0.009	1.10 ± 0.005	<0.001	1.04 ± 0.009	1.10 ± 0.005	<0.001
cfPWV, m/s	12.4 ± 0.11	11.6 ± 0.06	<0.001	12.4 ± 0.11	11.6 ± 0.06	<0.001
LV Ees, mm Hg/ml	2.92 ± 0.02	2.83 ± 0.01	0.001	2.93 ± 0.02	2.81 ± 0.01	<0.001
LV Ees/M/V, mm Hg/g	1.70 ± 0.02	1.60 ± 0.01	<0.001	1.75 ± 0.02	1.59 ± 0.01	<0.001
Ea/Ees	0.70 ± 0.005	0.66 ± 0.003	<0.001	0.70 ± 0.005	0.66 ± 0.003	<0.001

Values are mean ± SE or %. *Adjusted analysis by age, sex, body mass index, use of antihypertensive medication, diabetes mellitus, heart rate, and prevalent coronary heart disease or heart failure. LV mass/EDV ratio was added in the model for LV Ees and Ea/Ees ratio comparisons.

BSA = body surface area; cfPWV = carotid-femoral pulse-wave velocity; Ea = arterial elastance; EDV = end-diastolic volume; EDVI = end-diastolic volume index; Ees = end-systolic elastance; Ees/M/V = end-systolic elastance normalized for mass/volume ratio; LA = left atrial; LV = left ventricular; SVRI = systemic vascular resistance index; TAC = total arterial compliance.

medications, diabetes mellitus, heart rate, and history of coronary heart disease or HF. These covariates were selected on the basis of a priori knowledge, as they are potential confounders for the associations with cardiac structure and function (29,30). We included antihypertensive medication, rather than diagnosis of hypertension, to account for the drug effect on measures of Ea. Because LV concentricity influences Ees, analysis of race differences in Ees and Ea/Ees ratio were further adjusted by LV mass/end-diastolic volume. We also performed a separate analysis excluding body mass index from the model for measures of cardiac structure that were indexed by BSA or height (Online Appendix). We assessed the independent association between Ea and measures of cardiac structure and function with linear regression, adjusting for the same baseline clinical parameters. Then we tested for effect modification by race, using an Ea-race interaction term, and for effect modification by European ancestry among blacks, using an Ea-European ancestry (treated as continuous variable) interaction term. To evaluate if the effect modification by European ancestry among blacks was influenced by socioeconomic status, we further adjusted for low annual income at visit 4 (<$50,000) and educational level at visit 1 (low, midlevel, or high, as described elsewhere) and presented in the Online Appendix (31). Echocardiographic measures of cardiac structure and function for which there was a clear Ea-race interaction ($p < 0.001$) were subsequently analyzed for curvilinear associations using adjusted restricted cubic spline models. For all other analyses, p values <0.05 were considered to indicate statistical significance. There were no additional adjustments for multiple testing.

Finally, we performed 2 separate analysis: inverse probability weighting to correct for the possible effects of selective attrition (32) and exclusion of subjects with previous diagnoses of HF. Analyses were performed using Stata version 14 (Stata Corp., College Station, Texas).

RESULTS

STUDY PARTICIPANTS. The 5,727 study participants were 66 to 90 years of age, 59% were women, and 22% were black. Compared with whites, black participants were more frequently female and had a higher prevalence of obesity (46% vs. 31%, $p < 0.001$), and diabetes mellitus but a lower prevalence of coronary heart disease. The prevalence of hypertension was very high in this older population, particularly among blacks, but hypertension was defined using very sensitive criteria (see the Methods section). Even so, blacks were more likely to be using antihypertensive medication at visit 5 than whites. Also, blacks displayed higher systolic BP, diastolic BP, and heart rate during echocardiography (Table 1). The prevalence of HF was slightly higher among blacks.

CARDIAC STRUCTURE AND FUNCTION. Compared with whites, blacks presented slightly larger LV volumes and lower LV mass, but a similar prevalence of LV hypertrophy, after adjusting for age, sex, body mass index, use of antihypertensive medication, diabetes mellitus, and presence of coronary heart disease or HF (Table 2). Blacks also exhibited lower measures of LV systolic function, including LVEF, longitudinal strain, and s′ velocity.

LV early diastolic relaxation velocity (e′), which is relatively load independent, and estimated LV filling pressures (E/e′ ratio) were similar between racial groups, but peak E-wave velocity, deceleration time, and E/A ratio were lower among blacks compared with whites.

ARTERIAL FUNCTION AND VENTRICULAR-ARTERIAL COUPLING. Ea was higher, indicating higher arterial load, among blacks than among whites (Table 2). Systemic vascular resistance index was higher and total arterial compliance was lower among blacks, suggesting that both steady and pulsatile components of arterial load were implicated in such racial differences. Carotid-femoral pulse-wave velocity was slightly higher among blacks than whites, indicating elevated arterial stiffness. Ventricular stiffness was greater among blacks, as reflected by higher LV Ees after taking into account LV concentricity (Table 2).

ASSOCIATION BETWEEN EA AND CARDIAC STRUCTURE AND FUNCTION. We found that the association between Ea and measures of cardiac structure and function significantly differed between blacks and whites. Ea was positively associated with LV end-diastolic volume and LV mass among blacks but not among whites (Table 3). Overall, high Ea was associated with lower measures of systolic function, including longitudinal strain, s′, and LVEF, and race modified the association between Ea and LVEF.

Likewise, we found that high Ea was associated with worse LV diastolic function in blacks than in whites. Although Ea was negatively associated with e′ in both racial groups, this association was steeper among blacks; that is, among subjects with high Ea, e′ was lower in blacks than in whites. Furthermore, high Ea was associated with higher E/e′ ratio and LA volume index, indicating higher filling pressures, in blacks than in whites (Table 3). These findings were similar when we analyzed with inverse probability weighting (Online Tables 1 and 2) or after excluding participants with diagnosis of HF (Online Tables 3 and 4).

We also observed nonlinear relationships between Ea and cardiac function and structure and how they differed between blacks and whites. In Figure 1, we see that these relationships clearly diverged between race groups for measures of Ea above 2 mm Hg/ml: blacks with high Ea displayed higher LV mass and volume, higher LA volume, and higher E/e′ ratio compared with whites with similar levels of Ea.

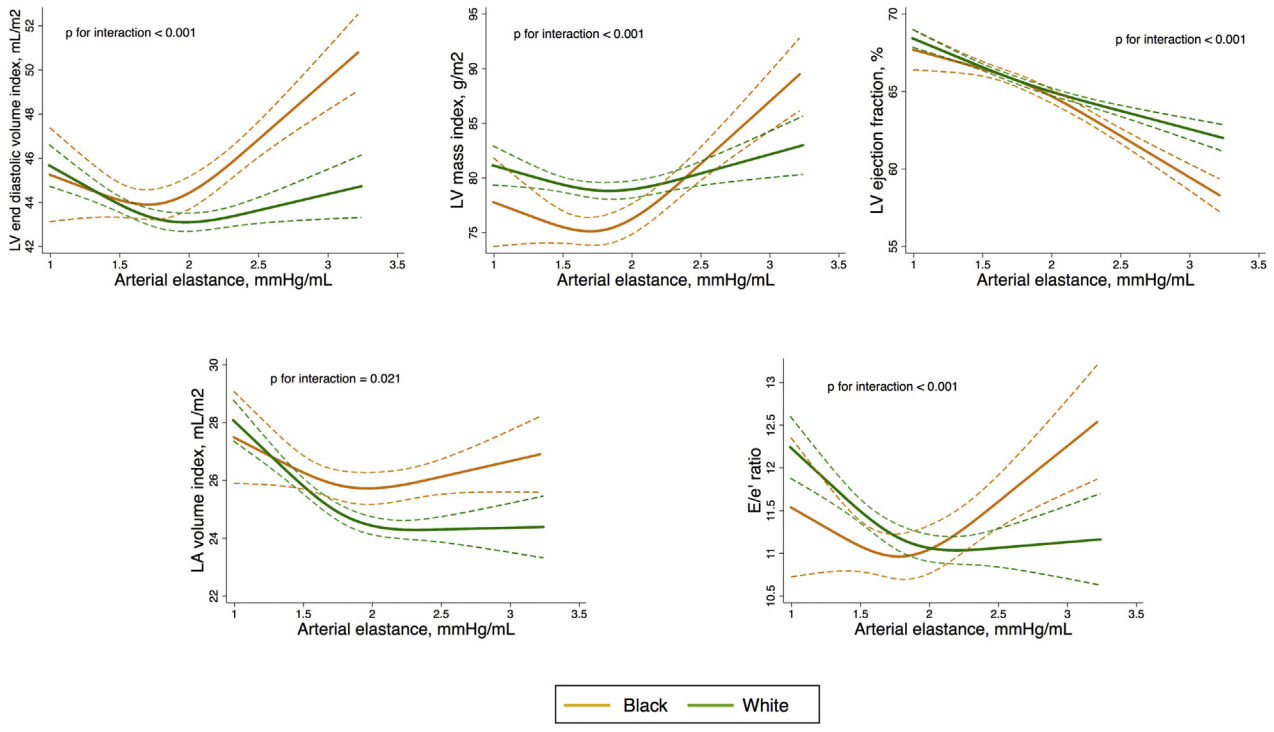
TABLE 3 Race-Specific Associations of Arterial Elastance With Cardiac Structure and Function, After Adjusting for Confounders

	Black		White		p Value for Interaction
	(n = 1,257)	p Value	(n = 4,233)	p Value	
Cardiac structure					
EDVI	1.56 ± 0.28	<0.001	−0.33 ± 0.17	0.048	<0.001
LV mass/BSA	3.21 ± 0.55	<0.001	0.16 ± 0.32	0.61	<0.001
LV mass/height$^{2.7}$	1.80 ± 0.27	<0.001	0.36 ± 0.15	0.020	<0.001
LV mass/EDV	0.02 ± 0.01	0.12	0.02 ± 0.01	0.007	0.90
LA volume index	0.03 ± 0.22	0.87	−0.92 ± 0.13	<0.001	<0.001
Systolic function					
Ejection fraction	−2.23 ± 0.18	<0.001	−1.38 ± 0.10	<0.001	<0.001
Peak longitudinal strain	0.74 ± 0.07	<0.001	0.59 ± 0.04	<0.001	0.20
s′	−0.32 ± 0.03	<0.001	−0.23 ± 0.02	<0.001	0.34
Diastolic function					
E-wave	−1.68 ± 0.47	<0.001	−4.00 ± 0.30	<0.001	0.003
A-wave	−2.41 ± 0.48	<0.001	−3.36 ± 0.31	<0.001	0.15
Deceleration time	−4.06 ± 1.16	<0.001	−4.48 ± 0.77	<0.001	0.58
E/A ratio	0.01 ± 0.01	0.12	−0.01 ± 0.005	0.011	0.06
e′	−0.33 ± 0.04	<0.001	−0.22 ± 0.02	<0.001	0.028
E/e′ ratio	0.42 ± 0.11	<0.001	−0.32 ± 0.06	<0.001	<0.001

Values are coefficients (β ± SE) for each 1-SD increase in arterial elastance adjusted for age, sex, body mass index, use of antihypertensive medication, diabetes mellitus, heart rate, and prevalent coronary heart disease or heart failure.

Abbreviations as in Table 2.

FIGURE 1 Race-Specific Associations of Arterial Elastance With Measures of Cardiac Structure and Function



Adjusted plot for age, sex, body mass index, use of antihypertensive medication, diabetes mellitus, heart rate, and prevalence of coronary heart disease or heart failure. **Dashed lines** = 95% prediction brands. LA = left atrial; LV = left ventricular.

The association between Ea and cardiac structure and function also differed according to genetic ancestry among blacks. Although blacks with below-median (0.153) European ancestry had direct associations between Ea and LV mass, LV and LA volumes, and E/e′ ratio, these associations were significantly attenuated among blacks with above-median European ancestry and were more similar to the associations observed among white participants (**Table 4**). These differences persisted after adjusting for annual income and educational level (Online Table 5).

TABLE 4 Race-Specific Associations of Arterial Elastance With Cardiac Structure and Function in Elderly Accounting for European Ancestry Among Blacks

	Black			
	Below-Median PEA* (n = 513)	Above-Median PEA* (n = 526)	White (n = 4,213)	p Value for Interaction
EDVI	2.57 ± 0.46†	0.47 ± 0.43	−0.33 ± 0.17	<0.001
LV mass/BSA	5.47 ± 0.85†	0.35 ± 0.87	0.16 ± 0.32	<0.001
LV mass/height$^{2.7}$	2.81 ± 0.42†	0.55 ± 0.44	0.36 ± 0.15‡	<0.001
LA volume index	0.83 ± 0.32‡	−0.83 ± 0.37‡	−0.92 ± 0.13†	<0.001
Ejection fraction	−2.14 ± 0.26†	−2.18 ± 0.29†	−1.38 ± 0.10†	0.001
E/e′ ratio	0.67 ± 0.17†	0.22 ± 0.18	−0.32 ± 0.06†	<0.001

Values are coefficients (β ± SE) for each 1-SD increase in arterial elastance adjusted for age, sex, body mass index, use of antihypertensive medication, diabetes mellitus, heart rate, and prevalent coronary heart disease or heart failure. *PEA was 0.11 ± 0.03 and 0.25 ± 0.10 for blacks with below- and above-median PEA, respectively. †p < 0.001; ‡p < 0.05.

PEA = proportion of European ancestry; other abbreviations as in Table 2.

DISCUSSION

In this large biracial cohort of older subjects, we showed for the first time that the association of Ea with cardiac structure and function differs between blacks and whites. Not only do blacks display higher arterial afterload (Ea) compared with whites, they also display more adverse changes in cardiac structure and function as Ea increases compared with whites, indicating greater vulnerability to high afterload (**Figure 2**). These data may help explain why blacks with hypertension are at greater risk for cardiovascular complications (1,7,33). This in turn suggests that intensive BP reduction, which lowers Ea and has been proved to reduce cardiovascular events, may be even more important among blacks to reduce the burden of cardiovascular disease (34).

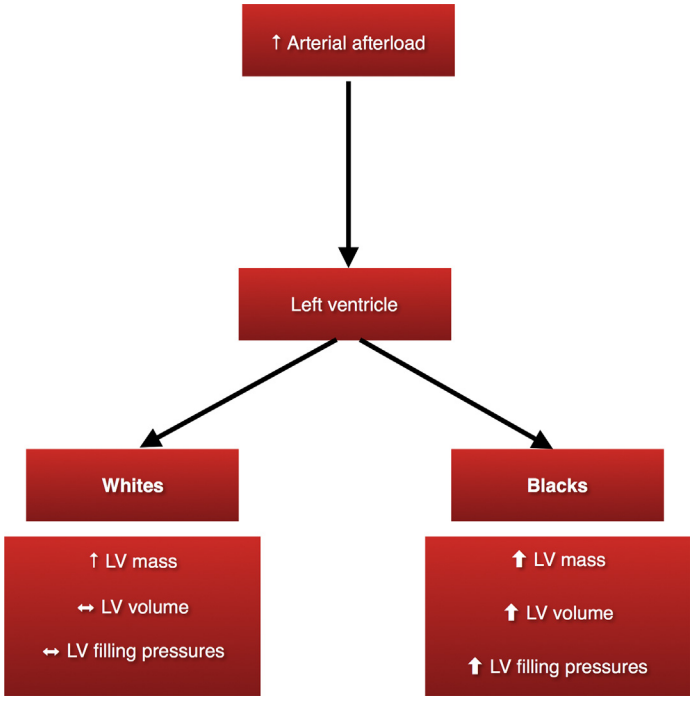
Previous studies have suggested that the higher prevalence of LV hypertrophy among blacks cannot be attributed exclusively to their higher predisposition to hypertension, in concordance with our findings (13,35–37). Blacks have higher LV mass than their white counterparts after adjusting for body size and the severity and duration of hypertension (13). It has been postulated that there are racial differences in cardiac adaptation to increased peripheral resistance (38). Peripheral resistance and systemic BP are closely related to LV systolic pressure, which is directly related to myocardial wall stress, and high peripheral resistance and arterial stiffness may be a trigger for LV hypertrophy and dysfunction (22,39,40). Ea is a composite parameter that better reflects the net impact of the arterial afterload toward the ventricle. Our results suggest that blacks develop more cardiac remodeling and dysfunction compared with whites with similar levels of Ea.

Whether an inherent racial susceptibility or environmental factors are implicated in the higher predisposition of blacks to LV remodeling is uncertain. Racial differences in health outcomes may be partly explained by disparities in socioeconomic status. For instance, low income and low education level have been associated with higher arterial stiffness and LV mass and can mediate the race disparities (10,41,42). However, racial differences in arterial stiffness are observed among people free of traditional cardiovascular risk factors and at very young ages, suggesting racial differences on arterial function and structure early in life (11,43).

We found that the association of high Ea with cardiac remodeling and dysfunction attenuates among blacks with above-median European ancestry, even after adjusting for socioeconomic status, which suggests a genetic basis to explain these racial differences. Accordingly, the genetic profile rather than self-reported race was associated with arterial stiffness in MESA (Multi-Ethnic Study of Atherosclerosis) (44). Blacks are more likely to carry a minor corin I555(P568) allele, which has been associated with enhanced cardiac hypertrophic response to pressure overload (45,46). Even so, we must interpret these results with caution, because the contribution of genetic ancestry to these phenotypic differences may still reflect environmental factors to some extent.

Furthermore, the association between Ea and cardiac remodeling can be unrelated to increased afterload, triggering LV hypertrophy. LV mass may increase prior to the development of overt hypertension (47), suggesting that the factors that promote LV hypertrophy may be unconnected to high BP. For instance, either norepinephrine or angiotensin II may directly affect LV size independently of BP (48,49). It is uncertain, however, whether these factors play a role in the higher predisposition of blacks to LV hypertrophy.

FIGURE 2 Race-Specific Changes in Left Ventricular Structure and Function in Response of High Arterial Afterload



LV = left ventricular.

Our study suggests that blacks have both higher Ea and greater afterload sensitivity for cardiac remodeling and dysfunction compared with whites, which may elucidate part of their higher predisposition to cardiovascular diseases, particularly HF (1). Hence, blacks are more likely not only to develop hypertension, the clinical expression of high Ea, but to experience its harmful effects on the heart. Recently, it was shown that treatment targeting a systolic BP to <120 mm Hg, compared with <140 mm Hg, results in lower rates of cardiovascular events among patients at high cardiovascular risk (34). Together, these data imply that intensive BP lowering may be particularly advantageous among blacks and increase even further the priority for better control of BP in black Americans, an enormous unmet public health need.

STUDY LIMITATIONS. Our study had some limitations that deserve attention. This was a cross-sectional study, which prevents us from establishing

a temporal sequence of the cardiovascular abnormalities. Racial differences in the association between Ea and cardiac remodeling can merely reflect the racial disparities in the hypertension course. Besides, there may be survivor bias in this cross-sectional study, and only approximately 60% of participants who were alive at visit 5 underwent echocardiography. We addressed this by performing inverse probability weighting analysis and found consistent results. In addition, although our results may provide mechanistic insights that help explain why blacks have higher predisposition to HF, we did not explore new mechanisms but the racial differences in ventricular-arterial coupling. Even though an increase in Ea should result in an increase in LV wall stress, we did not directly measure LV wall stress. We used noninvasive methods to assess Ea and Ees, which have greater variability compared with invasive measurements. Nevertheless, Doppler measures are feasible parameters to evaluate in large population-based studies and have been previously validated against gold-standard invasive methods. Finally, we cannot definitively exclude that the differences and relationships we observed are not due to other unmeasured confounding variables.

CONCLUSIONS

In this large community-based study, we demonstrated that the association of Ea with cardiac structure and function diverges between black and white Americans. These results suggest that blacks are more susceptible to changes in cardiac structure and function triggered by increased arterial load, which may explain their higher predisposition to develop HF. Further studies are needed to evaluate whether specific therapies that have an impact on arterial afterload can further reduce the cardiovascular risk among blacks.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Hypertension leads to changes in cardiac structure and function, which precede the clinical manifestations of cardiovascular diseases, triggered by high arterial afterload. High arterial afterload appears to cause more cardiac remodeling among blacks compared with whites. This helps explain why blacks have higher risk for developing cardiovascular diseases than whites.

TRANSLATIONAL OUTLOOK: Further studies are needed to evaluate: 1) which therapies, including antihypertensive drugs, can better reduce the arterial afterload; and 2) whether different classes of antihypertensive drugs have differential effects on the incidence of cardiovascular events according to race.

REFERENCES

1. Bahrami H, Kronmal R, Bluemke DA, et al. Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. Arch Intern Med 2008;168:2138–45.

2. Chang PP, Chambless LE, Shahar E, et al. Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study). Am J Cardiol 2014;113:504–10.

3. Yancy CW. Heart failure in African Americans. Am J Cardiol 2005;96 Suppl:3i–12i.

4. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003;107:714–20.

5. Segers P, Stergiopulos N, Westerhof N. Relation of effective arterial elastance to arterial system properties. Am J Physiol Heart Circ Physiol 2002;282:H1041–6.

6. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2013;62:e147–239.

7. Borlaug BA, Redfield MM, Melenovsky V, et al. Longitudinal changes in left ventricular stiffness: a community-based study. Circ Heart Fail 2013;6:944–52.

8. Wohlfahrt P, Redfield MM, Lopez-Jimenez F, et al. Impact of general and central adiposity on ventricular-arterial aging in women and men. J Am Coll Cardiol HF 2014;2:489–99.

9. Wohlfahrt P, Redfield MM, Melenovsky V, Lopez-Jimenez F, Rodeheffer RJ, Borlaug BA. Impact of chronic changes in arterial compliance and resistance on left ventricular ageing in humans. Eur J Heart Fail 2015;17:27–34.

10. Din-Dzietham R, Couper D, Evans G, Arnett DK, Jones DW. Arterial stiffness is greater in African Americans than in whites: evidence from the Forsyth County, North Carolina, ARIC cohort. Am J Hypertens 2004;17:304–13.

11. Morris AA, Patel RS, Binongo JNG, et al. Racial differences in arterial stiffness and microcirculatory function between black and white Americans. J Am Heart Assoc 2013;2:e002154.

12. Chrysant SG, Danisa K, Kem DC, Dillard BL, Smith WJ, Frohlich ED. Racial differences in pressure, volume and renin interrelationships in essential hypertension. Hypertension 1979;1:136–41.

13. Kizer JR, Arnett DK, Bella JN, et al. Differences in left ventricular structure between black and white hypertensive adults: the Hypertension

Genetic Epidemiology Network study. Hypertension 2004;43:1182–8.

14. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. Am J Epidemiol 1989;129:687–702.

15. Rosamond WD, Chang PP, Baggett C, et al. Classification of heart failure in the Atherosclerosis Risk in Communities (ARIC) study: a comparison of diagnostic criteria. Circ Heart Fail 2012;5:152–9.

16. Shah AM, Cheng S, Skali H, et al. Rationale and design of a multicenter echocardiographic study to assess the relationship between cardiac structure and function and heart failure risk in a biracial cohort of community-dwelling elderly persons: the Atherosclerosis Risk in Communities study. Circ Cardiovasc Imaging 2014;7:173–81.

17. Picard MH, Adams D, Bierig SM, et al. American Society of Echocardiography recommendations for quality echocardiography laboratory operations. J Am Soc Echocardiogr 2011;24:1–10.

18. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.

19. Chirinos JA, Segers P, De Buyzere ML, et al. Left ventricular mass: allometric scaling, normative values, effect of obesity, and prognostic performance. Hypertension 2010;56:91–8.

20. Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513–21.

21. Chen CH, Fetics B, Nevo E, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001;38:2028–34.

22. Coutinho T, Borlaug BA, Pellikka PA, Turner ST, Kullo IJ. Sex differences in arterial stiffness and ventricular-arterial interactions. J Am Coll Cardiol 2013;61:96–103.

23. Chemla D, Hébert JL, Coirault C, et al. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol 1998;274:H500–5.

24. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007;115:1982–90.

25. Meyer ML, Tanaka H, Palta P, et al. Correlates of segmental pulse wave velocity in older adults: the Atherosclerosis Risk in Communities (ARIC) study. Am J Hypertens 2015:hpv079.

26. Gaasch WH, Little WC. Assessment of left ventricular diastolic function and recognition of diastolic heart failure. Circulation 2007;116:591–3.

27. Cheng C-Y, Reich D, Coresh J, et al. Admixture mapping of obesity-related traits in African Americans: the Atherosclerosis Risk in Communities (ARIC) study. Obesity (Silver Spring) 2010; 18:563–72.

28. Fan JB, Oliphant A, Shen R, et al. Highly parallel SNP genotyping. Cold Spring Harb Symp Quant Biol 2003;68:69–78.

29. Nadruz W Jr., Claggett B, Goncalves A, et al. Smoking and cardiac structure and function in the elderly: the ARIC study (Atherosclerosis Risk in Communities). Circ Cardiovasc Imaging 2016;9: e004950.

30. Goncalves A, Jhund PS, Claggett B, et al. Relationship between alcohol consumption and cardiac structure and function in the elderly: the Atherosclerosis Risk In Communities Study. Circ Cardiovasc Imaging 2015;8.

31. Fretz A, Schneider ALC, McEvoy JW, et al. The association of socioeconomic status with subclinical myocardial damage, incident cardiovascular events, and mortality in the ARIC study. Am J Epidemiol 2016;183:452–61.

32. Gottesman RF, Rawlings AM, Sharrett AR, et al. Impact of differential attrition on the association of education with cognitive change over 20 years of follow-up: the ARIC neurocognitive study. Am J Epidemiol 2014;179:956–66.

33. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 2011;32:670–9.

34. SPRINT Research Group, Wright JT Jr., Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–16.

35. Wang J, Chen W, Ruan L, Toprak A, Srinivasan SR, Berenson GS. Differential effect of elevated blood pressure on left ventricular geometry types in black and white young adults in a community (from the Bogalusa Heart Study). Am J Cardiol 2011;107:717–22.

36. Drazner MH, Dries DL, Peshock RM, et al. Left ventricular hypertrophy is more prevalent in blacks than whites in the general population: the Dallas Heart Study. Hypertension 2005;46:124–9.

37. Gardin JM, Wagenknecht LE, Anton-Culver H, et al. Relationship of cardiovascular risk factors to echocardiographic left ventricular mass in healthy young black and white adult men and women. The CARDIA study. Coronary Artery Risk Development in Young Adults. Circulation 1995;92:380–7.

38. Dunn FG, Oigman W, Sungaard-Riise K, et al. Racial differences in cardiac adaptation to essential hypertension determined by echocardiographic indexes. J Am Coll Cardiol 1983;1:1348–51.

39. Fernandes VRS, Polak JF, Cheng S, et al. Arterial stiffness is associated with regional ventricular systolic and diastolic dysfunction: the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol 2008;28:194–201.

40. Chaturvedi N, Bulpitt CJ, Leggetter S, et al. Ethnic differences in vascular stiffness and relations to hypertensive target organ damage. J Hypertens 2004;22:1731–7.

41. Dekkers C, Treiber FA, Kapuku G, Van Den Oord EJCG, Snieder H. Growth of left ventricular mass in African American and European American youth. Hypertension 2002;39:943–51.

42. Thurston RC, Matthews KA. Racial and socioeconomic disparities in arterial stiffness and intima media thickness among adolescents. Soc Sci Med 2009;68:807–13.

43. Collins RT, Somes GW, Alpert BS. Differences in arterial compliance among normotensive adolescent groups: Collins arterial compliance in adolescents. Pediatr Cardiol 2008;29:929–34.

44. Wassel CL, Jacobs DR, Duprez DA, et al. Association of self-reported race/ethnicity and genetic ancestry with arterial elasticity: the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Soc Hypertens 2011;5:463–72.

45. Dries DL, Victor RG, Rame JE, et al. Corin gene minor allele defined by 2 missense mutations is common in blacks and associated with high blood pressure and hypertension. Circulation 2005;112: 2403–10.

46. Rame JE, Drazner MH, Post W, et al. Corin I555(P568) allele is associated with enhanced cardiac hypertrophic response to increased systemic afterload. Hypertension 2007;49: 857–64.

47. Post WS, Larson MG, Levy D. Impact of left ventricular structure on the incidence of hypertension. The Framingham Heart Study. Circulation 1994;90:179–85.

48. Harrap SB, Dominiczak AF, Fraser R, et al. Plasma angiotensin II, predisposition to hypertension, and left ventricular size in healthy young adults. Circulation 1996;93:1148–54.

49. Schlaich MP, Kaye DM, Lambert E, Sommerville M, Socratous F, Esler MD. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. Circulation 2003;108:560–5.

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APPENDIX For supplemental tables, please see the online version of this article.