

Clinical Correlates of Aortic Stiffness and Wave Amplitude in Black Men and Women in the Community

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Background—Black individuals have greater risk for cardiovascular disease (CVD) than whites. Identifying CVD risk factors associated with abnormal aortic hemodynamics in blacks may optimize CVD prevention and treatment strategies.

Methods and Results—Jackson Heart Study participants underwent applanation tonometry (2011–2016) with assessment of carotid-femoral pulse wave velocity (CFPWV) and forward wave amplitude (FWA). CVD risk factors were assessed during examination 3 (2009–2012). We examined the association of risk factors with binary and continuous CFPWV and FWA in multivariable stepwise models. We evaluated for effect modification by sex to determine differential associations of risk factors with aortic hemodynamics in men and women. We examined 1322 individuals (mean age 66 ± 11 years, 66% women). Age was strongly associated with elevated CFPWV (odds ratio, 4.76; 95% confidence interval, 3.84–5.89 [$P < 0.0001$]) and FWA (odds ratio, 2.30; 95% CI, 1.98–2.69 [$P < 0.0001$]). Men had greater odds of elevated CFPWV compared with women (odds ratio, 1.54; 95% confidence interval, 1.11–2.13 [$P = 0.009$]). Heart rate, mean arterial pressure, and use of antihypertensive medications were associated with elevated CFPWV and FWA (all $P \leq 0.02$). Additionally, total/high-density lipoprotein cholesterol and fasting glucose were associated with elevated CFPWV (both $P \leq 0.002$) and use of diabetes mellitus medications was associated with elevated FWA ($P \leq 0.0001$). We observed a steeper association of age and mean arterial pressure with unfavorable aortic hemodynamics in women than men.

Conclusions—In blacks in the community, differential CVD risk factors are associated with aortic stiffness and FWA. Future work may determine the impact of risk factor modification on abnormal central aortic hemodynamics and CVD outcomes. (*J Am Heart Assoc.* 2018;7:e008431. DOI: 10.1161/JAHA.117.008431.)

Key Words: aortic stiffness • epidemiology • race • risk factor

Elevated global aortic stiffness is associated with significant morbidity and mortality, including cardiovascular disease (CVD)^{1–4} and cerebrovascular disease.^{5–7} Elevated aortic stiffness and forward wave amplitude (FWA) are associated with development of hypertension, with the latter a dominant contributor to accelerated pressure pulsatility with

age.^{8,9} However, the majority of data evaluating stiffness along the length of the aorta are in whites of European ancestry, with underrepresentation of people of other races and ethnicities, including those of African ancestry. Compared with non-Hispanic whites, blacks have a higher prevalence of hypertension, stroke, heart failure, and CVD, and a higher incidence of CVD death.¹⁰ Evidence suggests that blacks also have greater aortic stiffness as compared with whites,^{11,12} which may contribute to their greater CVD risk.

Whereas risk factors for greater aortic stiffness and wave reflection are established for white Americans, they are less well investigated in blacks. Elucidating key risk factors for and any sex differences in abnormal aortic hemodynamics in this minority group are important to develop improved strategies and targets for prevention and treatment of CVD in black men and women. We hypothesized that among CVD risk factors, age and blood pressure (BP) would be related to vascular stiffness in this group. Thus, we chose to test our hypotheses in the community-based JHS (Jackson Heart Study) cohort using measures of carotid-femoral pulse wave velocity (CFPWV) and FWA, which are 2 noninvasive measures that

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Clinical Perspective

What Is New?

- Cardiovascular disease risk factors including blood pressure, dyslipidemia, and dysglycemia were associated with abnormal central aortic hemodynamics, particularly in older black women.

What Are the Clinical Implications?

- Optimizing treatment of these cardiovascular disease risk factors, especially at younger ages, may mitigate cardiovascular disease outcomes associated with adverse aortic hemodynamics among blacks.

provide additive information regarding aortic hemodynamics and stiffness.

Methods

The data, analytic methods, and study materials are available to other researchers for purposes of reproducing the results or replicating the procedure. Data are publicly available at National Institutes of Health BioLINCC, the biologic specimen and data repository information coordinating center of the National Heart, Lung, and Blood Institute.¹³

Study Participants and Assessment of Covariates

JHS is a longitudinal community cohort study based in Jackson, Mississippi. The methods of recruitment and study characteristics have been previously described.^{14,15} Briefly, beginning with study initiation with examination 1 (2000–2004), participants have clinical examinations at about 3-year cycles, with interval assessment of health via telephone interviews and questionnaires. Arterial tonometry measures were obtained between 2011 and 2016 in 2235 participants who participated in examination 3 (2009–2012). Of these 1995 participants who received tonometry and participated in examination 3, 497 were excluded for inadequate tonometry data and 176 for missing covariates.

Clinical covariates were taken at examination 3, with serum samples obtained after an overnight fast. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL, random blood glucose >200 mg/dL, the use of hypoglycemic agents, or physician diagnosis. Hypertension was defined as systolic BP (SBP) ≥ 140 mm Hg, DBP ≥ 90 mm Hg, or the use of antihypertensive medications. Metabolic syndrome was defined as the presence of ≥ 3 of the following criteria: abdominal obesity (≥ 101.6 cm in men and ≥ 88.9 cm in women), hypertriglyceridemia (≥ 150 mg/dL), reduced high-density lipoprotein

(HDL) cholesterol (<40 mg/dL in men and <50 mg/dL in women), elevated BP (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic), or elevated fasting glucose (≥ 100 mg/dL).¹⁶ Low-density lipoprotein (LDL) was calculated using the Friedewald equation.^{17,18} Cigarette smoking was considered present if the participant smoked ≥ 1 cigarette daily in the past 12 months.

The study protocol was approved by the institutional review board of Jackson State University, Tougaloo College, and the University of Mississippi Medical Center. Each participant provided written informed consent.

Tonometry Data Acquisition

The approach to data acquisition and analysis has been described in detail.⁹ Measures were taken on the right side of the body. After 5 minutes of rest, systolic and diastolic BPs were measured in the right brachial artery, in the supine position with a semiautomatic auscultatory device. Applanation tonometry with simultaneous ECG was performed on the carotid and femoral arteries using a custom tonometer (Cardiovascular Engineering, Inc). Next, we obtained 2-dimensional echocardiographic left ventricular outflow tract parasternal long-axis images, followed by left ventricular outflow tract pulsed Doppler from an apical 5-chamber view. Body surface measurements were made from the suprasternal notch to the carotid artery using a fiberglass tape measure and from the suprasternal notch to the femoral recording site using a caliper (to avoid overestimation of the transit distance). Carotid-femoral pulse wave transit distance was calculated as the difference between these 2 measures. We digitized tonometry and ECG data at 1000 Hz during acquisition and analyzed images in the core laboratory (Cardiovascular Engineering, Inc).

Analysis of Tonometry Waveforms

We signal averaged arterial waveforms using the R wave on ECG as a fiducial point. We calibrated brachial pressure waveform using systolic and diastolic cuff pressures. We used diastolic and integrated mean brachial pressures to calibrate the carotid and femoral pressure tracings, with calibrated carotid pressure considered a surrogate of central pressure.¹⁹ We separated forward and reflected pressure waves in the time domain and assessed the amplitude (peak minus trough) of each wave. We calculated CFPWV as the ratio of the transit distance and transit time between the carotid and femoral arteries, as previously described using tonometry waveforms and body surface measures.⁹ FWA was calculated as the difference between the pressure at the first systolic inflection point or peak of the carotid pressure waveform, and the waveform foot.²⁰ The excellent reproducibility data of central hemodynamic variables using these methods have previously

been reported.^{21,22} Noninvasive hemodynamic measures closely correlate with invasive hemodynamics.¹⁹

Statistical Analysis

Characteristics of the cohort were tabulated using means and SDs or proportions. Triglycerides were log-transformed to normalize the distribution. CFPWV was inverse-transformed and multiplied by -1000 to convert units to ms/m and restore the direction of effect.

To define an elevation of CFPWV and FWA, we first identified a reference sample of JHS participants free of hypertension, diabetes mellitus, medical treatment for hypertension or diabetes mellitus, smoking, or prevalent CVD. Within this healthy sample, we defined the 90th percentile value for CFPWV and FWA among men and women separately, and applied this cut point to define elevated CFPWV and FWA in logistic regression models. Forward selection stepwise logistic regression models were conducted, with CFPWV and FWA as binary dependent variables, with age and sex forced into the models. The additional covariates offered to the selection model included heart rate; body mass index; mean arterial pressure (MAP); total/HDL cholesterol; triglycerides; fasting glucose; diabetes mellitus; prevalent CVD; hypertension; use of medications for BP, diabetes mellitus, and lipid-lowering; current smoking; or hormone replacement therapy. We additionally adjusted for the time between tonometry and covariate measurements in the continuous analysis.

We evaluated for effect modification of the association of CVD risk factors with CFPWV and FWA by age and sex, by including age, sex, age², and age²*sex interaction terms in the models. For significant sex interactions, we then examined sex-stratified analyses of the association of risk factors with elevated CFPWV and FWA to evaluate the association in men and women separately. We also conducted linear regression analyses to evaluate the continuous association of the risk factors with CFPWV and FWA as continuous variables. We plotted the association of age with CFPWV and FWA to evaluate their continuous relations. A 2-sided $P \leq 0.05$ was considered significant. Odds ratios (ORs) and estimated beta coefficients (B) for the association of variables with CFPWV and FWA were standardized and presented per SD unit (SDU) increment or presence of predictor variable for each SDU increment of CFPWV or FWA. We used SAS/STAT 12.3 software (SAS Institute) for our analyses.

Results

Characteristics of Participants

The characteristics of the 1322 JHS participants are presented in Table 1. The sample included middle-aged to

Table 1. Characteristics of JHS Participants

	Men (n=450)	Women (n=872)
Clinical characteristics		
Age, y	65 (11)	67 (10)
Body mass index, kg/m ²	29.7 (5.2)	31.8 (6.2)
BP, mm Hg		
Mean arterial pressure	98 (11)	98 (12)
Systolic BP	137 (17)	137 (19)
Diastolic BP	73 (10)	70 (10)
Pulse pressure	63 (19)	69 (22)
Heart rate, min ⁻¹	64 (10)	65 (10)
Cholesterol, mg/dL		
Total/HDL cholesterol ratio	3.9 (1.1)	3.4 (1)
Calculated LDL cholesterol	120 (37)	121 (36)
Triglycerides, mg/dL	89 (66, 125)	84 (63, 110)
Fasting glucose, mg/dL	110 (36)	104 (33)
Diabetes mellitus	19	22
Metabolic syndrome	29	35
Cardiovascular disease	9	7
Use of antihypertensive medications	68	77
Use of lipid-lowering medications	30	33
Smoked cigarettes (within the past 12 mo)	13	8
Hormone replacement	...	33
Tonometry measures		
Carotid-femoral pulse wave velocity, m/s	11.3 (4.0)	11.1 (4.3)
Forward wave amplitude, mm Hg	52 (15)	54 (17)

Continuous variables are presented as mean (SD) except for triglycerides, which are presented as median (interquartile range). Binary variables are presented as percentages. Values were taken at the time of examination 3 except for age, which was recorded at tonometry visit. There was an average of 2.5 ± 1.0 years between examination 3 and tonometry. BP indicates blood pressure; HDL, high-density lipoprotein; JHS, Jackson Heart Study; LDL, low-density lipoprotein.

older adults (mean age, 66 ± 11 years), with a predominance of women (66%). There was a relatively high prevalence of diabetes mellitus, metabolic syndrome, and use of antihypertensive and lipid-lowering medications. In comparison, the characteristics of individuals excluded for inadequate tonometry data or missing covariates are presented in Table 2. Individuals with missing covariates were more likely men, had slightly greater body mass index, and had a greater proportion of diabetes mellitus and metabolic syndrome than individuals who completed the study. However, participant age, prevalent CVD, and tonometry measures were similar between individuals included in the study and those with missing covariates.

Table 2. Characteristics of JHS Participants With Complete and Missing Covariates

	Complete (n=1322)	Missing Covariates (n=673)
Clinical characteristics		
Age, y	66 (11)	65 (12)
Women	66	61
Body mass index, kg/m ²	31 (6)	33 (8)
BP, mm Hg		
Mean arterial pressure	98 (12)	99 (13)
Systolic BP	137 (18)	138 (20)
Diastolic BP	71 (10)	72 (11)
Pulse pressure	67 (21)	67 (22)
Heart rate, min ⁻¹	65 (10)	67 (11)
Cholesterol, mg/dL		
Total/HDL cholesterol ratio	3.6 (1.1)	3.7 (1.1)
Calculated LDL cholesterol	121 (37)	120 (37)
Triglycerides, mg/dL	85 (64, 115)	85 (63, 118)
Fasting glucose, mg/dL	106 (34)	104 (30)
Diabetes mellitus	21	31
Metabolic syndrome	33	43
Cardiovascular disease	8	12
Use of antihypertensive medications	74	77
Use of lipid-lowering medications	32	36
Smoked cigarettes (within the past 12 mo)	10	11
Hormone replacement therapy	22	19
Tonometry measures		
Carotid-femoral pulse wave velocity, m/s	11 (4)	12 (5)
Forward pressure wave, mm Hg	54 (16)	54 (16)

Continuous variables are presented as mean (SD) except for triglycerides, which are presented as median (interquartile range). Binary variables are presented as percentages. Values were taken at the time of examination 3 except for age, which was recorded at tonometry visit. BP indicates blood pressure; HDL, high-density lipoprotein; JHS, Jackson Heart Study; LDL, low-density lipoprotein.

Associations of Risk Factors With Arterial Hemodynamics

Advancing age was positively related to CFPWV and FWA, with an over 4-fold increase in likelihood of having high CFPWV per SDU greater age (Table 3). As compared with women, men had higher odds of elevated CFPWV (OR, 1.54; 95% confidence interval [CI], 1.11–2.13 [$P=0.009$]). There was a trend toward higher FWA in women versus men ($P=0.05$). Higher mean heart rate, MAP, total/HDL cholesterol, fasting glucose, and use of BP medications were directly associated

Table 3. Cardiovascular Risk Factors and Risk for High CFPWV or Forward Wave Amplitude, Including Mean Arterial Pressure

	OR (95% CI)	P Value
CFPWV		
Age	4.76 (3.84–5.89)	<0.0001
Male sex	1.54 (1.11–2.13)	0.009
Heart rate	1.51 (1.29–1.77)	<0.0001
Mean arterial pressure	2.25 (1.90–2.63)	<0.0001
Total/HDL cholesterol	1.29 (1.10–1.51)	0.002
Fasting glucose	1.37 (1.19–1.57)	<0.0001
Antihypertensive medications	1.63 (1.09–2.45)	<0.0001
Forward wave amplitude		
Age	2.30 (1.98–2.69)	<0.0001
Male sex	0.76 (0.58–1.00)	0.05
Heart rate	0.70 (0.60–0.80)	<0.0001
Mean arterial pressure	2.79 (2.38–3.26)	<0.0001
Antihypertensive medications	1.47 (1.07–2.02)	0.02
Diabetes mellitus medications	2.24 (1.62–3.09)	<0.0001

C statistics for carotid-femoral pulse wave velocity (CFPWV) and forward wave amplitude models: 0.85 and 0.80, respectively. Odds ratios (ORs) are presented per SD unit increment in continuous predictor variable or presence of a dichotomous variable. Age, sex, and age-sex interaction were forced into stepwise selection models offering the following covariates: body mass index; mean arterial pressure; total/high-density lipoprotein (HDL) cholesterol; triglycerides; fasting glucose; diabetes mellitus; prevalent cardiovascular disease; hypertension; use of medications for blood pressure, diabetes mellitus, and lipid-lowering; current smoking; or hormone replacement therapy. Values were taken at the time of examination 3 except for age, which was recorded at tonometry visit. High CFPWV and forward wave amplitude were defined as >90th percentile of sex-specific value in the reference sample free of hypertension, diabetes mellitus, medical treatment for hypertension or diabetes mellitus, smoking, or prevalent cardiovascular disease. CI indicates confidence interval.

with elevated CFPWV. When LDL was substituted for total/HDL cholesterol in the analysis of association of risk factors with CFPWV, LDL was not retained in the final model (OR, 1.14; 95% CI, 0.99–1.33 [$P=0.07$]). MAP and use of antihypertensive and diabetes mellitus medications were directly associated with elevated FWA, but heart rate was inversely associated with high FWA. When SBP instead of MAP was included in multivariable models, similar associations of risk factors with high CFPWV were observed, including a similar OR of the association of SBP with high CFPWV and similar model C statistic (Table 4). However, smoking rather than hypertensive medication use was retained in the model. When SBP was substituted for MAP in multivariable models predicting high FWA, the OR of SBP for high FWA was greater than that for MAP, and body mass index was significantly associated with high FWA. The model C statistic was slightly greater using SBP.

The analysis of a continuous association between risk factors and CFPWV and FWA revealed additional findings not

Table 4. Cardiovascular Risk Factors and Risk for High CFPWV or Forward Wave Amplitude, including Systolic BP

	OR (95% CI)	P Value
CFPWV		
Age	4.18 (3.18–5.48)	<0.0001
Male sex	1.89 (1.30–2.75)	0.0008
Heart rate	1.91 (1.61–2.26)	<0.0001
Systolic BP	2.98 (2.48–3.59)	<0.0001
Total/HDL cholesterol ratio	1.26 (1.07–1.48)	0.005
Fasting glucose	1.30 (1.13–1.50)	0.0002
Current smoking	0.45 (0.25–0.82)	0.009
Forward wave amplitude		
Age	1.76 (1.42–2.17)	<0.0001
Male sex	0.70 (0.51–0.97)	0.03
Heart rate	0.82 (0.70–0.97)	0.02
Systolic BP	7.87 (6.16–10.05)	<0.0001
Body mass index	1.21 (1.01–1.44)	0.03
Diabetes mellitus medications	1.82 (1.26–2.63)	0.001

C statistics for carotid-femoral pulse wave velocity (CFPWV) and forward wave amplitude models: 0.87 and 0.88, respectively. Odds ratios (ORs) are presented per SD unit increment in continuous predictor variable or presence of a dichotomous variable. Age, sex, and age-sex interaction were forced into stepwise selection models offering the following covariates: body mass index; total/high-density lipoprotein cholesterol (HDL); triglycerides; fasting glucose; prevalent cardiovascular disease; hypertension; current smoking; use of medications for blood pressure (BP), diabetes mellitus, and lipid-lowering; or hormone replacement therapy. High CFPWV and forward wave amplitude were defined as >90th percentile of sex-specific value in the reference sample free of hypertension, diabetes mellitus, medical treatment for hypertension or diabetes mellitus, smoking, or prevalent cardiovascular disease. CI indicates confidence interval.

observed in the analysis of binary aortic hemodynamic variables (Table 5). The correlates of CFPWV were similar (age, male sex, heart rate, MAP, and fasting glucose). CFPWV and FWA increased with age in both men and women, but the magnitude of this change with age was greater for CFPWV (Table 5 and Figure 1). The associations of CFPWV and FWA with age appeared linear, with nonsignificance of these hemodynamic measures with age² in logistic regression models ($P=0.80$ and $P=0.85$, respectively). Men had lower FWA compared with women ($B=-0.13$; 95% CI, -0.22 to -0.04 [$P<0.0001$]). Table 6 presents similar associations of risk factors including SBP with continuous CFPWV and FWA. The model R^2 for FWA was greater when SBP rather than MAP was used in the multivariable model.

Effect Modification by Sex in Risk Factors With Aortic Stiffness and Wave Amplitude

Secondary analysis of effect modification by sex in the association of risk factors with aortic stiffness and wave amplitude indicated significant differences with age, lipids, and

Table 5. Continuous Association Between Cardiovascular Risk Factors and Aortic Hemodynamics, Including Mean Arterial Pressure

	Estimated β (95% CI)	P Value
CFPWV		
Age*	0.55 (0.51–0.60)	<0.0001
Male sex	0.16 (0.07–0.24)	0.004
Heart rate	0.15 (0.11–0.20)	<0.0001
Mean arterial pressure	0.28 (0.23–0.32)	<0.0001
Fasting glucose	0.11 (0.07–0.15)	<0.0001
Forward wave amplitude		
Age*	0.37 (0.33–0.42)	<0.0001
Male sex	-0.13 (-0.22 to -0.04)	0.004
Heart rate	-0.15 (-0.19 to -0.10)	<0.0001
Mean arterial pressure	0.46 (0.42–0.51)	<0.0001
Diabetes mellitus medications	0.33 (0.22–0.43)	<0.0001

R^2 values for carotid-femoral pulse wave velocity (CFPWV) and forward wave amplitude models: 0.41 and 0.37, respectively. All continuous variables are standardized and presented as estimated β per SD unit increment or presence of predictor variable for each SD unit increment CFPWV or forward wave amplitude. Age, sex, and age-sex interaction were forced into stepwise selection models including the following covariates: body mass index; mean arterial pressure; total/high-density lipoprotein cholesterol; triglycerides; fasting glucose; diabetes mellitus; prevalent cardiovascular disease; hypertension; use of medications for blood pressure, diabetes mellitus, and lipid-lowering; current smoking; hormone replacement therapy; and time between tonometry and covariate measurements. CI indicates confidence interval.

*Age at time of vascular function laboratory visit.

BP. Women had higher odds of elevated CFPWV per SDU older age than men (OR, 5.82; 95% CI, 4.32–7.84 [$P<0.0001$]) versus OR, 3.70; 95% CI, 2.71–5.05 [$P<0.0001$]). Additionally, there was a greater effect size of the association between continuous age and FWA in women as compared with men ($B=0.40$; 95% CI, 0.35–0.46 [$P<0.0001$]) versus $B=0.32$, 95% CI, 0.24–0.39 [$P<0.0001$]). The associations of age with CFPWV and FWA are shown in Figure 2, whereby women have steeper age-CFPWV and age-FWA curves. As compared with men, women also had greater magnitude of association between total/HDL cholesterol and elevated CFPWV (OR per SDU total/HDL cholesterol, 1.46; 95% CI, 1.18–1.81 [$P=0.0005$]) versus OR, 1.09; 95% CI, 0.86–1.37 [$P=0.48$]). However, there was no significant association of LDL with elevated CFPWV (OR per SDU LDL, 1.17; 95% CI, 0.97–1.42 [$P=0.1$]). Finally, we observed a steeper association of MAP with FWA in women as compared with men (women: $B=0.49$, 95% CI, 0.44–0.55 [$P<0.0001$]) versus men: $B=0.40$; 95% CI, 0.32–0.48 [$P<0.0001$]).

Discussion

In this study of black adults living in the community, we observed associations in the association of age, sex, and CVD

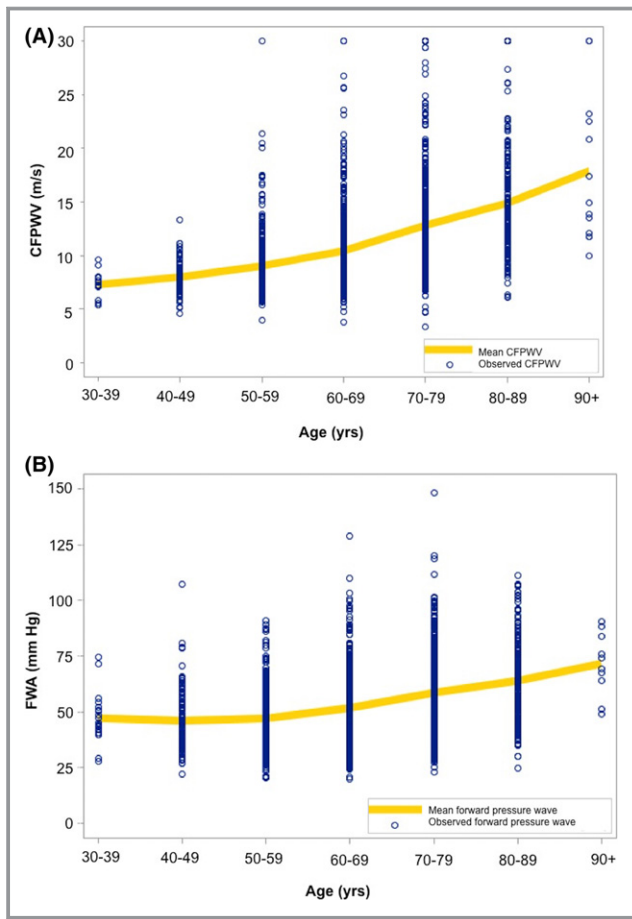


Figure 1. Association of age with carotid-femoral pulse wave velocity (CFPWV; A) and forward wave amplitude (FWA; B). Both CFPWV and FWA rose with greater age.

risk factors with CFPWV and FWA. We chose to study CFPWV and FWA, which are 2 complementary measures of arterial hemodynamics, to glean understanding of these dual contributions to the mechanisms of arterial stiffness. Whereas CFPWV measures global aortic stiffness along the thoracic and abdominal aorta, FWA reflects the interaction between aortic flow and characteristic impedance, and thus aortic diameter. Both elevated CFPWV and FWA have been associated with adverse prognosis.^{1–3,23} Age, MAP, total/HDL (but not LDL) cholesterol, fasting glucose, and diabetes mellitus were associated with elevations in arterial hemodynamic measures in our cohort. Higher heart rate was associated with CFPWV, and lower heart rate with FWA. Similar associations, but improved model prediction, were noted when SBP rather than MAP was included in risk factor models predicting higher FWA, but model prediction was similar for CFPWV. Sex differences were noted, with greater CFPWV in men but greater FWA in women. We observed effect modification by sex in the association of risk factors with aortic stiffness and wave amplitude, whereby women as compared with men had

Table 6. Continuous Association Between Cardiovascular Risk Factors and Aortic Hemodynamics, Including Systolic BP

	Estimated β (95% CI)	P Value
CFPWV		
Age*	0.44 (0.38–0.50)	<0.0001
Male sex	0.16 (0.08–0.25)	0.0002
Heart rate	0.21 (0.17–0.25)	<0.0001
Systolic BP	0.33 (0.29–0.38)	<0.0001
Fasting glucose	0.10 (0.06–0.14)	<0.0001
Forward wave amplitude		
Age*	0.20 (0.15–0.25)	<0.0001
Male sex	–0.14 (–0.21 to –0.07)	0.0001
Heart rate	–0.04 (–0.08 to –0.01)	0.02
Systolic BP	0.71 (0.67–0.75)	<0.0001
Diabetes mellitus medications	0.19 (0.10–0.27)	<0.0001

R^2 values for carotid-femoral pulse wave velocity (CFPWV) and forward wave amplitude models: 0.43 and 0.61, respectively. All continuous variables are standardized and presented as estimated β per SD unit increment or presence of predictor variable for each SD unit increment CFPWV or forward wave amplitude. Age, sex, and age-sex interaction were forced into stepwise selection models including the following covariates: body mass index; total/high-density lipoprotein cholesterol; triglycerides; fasting glucose; prevalent cardiovascular disease; hypertension; use of medications for blood pressure (BP), diabetes mellitus, and lipid-lowering; current smoking; hormone replacement therapy; and time between tonometry and covariate measurements. CI indicates confidence interval.

*Age at time of vascular function laboratory visit.

greater effect sizes in the association of age with CFPWV and FWA, and a steeper association of MAP with FWA.

Risk Factors, Aortic Stiffness, and Wave Magnitude

Among the CVD risk factors studied, age was a strong correlate of elevated CFPWV and FWA. In fact, of the risk factors examined, age was the strongest correlate of CFPWV. Age-related differences in CFPWV were more marked after the age of 60 years, consistent with that observed in predominantly white Americans in FHS (Framingham Heart Study).^{20,24} We also identified that elevated heart rate and fasting serum glucose were associated with aortic stiffness. We observed an association of elevated CFPWV with greater total/HDL cholesterol, similar to that seen in FHS of predominantly non-Hispanic whites.²⁴ Our results are consistent with a study of aortic stiffness assessed by cardiovascular magnetic resonance in MESA (Multi-Ethnic Study of Atherosclerosis), in which lower distensibility (greater stiffness) was associated with advancing age, hypertension, smoking, black race, and lower HDL cholesterol.²⁵ While our findings, together with those from MESA, suggest an association of lipid abnormalities with arterial stiffness in blacks,

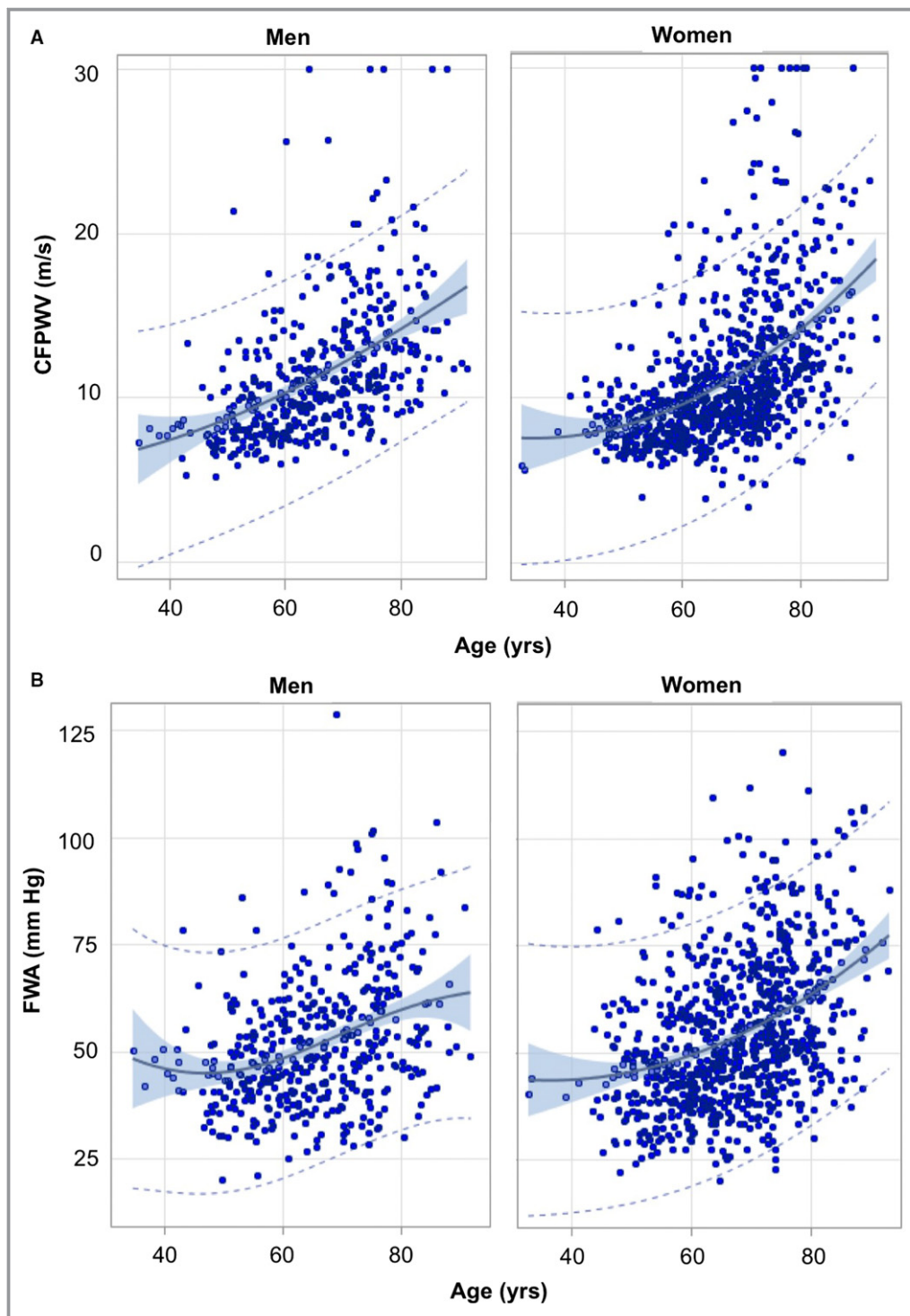


Figure 2. Sex-specific association of age with carotid-femoral pulse wave velocity (CFPWV; A) and forward wave amplitude (FWA; B). Scatterplots illustrate the continuous positive association of age with both measures of aortic hemodynamics, with steeper association associated with age in women.

total/HDL cholesterol is affected by variables including sex and BMI that may confound interpretation of results. In our multivariable models, BMI was associated with FWA in models including SBP but not in other models, indicating a lack of association with CFPWV. We observed a significant sex

difference in the association of total/HDL cholesterol ratio with arterial stiffness and hemodynamic measures with an association observed in women but not men, whereas no association between calculated LDL with these measures was observed in either men or women. Thus, collectively, our

findings suggest that further investigation of the role of lipid levels, including triglycerides and measured LDL, in arterial stiffness and hemodynamics may be indicated.

Consistent with our findings, a meta-analysis of the association of risk factors to CFPWV²⁶ identified a strong association with advancing age and BP but a variable association with other traditional CVD risk factors. Collectively, these investigations suggest that the relative contributions of many traditional CVD risk factors (other than age and BP) to CFPWV may be modest and that the risk for CVD and non-CVD morbidity and mortality associated with elevated CFPWV may be caused by other unmeasured factors.

In contrast to CFPWV, BP (particularly SBP) rather than age was the strongest correlate of elevated FWA in our study. This finding is likely secondary to the influences of distending pressure and flow on FWA and vice versa. The associations of FWA with BP and diabetes mellitus are similar to those seen in non-Hispanic whites²⁴ and consistent with literature that FWA is a key determinant of pulse pressure.^{27,28} In both our study as well as FHS, heart rate was inversely associated with FWA. FWA is a measure of pressure and flow association in the proximal aorta, rather than just aortic wall stiffness per se. Thus, FWA may capture stroke volume, and the inverse association with heart rate may reflect regulation of flow (eg, lower heart rate for a greater stroke volume). We observed that smoking was associated with arterial stiffness in models including SBP but not MAP, suggesting a contribution of chronic smoking to arterial stiffness. The association of chronic cigarette smoking with arterial stiffness, pressure pulsatility, and wave reflection is somewhat mixed, possibly relating to the definition and duration of smoking exposure. Whereas many studies show an association of smoking with CFPWV and wave reflection,^{29–31} others have not observed an association.^{4,26,31} There have been few studies examining the association of current smoking with FWA. Smoking was not associated with FWA in our models.

Sex Differences in Arterial Hemodynamics

In the current study, similar to whites, men were more likely to have greater CFPWV than women, whereas this was reversed for the association with FWA. The FHS demonstrated that women have a similar to lower CFPWV and FWA compared with men until later ages, when both mean measures surpass those in men.²⁰ This increase occurs earlier postmenopause for FWA and later for CFPWV, a phenomenon that may explain our findings of lower CFPWV and greater FWA in older aged black women as compared with men. Effect modification in the association of risk factors with CFPWV and FWA shed light on the causes of sex differences in these measures with age. Although age was associated with aortic stiffness and forward pressure wave amplitude in both sexes, the association was

stronger in women, with greater effect size in the association between age and CFPWV and FWA in women as compared with men. This trend has also been seen in non-Hispanic whites with acceleration of an age association after age 60 years.²⁴ Similarly, we observed a more marked association of MAP with FWA in women as compared with men. There is a steep rise in pulse pressure in women after the age of 60 years.^{32,33} Additionally, previous reports have demonstrated greater pulse pressure and augmentation index in studies of older women as compared with men in epidemiologic studies.^{34,35} As FWA is the main contributor to pressure pulsatility, our findings are consistent with a sharper rise in abnormal pressure wave characteristics in women, particularly later in life. Taken together, our collective results suggest a rise in aortic stiffness and pulsatile hemodynamics in women in later life, which may contribute to greater risk for CVD and heart failure in older women. The mechanisms for sex differences in pulsatile hemodynamics and aging are complex and multifactorial, relating at least in part to differences or changes in body size between men and women and differential sex hormones and estrogen signaling, with differential effects on autonomic BP regulation.^{36,37}

Study Limitations

The JHS is a longitudinally followed, well-phenotyped community-based cohort dedicated to understanding CVD in blacks, a historically underrepresented group in epidemiological cohort studies. Some limitations of the study deserve consideration. As measures of aortic hemodynamics, we studied CFPWV and FWA, which assess global thoracoabdominal aortic stiffness and wave amplitude. Although we did not evaluate local properties of aortic stiffness, our results are generally consistent with cardiovascular magnetic resonance studies that report regional aortic stiffness measures.^{38,39} An additional consideration is possible inaccuracies of measurement of pulse wave transit distance, and thus CFPWV, in obese individuals, although results were consistent with both CFPWV and FWA. Additionally, given the cross-sectional observational design, we can infer associations but cannot conclude direct causality or temporality between risk factors and CFPWV and FWA. The association of traditional CVD risk factors with CFPWV has been slight to modest across studies, and it is possible that other yet-unmeasured risk factors have a stronger association with aortic hemodynamics than those evaluated in the current study. While we adjusted for known associations of BP including medications, there remains the possibility of residual confounding by unmeasurable factors, eg, medication type or volume status, although these may have lower relative weight compared with the major factors accounted for in analyses. Furthermore, although representative of the black community of Jackson, Mississippi, our results

may not be generalizable to those of African ancestry elsewhere in the United States or abroad. Finally, although we discuss our results in relation to those of population studies including whites and other races, these other groups were not included in our analyses for direct comparison. The contributions of risk factors and arterial stiffness to prognosis and the relative benefits of therapies to address arterial stiffness in different racial and ethnic groups are areas for further study.

Conclusions

In our longitudinally followed community cohort of blacks, several risk factors, predominantly age, BP, and heart rate, were associated with global aortic stiffness and pulsatile hemodynamics, findings that are salient in light of the aging population. We observed that the association of several risk factors with vascular hemodynamics varied between men and women, which may explain the varying magnitude of CVD risk between men and women in response to any particular risk factor. The implications of abnormal hemodynamics and their relative contributions to overall prognosis in blacks are areas for further investigation.

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Disclosures

Mitchell is the owner of Cardiovascular Engineering, Inc, a company that develops and manufactures devices to measure vascular stiffness, and is a consultant to and receives honoraria from Novartis, Merck, Servier, and Philips. The remaining authors have no disclosures to report.

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