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ORIGINAL RESEARCH

Clinical Associations of Vascular Stiffness, Microvascular Dysfunction, and Prevalent Cardiovascular Disease in a Black Cohort: The Jackson Heart Study

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BACKGROUND: Measures of vascular dysfunction are related to adverse cardiovascular disease (CVD) outcomes in non-Hispanic, White populations; however, data from Black individuals are limited. We aimed to investigate the associations between novel hemodynamic measures and prevalent CVD in a sample of Black individuals.

METHODS AND RESULTS: Among older Black participants of the Jackson Heart Study, we assessed noninvasive vascular hemodynamic measures using arterial tonometry and Doppler ultrasound. We assessed 5 measures of aortic stiffness and wave reflection (carotid-femoral pulse wave velocity, pulse wave velocity ratio, forward pressure wave amplitude, central pulse pressure, and augmentation index), and 2 measures of microvascular function (baseline and hyperemic brachial flow velocity). Using multivariable logistic regression models, we examined the relations between vascular hemodynamic measures and prevalent CVD. In models adjusted for traditional CVD risk factors, higher carotid-femoral pulse wave velocity (odds ratio [OR],1.25; 95% CI, 1.01–1.55; *P*=0.04), lower augmentation index (OR, 0.84; 95% CI, 0.70–0.99; *P*=0.05), and lower hyperemic brachial flow velocity (OR, 0.77; 95% CI, 0.65–0.90; *P*=0.001) were associated with higher odds of CVD. After further adjustment for hypertension treatment, lower augmentation index (OR, 0.84; 95% CI, 0.70–0.99; *P*=0.04) and hyperemic brachial flow velocity (OR, 0.79; 95% CI, 0.67–0.94; *P*=0.006), but not carotid-femoral pulse wave velocity (OR, 1.23; 95% CI, 0.99–1.051; *P*=0.06), were associated with higher odds of CVD.

CONCLUSIONS: In a sample of older Black individuals, more severe microvascular damage and aortic stiffness were associated with prevalent CVD. Further research on hemodynamic mechanisms that contribute to cardiovascular risk among older Black individuals is merited.

Key Words: aortic stiffness ■ cardiovascular disease ■ microvascular function ■ ultrasound ■ vascular function

Several studies reveal that measures of vascular function are powerful predictors of cardiovascular disease (CVD) risk. Specifically, novel markers of arterial stiffness and pressure pulsatility, such as central pulse pressure and pulse wave velocity, are predictive of CVD incidence and progression.[1-10] Black individuals have a disproportionately high CVD burden. For example, they have the highest mortality rates attributable to CVD as compared with any other racial/ethnic group in the United States.[11] In addition, studies suggest that aortic stiffness may occur earlier or may be accelerated in the Black as compared with

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CLINICAL PERSPECTIVE

What Is New?

- Relations between aortic stiffness and microvascular function and cardiovascular disease (CVD) have not been thoroughly assessed within more diverse, community-based samples, particularly within Black individuals.
- We present an original, comprehensive assessment of noninvasive indicators of vascular dysfunction in a well-characterized and established Black cohort in the United States.
- The goal of the present analysis was to examine the associations between novel hemodynamic measures and prevalent CVD in a sample of Black participants.

What Are the Clinical Implications?

- Our study suggests that among Black individuals (a population with elevated CVD risk) easily accessible, noninvasive indicators of large and small vascular dysfunction are important clinical markers of prevalent CVD.
- Our results add to the growing literature that implicates aortic stiffness and downstream microvascular dysfunction as important contributors to CVD.
- Clinicians may consider assessment and incorporation of noninvasive indicators of large and small vascular function into their practice, particularly in high-risk populations (eg, older Black individuals).

Nonstandard Abbreviations and Acronyms

AI	augmentation index
CFPWV	carotid-femoral pulse wave velocity
CPP	central pulse pressure
DM	diabetes mellitus
FWA	forward pressure wave amplitude
JHS	Jackson Heart Study
PWVR	pulse wave velocity ratio

the White population,[12,13] which may contribute to the increased prevalence of CVD and higher rates of CVD mortality in this population.

Previously, vascular stiffness and pulsatility measures derived from peripheral tonometry have been related to cardiovascular outcomes in a non-Hispanic, White sample population.[14] However, little is known regarding associations of vascular function measures with CVD in Black individuals. Thus, the current study examined the relations between multiple measures of aortic stiffness and microvascular dysfunction and prevalent CVD in Black participants of the Jackson Heart Study (JHS). We hypothesized that indicators of arterial stiffness and microvascular dysfunction are associated with higher odds for prevalent CVD, independent of traditional CVD risk factors, among Black participants.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The procedure for requesting data from the JHS can be found at https://www.jacksonheartstudy.org/.

Participants

JHS is a community-based cohort study investigating risk factors for CVD in a Black population; the details and design of the JHS have been described.[15,16] JHS was established from the former participants of the Atherosclerosis Risk in Communities Study. A subset of participants from the third examination cycle (2008–2013) and the fourth examination cycle who underwent arterial tonometry assessment (2012–2017) was eligible for this investigation (N=2884). We obtained 2 separate samples from the eligible participants. To assess the relations between measures of aortic stiffness and wave reflection and prevalent CVD (sample 1), we excluded participants who had missing or incomplete tonometry data (N=959) or missing covariate data (N=176). To assess the relations between measures of microvascular function and prevalent CVD (sample 2), we excluded participants who had missing or incomplete ultrasound Doppler flow data (N=134) or covariate data (N=321). Figure 1 presents a flow chart of the samples for the current analysis. We obtained written informed consent from all study participants, and the Institutional Review Board of the University of Mississippi Medical Center approved the research protocol.

Arterial Stiffness and Wave Reflection Assessment

We assessed applanation tonometry with participants in the supine position after a 5-minute rest, as previously described.[1] Using a custom tonometer, we obtained arterial tonometry with simultaneous electrocardiography from brachial, radial, femoral, and carotid arteries. We obtained auscultatory brachial systolic and diastolic blood pressures from the right arm using a computer-controlled device at the

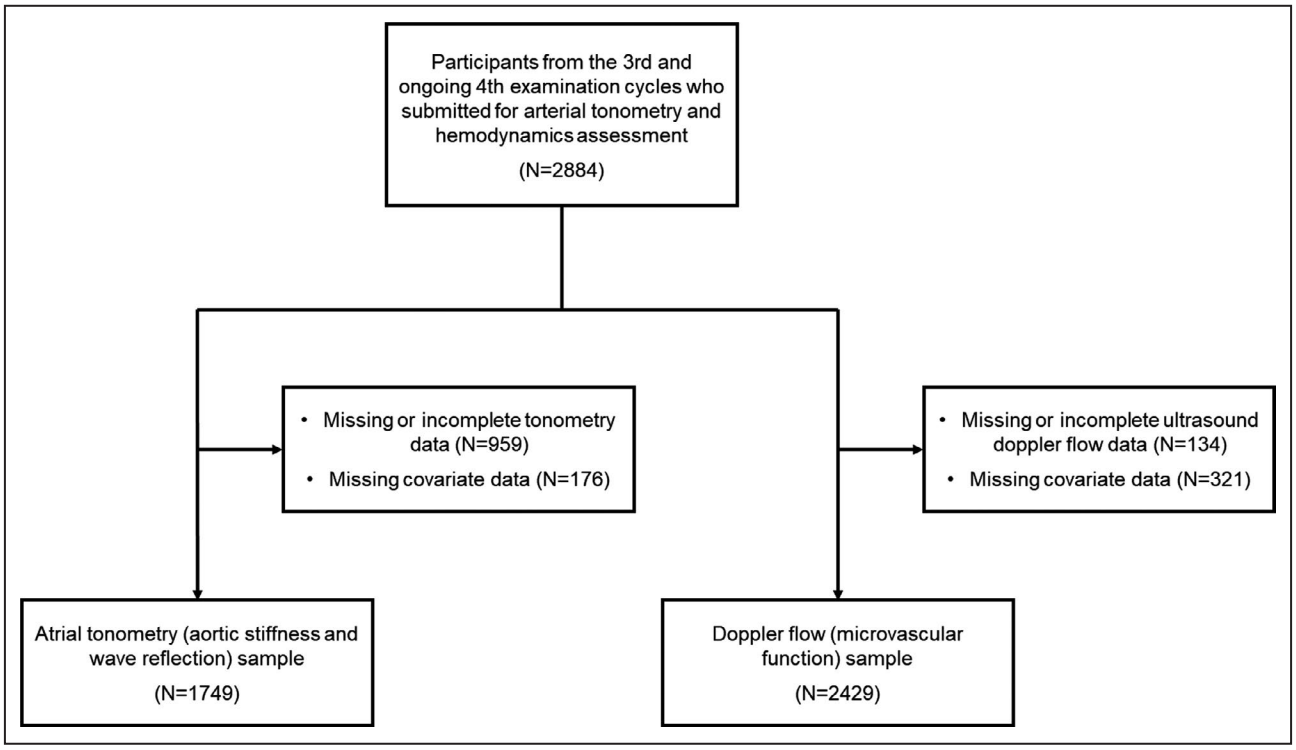

Figure 1. Flow chart for inclusion of participants for the present analyses.

time of tonometry. We obtained 2-dimensional echocardiographic images of the left ventricular outflow tract along the parasternal long axis followed by pulsed Doppler of the left ventricular outflow tract. At the time of primary acquisition, we digitized and later transferred these data to the core laboratory (Cardiovascular Engineering, Inc, Norwood, MA), where technicians performed analyses blinded to clinical data. Using the electrocardiographic R-wave as a reference, we signal-averaged the tonometry waveforms.[1] We used systolic and diastolic blood pressures obtained during tonometry to calibrate the signal-averaged brachial pressure waveforms. We integrated the brachial waveform to calculate mean arterial pressure (MAP), and used diastolic pressures and the integrated MAP to calibrate carotid pressure tracings.[17] We used the calibrated carotid pressure as a surrogate for central pressure.[17] For carotid-femoral transit distance, we adjusted for parallel transmission as previously described.[18] We calculated the carotid-femoral pulse wave velocity (CFPWV) and carotid-brachial pulse wave velocity as the ratio of the adjusted transit distance and the pulse transit time difference between carotid and femoral or brachial sites, respectively. We calculated the pulse wave velocity ratio (PWVR) as the CFPWV divided by the carotid-brachial pulse wave velocity. We calculated the central pulse pressure (CPP) as the difference between the carotid systolic and diastolic blood pressures. We defined the forward pressure wave amplitude (FWA) as the difference between pressure at the foot and at the peak of the forward pressure waveform by performing time domain wave separation analysis using central pressure and flow.[18] We calculated the augmentation index (AI) as the fraction of CPP attributable to late systolic pressure.

Microvascular Function Assessment

Baseline flow velocity in the brachial artery is governed by forearm microvascular structure and tone.[19,20] In addition, hyperemic flow velocity in the brachial artery reflects the approximate maximal microvessel dilation of the forearm produced by ischemia-induced vasodilator generation, including nitric oxide.[20-23] Thus, both are surrogate markers of microvascular function. We assessed microvascular function using ultrasound image acquisition and analyses as described previously.[20,24] We acquired brachial artery Doppler flow at baseline and following 5 minutes of ischemia that was produced by inflating a cuff positioned on the forearm. Technicians placed the cuff just distal to the antecubital fold, and inflated to approximately 50 mm Hg above systolic blood pressure. After cuff deflation, sonographers monitored and recorded flow (for 15 seconds after cuff release) until flow peaked. We assessed the brachial artery images and Doppler flow with a Siemens

Acuson S2000 ultrasound system mounted with 4Vc and 9L4 transducers using a carrier frequency of 4.0 MHz and an insonation angle of approximately 60°, and we digitized ultrasound data during acquisition and transferred those data to the core laboratory (Cardiovascular Engineering) for blinded analyses. Using a semiautomated signal-averaging technique,[21] we analyzed flows from the digitized Doppler audio data and visually confirmed timing of peak flow from a raw spectral analysis of distinct beats. We labeled 3 to 5 beats (representing the peak flow) for inclusion in the signal-averaged spectrum. Using the ECG as a fiducial point, we signal-averaged flow spectra and corrected them for the actual insonation angle.

Clinical Evaluation

Prevalent CVD included histories of myocardial infarction, coronary heart disease, heart failure, and stroke; these events were defined and adjudicated as previously described.[25] We measured serum cholesterol levels from a fasting blood test. We calculated the cholesterol ratio as the ratio of total to high-density lipoprotein (HDL) cholesterol. We defined the presence of diabetes mellitus (DM) as fasting serum glucose ≥126 mg/dL, the patient's use of DM medications within 2 weeks of the clinic visit, or prior physician-diagnosed DM. We assessed height and weight during the examination, and we calculated body mass index (BMI) as the ratio of body weight (in kilograms) and the square of height (in meters). We assessed age, sex, smoking status (currently smoking versus nonsmoking), and the use of antihypertensive medications via a questionnaire, and assessed heart rate (measured in beats per minute) during tonometry.

Statistical Analysis

Sample characteristics for the included sample were tabulated by prevalent CVD. We also compared clinical characteristics between included and excluded participants using *t* tests for continuous variables and chi-square tests for dichotomous variables.

We assessed multivariable cross-sectional relations between prevalent CVD and measures of arterial stiffness and microvascular function using logistic regression models. We calculated odds ratios with 3 levels of adjustment: the first model included adjustment for age and sex (model 1); the second model included adjustments for age, sex, MAP, heart rate, BMI, total/HDL cholesterol ratio, prevalent DM, and active smoking (model 2); and the third model included adjustments for age, sex, MAP, heart rate, BMI, total/HDL cholesterol ratio, prevalent DM, active smoking, and use of antihypertensive medications (model 3). For vascular predictors whose effects were attenuated after adjustment for standard risk factors, we performed stepwise regression analyses to assess the roles of CVD risk factors in the relations between vascular predictors and prevalent CVD. We also assessed cross-sectional relation between measures of arterial stiffness and microvascular function and the history of each of the 3 most common CVD subtypes—myocardial infarction, heart failure, and stroke—separately using multivariable logistic regression models. We selected these covariates a priori based on literature review. To normalize the distribution and limit heteroscedasticity, we inverted and then multiplied CFPWV by –1000 so that higher values corresponded to higher aortic stiffness. We entered continuous variables as standardized *z*-scores in all models. We assessed the presence of effect modification (interaction) by median age and sex for significant and marginally significant relations between various vascular measures and the presence of CVD by incorporating corresponding interaction terms into the analyses. To illustrate relations between categories of vascular predictors and the presence of CVD, we segregated continuous predictor variables by quartiles (Q1–Q4), and we performed multivariable logistic regression analyses adjusting for age, sex, MAP, heart rate, BMI, total/HDL cholesterol ratio, prevalent DM, active smoking, and the use of antihypertensive medications.

We performed all analyses with SAS version 9.4 for Windows (SAS Institute, Cary, NC). We considered 2-tailed $P<0.05$ statistically significant for the analyses, except for the assessment of interactions, where $P<0.10$ was considered statistically significant.

RESULTS

We present the characteristics and vascular data of the participants stratified by presence of CVD in Table 1. The participants with prevalent CVD were older, were less likely to be women, and had a higher prevalence of current smoking and DM. A comparison of the clinical characteristics between included and excluded participants is presented in Table S1; the clinical characteristics between included and excluded participants were similar.

We present the multivariable cross-sectional relations between individual measures of aortic stiffness and presence of CVD in Table 2. In models adjusted for age and sex (model 1), higher CFPWV, FWA, and CPP were associated with higher odds of prevalent CVD. After further adjustment for MAP, heart rate, BMI, total/HDL cholesterol ratio, prevalent DM, and active smoking (model 2), relations between higher CFPWV, lower AI, and prevalent CVD persisted. After further adjustment for antihypertension

Table 1. Comparison of Demographic Characteristics and Vascular Measures of Participants Without and With Prevalent Cardiovascular Disease

Variable	CVD Absent (N=1545)	CVD Present (N=204)
Age, y	65±11	71±10
Women, N (%)	985 (64)	121 (59)
Body mass index, kg/m^2	31.0±6.0	31.3±6.5
Ratio of total to HDL cholesterol	3.6±1.1	3.6±1.2
Medical history		
Active smoking, N (%)	153 (10)	30 (15)
Prevalent diabetes mellitus, N (%)	393 (25)	87 (43)
Antihypertensive medication use	1093 (71)	183 (90)
Arterial tonometry measures		
Heart rate, beats/min	65±10	65±10
Mean arterial pressure, mm Hg	99±12	101±13
Central pulse pressure, mm Hg	65±20	74±24
Forward pressure wave amplitude, mm Hg	53±16	60±20
Augmentation index, %	17±12	15±13
Carotid-femoral pulse wave velocity, m/s	10.9±4.2	12.9±5.0
Carotid-brachial pulse wave velocity, m/s	9.4±2.1	9.8±2.3
Pulse wave velocity ratio	1.1±0.4	1.3±0.5
Doppler ultrasound measures*		
Baseline brachial flow velocity, cm/s	5.51±3.26	4.97±2.93
Hyperemic brachial flow velocity, cm/s	48.36±18.98	39.69±15.33

All values are mean±standard deviation except as noted. CVD indicates cardiovascular disease; and HDL, high-density cholesterol.
*CVD absent, n=2153; CVD present, N=276.

treatment (model 3), however, the relation between higher CFPWV and prevalent CVD was attenuated, but lower AI was significantly associated with higher odds for prevalent CVD. We observed a linear relation between quartiles of CFPWV and risk factor adjusted log odds of CVD, but the relation between quartiles of AI and risk factor adjusted log odds of CVD was nonlinear (Figure 2). However, linearity of the observed associations by quartiles may be a reflection of quartile groupings. Participants in the quartile group III (16.272% to <24.209%) in comparison with those in the lowest (<9.024%) quartile group of AI had an adjusted odds ratio of 0.55 (95% CI, 0.34–0.88; *P*=0.01) in a model that adjusted for traditional risk factors. We did not observe evidence of effect modification by sex or median age (65 years) for the relation between vascular tonometry measures and prevalent CVD (Table S2). In Table S3, we present stepwise models for the relations between measures of arterial stiffness and presence of CVD. Relations between indicators of aortic stiffness and prevalent CVD were progressively attenuated as additional candidate CVD risk factors and other putative confounders were considered in the models. In Table S4, we present multivariable-adjusted relations between measures of arterial stiffness and wave reflection and history of stroke, heart failure, and myocardial infarction (separate models for each outcome). Higher CPP was associated with higher odds of prevalent heart failure. All other cross-sectional relations between measures of arterial stiffness and wave reflection and CVD subtypes were not statistically significant.

We present multivariable cross-sectional relations between individual measures of microvascular function and the presence of CVD in Table 3. In models adjusted for age and sex (model 1), lower hyperemic brachial flow velocity, but not baseline flow velocity, was associated with higher odds of prevalent CVD, which persisted after further adjustment for MAP, heart rate, BMI, total/HDL cholesterol ratio, prevalent DM, active smoking, and antihypertensive treatment (model 3). Participants in the highest (≥59.0 cm/s) in comparison with those in the lowest (<33.2 cm/s) quartile of the hyperemic brachial flow velocity group had an adjusted odds ratio of 0.53 (95% CI, 0.33–0.83; *P*=0.006) in a model that adjusted for traditional risk factors (Figure 2). We did not find evidence of effect modification by

Table 2. Multivariable Adjusted Relations Between Individual Measures of Arterial Stiffness and Wave Reflection and Presence of Cardiovascular Disease (N=1749)

Vascular Measure	OR (95% CI) Age- and Sex-Adjusted (Model 1)	*P* Value	OR (95% CI) Multivariable-Adjusted (Model 2)*	*P* Value	OR (95% CI) Multivariable-Adjusted (Model 3)†	*P* Value
Carotid-femoral PWV	1.34 (1.11–1.63)	0.003	1.25 (1.01–1.55)	0.04	1.23 (0.99–1.51)	0.06
Pulse wave velocity ratio	1.16 (0.99–1.35)	0.06	1.09 (0.93–1.28)	0.27	1.09 (0.93–1.27)	0.31
Forward pressure wave amplitude	1.26 (1.09–1.47)	0.002	1.15 (0.97–1.37)	0.11	1.14 (0.96–1.36)	0.13
Central pulse pressure	1.25 (1.08–1.46)	0.004	1.16 (0.95–1.40)	0.14	1.14 (0.94–1.38)	0.18
Augmentation index	0.90 (0.77–1.06)	0.20	0.84 (0.70–0.99)	0.05	0.84 (0.70–0.99)	0.04

Odds ratios (ORs) expressed per 1 standard deviation higher value. PWV indicates pulse wave velocity.
*Multivariable models adjusted for age, sex, mean arterial pressure, heart rate, body mass index, cholesterol ratio, prevalent diabetes mellitus, and active smoking.
†Multivariable models adjusted for age, sex, mean arterial pressure, heart rate, body mass index, cholesterol ratio, prevalent diabetes mellitus, active smoking, and antihypertension treatment.

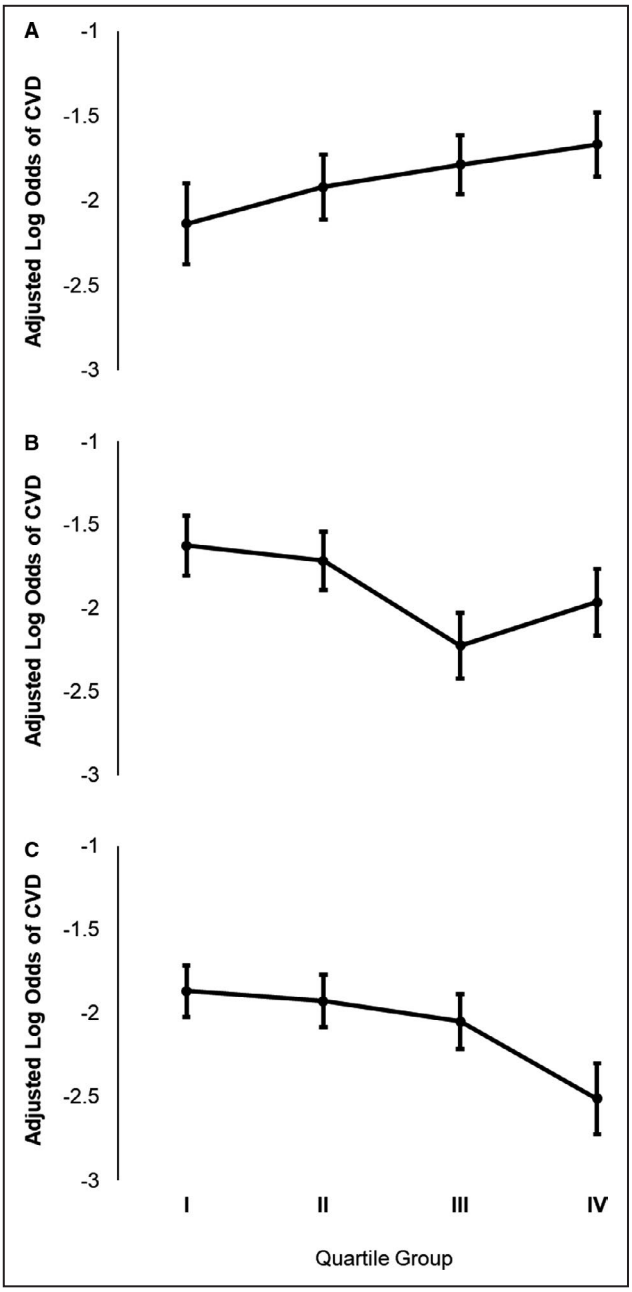

Figure 2. Relations between quartiles of (A) carotid-femoral pulse wave velocity, (B) augmentation index, and (C) hyperemic flow velocity and presence of cardiovascular disease (CVD).

The adjusted log odds for CVD were plotted for each quartile of carotid-femoral pulse wave velocity (N=1749: group I, <8.2 m/s; group II, 8.2 to <10.0 m/s; group III, 10.0 to <12.7 m/s; and group IV: ≥12.7 m/s); augmentation index (N=1749: group I, <9.024 %; group II, 9.024 to <16.272 %; group III, 16.272 to <24.209 %; and group IV: ≥25.209 %); and brachial hyperemic flow velocity (N=2429: group I, <33.2 cm/s; group II, 33.2 to <45.5 cm/s; group III, 45.5 to <59.0 cm/s; and group IV, ≥59.0 cm/s). All models were adjusted for age, sex, mean arterial pressure, heart rate, body mass index, total/HDL cholesterol ratio, prevalent diabetes mellitus, active smoking, and antihypertension treatment. CVD indicates cardiovascular disease; and HDL, high-density lipoprotein.

sex or median age (65 years) for the relations between hyperemic flow velocity and prevalent CVD (Table S2). Additionally, lower hyperemic brachial flow velocity, but not baseline flow velocity, was associated with higher odds of all CVD subtypes (Table S5).

DISCUSSION

Principal Findings

Our community-based study evaluated cross-sectional relations between measures of aortic stiffness and microvascular function and prevalent CVD in older Black participants. Higher CFPWV, but lower hyperemic brachial flow velocity and AI, were each associated with higher odds of prevalent CVD in models adjusted for traditional risk factors. After further consideration of antihypertensive medication use, the relation between CFPWV and prevalent CVD was attenuated. PWVR, FWA, and CPP were not associated with prevalent CVD in multivariable-adjusted models. Thus, among older Black participants, impedance matching (ie, lower AI with higher aortic stiffness) and microvascular dysfunction were associated with prevalent CVD.

Arterial Tonometry Measures and Prevalent CVD

In our sample, higher CFPWV—the reference measure of aortic stiffness—was associated with higher odds of prevalent CVD in models adjusted for traditional risk factors that did not consider use of antihypertensive medications (model 2). Aging is associated with progressive stiffening of the aorta caused by fragmentation of elastic fibers and concurrent calcification and deposition of collagen within the media of the aorta. Stiffening of the aorta creates a larger forward wave, a wider central pulse pressure, and earlier return of the reflected wave (increased pressure augmentation); therefore, measures of aortic stiffening and pressure pulsatility begin to rise in parallel, particularly among middle-aged individuals.[18,26,27] Elevated aortic stiffness is associated with greater cumulative exposure to CVD risk factors that contribute to higher CVD risk. In a recent JHS study, we reported that elevated CFPWV was associated with higher heart rate, MAP, systolic blood pressure, total/HDL cholesterol ratio, and fasting glucose, as well as higher odds of DM and use of antihypertensive medications.[28] Because Black individuals have a higher prevalence of hypertension (compared with White individuals), high exposure to antihypertensive medications is an inherent characteristic of an older, Black cohort. Indeed, the prevalence of antihypertensive

Table 3. Multivariable Adjusted Relations Between Individual Measures of Microvascular Function and Presence of Cardiovascular Disease (N=2429)

Vascular Measure	OR (95% CI) Age- and Sex-Adjusted (Model 1)	*P* Value	OR (95% CI) Multivariable-Adjusted (Model 2)*	*P* Value	OR (95% CI) Multivariable-Adjusted (Model 3)†	*P* Value
Baseline brachial flow velocity	0.96 (0.83–1.10)	0.53	0.94 (0.82–1.09)	0.42	0.95 (0.82–1.10)	0.49
Hyperemic brachial flow velocity	0.75 (0.64–0.89)	<0.001	0.77 (0.65–0.90)	0.001	0.79 (0.67–0.94)	0.006

Odds ratios (ORs) expressed per 1 standard deviation higher value.

*Multivariable-adjusted models adjusted for age, sex, mean arterial pressure, heart rate, body mass index, cholesterol ratio, prevalent diabetes mellitus, and active smoking.

†Multivariable models adjusted for age, sex, mean arterial pressure, heart rate, body mass index, cholesterol ratio, prevalent diabetes mellitus, active smoking, and antihypertension treatment.

medications in the current sample was high (73%). In addition, the proportion of participants exposed to antihypertensive treatment was significantly greater among those with prevalent CVD. After further consideration of antihypertensive use (model 3), the relation between CFPWV and prevalent CVD was attenuated. Previous studies have revealed that elevated aortic stiffness precedes incident hypertension—the leading modifiable risk factor for CVD—and likely contributes to hypertension development.[5,29-31] However, multiple studies also demonstrate that hypertension treatment, primarily by blocking the renin–angiotensin–aldosterone system, may reverse aortic stiffness via a blood pressure-independent mechanism.[32-36] Thus, the observed attenuated relation between CFPWV and prevalent CVD by antihypertensives is consistent with the hypothesis that long-term hypertension treatment may beneficially modify large vessel tone. However, the effect of antihypertensives on preventing stiffness-related CVD events is unknown; therefore, additional clinical trials and other prospective studies are needed to assess the efficacy of existing and novel antihypertensives as potential therapies for aberrant aortic stiffness. Additionally, although antihypertensive medication use was a strong modifier of the observed relation between arterial stiffness measures and prevalent CVD (Table S3), confounding by other risk factors may be more important in the Black population than in other groups.

Framingham investigators showed that higher aortic stiffness, but not CPP, was predictive of CVD events within a sample of participants predominately of European ascestry.[1] Recently, Niiranen et al demonstrated that pulse pressure-aortic stiffness mismatch (ie, discordant high and low CPP and CFPWV phenotype) is common among middle-aged to older individuals.[37] Furthermore, they observed that individuals with high CPP, but low CFPWV, had the lowest risk for CVD events (compared with the other participants grouped by CPP and CFPWV status).[37] Although CPP is often considered a surrogate for aortic stiffness, CPP is not a direct measure of aortic stiffness and is only moderately correlated with CFPWV.[37-39] Our results are consistent with the concept that assessing CPP as a surrogate for aortic stiffness may not adequately predict CVD outcomes.

Other investigators have examined PWVR (a measure of central-to-peripheral stiffness gradient). In a sample of patients with kidney disease, Fortier et al indicated PWVR predicted mortality, which suggested that PWVR may be a clinically relevant measure to ascertain CVD risk among populations with higher baseline risk, such as the Black population.[40] Subsequently, in a Framingham sample of low-to-moderate risk participants, PWVR predicted incident CVD.[41] Yet, we did not observe a significant association between PWVR and prevalent CVD. In the aforementioned Framingham study, though both CFPWV and PWVR were associated with higher CVD risk, carotid-radial PWV was not.[41] Additionally, PWVR did not provide incremental predictive value of mortality compared with CFPWV.[41] Thus, the loss of stiffness gradient reflected by PWVR among individuals with low-to-moderate risk may be attributable to the increase in large artery stiffness rather than a decrease in peripheral stiffness. Here, we observed higher CFPWV, as well as a higher carotid-brachial PWV, among participants with prevalent CVD compared with participants without CVD, resulting in similar PWVR for both groups. These data suggest that Black individuals with a history of CVD may have disproportionate stiffening of large central arteries with modest concurrent stiffening of peripheral arteries, resulting in impedance matching rather than reversal of the arterial stiffness gradient, which may further explain discrepancies for PWVR with prior studies. Consistent with these observations, we observed that lower AI was associated with higher odds of prevalent CVD. Lower AI along with higher CFPWV indicates reduced wave reflection as a result of impedance matching between the aorta and muscular arteries.[42] Therefore, similar to PWVR, the significant relation between lower AI and prevalent CVD may be primarily attributable

to severe aortic stiffness and impedance matching because AI alone is not a reliable surrogate for aortic stiffness or wave reflection, particularly for older individuals.[18,26,43] However, future prospective studies should assess the relative prognostic value of various hemodynamic measures in this cohort.

Contrary to previous Framingham studies,[10,44] FWA was not associated with prevalent CVD in this cross-sectional study of older Black participants. Compared with CFPWV, which is an assessment of global stiffness along the entire aorta, FWA is a composite measure of proximal aortic stiffness (assessed by characteristic impedance) and aortic flow. Of the 2 components of FWA, elevated characteristic impedance has been implicated in greater CVD risk.[10] Although related to CFPWV, characteristic impedance is sensitive to changes in aortic cross-sectional area and may provide discordant information during age-related stiffening. For example, if the aorta stiffens while aortic diameter remains constant, both characteristic impedance and CFPWV will increase in parallel; however, if the aorta stiffens but the aortic lumen diameter increases, CFPWV will increase without a comparable increase in characteristic impedance and FWA. In this sample of the Black population, we posit that severe aortic stiffening may promote adaptive remodeling to a larger aortic lumen diameter that acts as a mechanism to dampen FWA. Recently, Kamimura et al reported that higher proximal aortic diameter was associated with elevated risk of CVD events and all-cause mortality in a younger JHS sample.[45] Because the biomechanical properties of large arteries vary among individuals, the remodeling ability within a population is likely heterogeneous. Nonetheless, remodeling to larger proximal aortic diameters in the presence of abnormal aortic stiffness may underlie the marginally discordant relations we observed for FWA and CFPWV with prevalent CVD in the present study. In the aforementioned prospective Framingham studies, CVD risk was assessed during middle age, when the rapid transition from a relatively compliant to stiffer proximal aorta occurs. Because aortic stiffening occurs earlier in black individuals,[12,13] the current sample may have endured more severe and prolonged CVD burden, which when exacerbated by accumulation of CVD-related comorbidities may have contributed to higher mortality. Thus, individuals with high proximal aortic stiffness, who were unable to remodel their aortic lumen diameters (ie, individuals with concordantly high FWA and CFPWV), may be underrepresented in this cross section of participants. Further investigation with younger and more diverse participants is warranted to elucidate the role of earlier changes in vascular remodeling that contribute to CVD risk and to identify factors that may underlie disparities in CVD risk.

Microvascular Dysfunction and Prevalent CVD

Over the past decades, multiple noninvasive ultrasound methods have contributed to our understanding of CVD pathophysiology. In the current study, we assessed brachial artery flows as surrogate markers of microvascular function. Similar to previous longitudinal studies,[44,46] we observed that lower brachial hyperemic flow velocity was associated with CVD. These findings further implicate structural and functional abnormalities of peripheral small vessels as opposed to endothelial dysfunction as contributors to CVD risk. Furthermore, in a JHS sample, we recently observed a significant relation between higher aortic stiffness and lower flow reserve during reactive hyperemia after adjustment for traditional CVD risk factors.[24] With increasing age, the aorta stiffens disproportionately to the muscular arteries in the periphery, contributing to impedance matching, which results in lower wave reflection and higher transmission of pulsatile energy down the arterial tree.[26,47] Thus, impedance matching exposes the peripheral microcirculation to potentially damaging levels of pressure and pulsatility.[26,47] Microvascular damage and dysfunction may represent an important mechanistic link between higher aortic stiffness and CVD in Black individuals. Indeed, prior studies suggest that elevated aortic stiffness contributes to targeted damage in the brain and kidneys and contributes to incident CVD events via mechanisms that include microvascular dysfunction.[44,48,49] Given the known disparities for CVD, additional studies that assess the role of microvascular dysfunction on the relative risks for Black individuals as compared with individuals from other racial/ethnic groups are merited.

Study Limitations

The present study has limitations that should be considered. We employed a cross-sectional observational study design; this limited our ability to infer causal and temporal relations between vascular hemodynamic measures and incident CVD. Furthermore, the lack of longitudinal models may have also contributed to the comparatively weaker associations in the present study when compared with established prospective data. Our study is susceptible to type 1 error because we did not adjust for multiple testing. The samples for this investigation were older Black individuals; therefore, our findings may not be generalizable to younger individuals or individuals of other ethnic groups. Our sample was composed of older participants, and because aortic stiffness increases with age, we have less variation in CFPWV to resolve differences in prevalent CVD between exposure groups. In addition, our analytic sample was taken from 2 different examination

cycles; therefore, our study is susceptible to survivorship bias. Without enrolled participants from various ethnic/racial groups, direct comparisons of these relations are inappropriate and beyond the scope of the present study. Although we adjusted for known CVD risk factors, the possibility of residual confounding by unmeasured or unknown factors remains. Consideration of these limitations should be balanced with acknowledgment of the study's strengths. JHS is a well-characterized, community-based cohort purposed to further understand CVD in the Black population. Thus, here we were able to investigate the relations of elevated aortic stiffness and microvascular in an underrepresented and understudied group using novel vascular tonometry and ultrasound techniques.

CONCLUSIONS

In a cross-section of an older Black cohort, markers of impedance matching and microvascular dysfunction were associated with higher odds of prevalent CVD. Our results, observed in a population with elevated CVD risk, contribute to the growing body of evidence that implicates aortic stiffness and downstream microvascular dysfunction as important correlates of CVD. Prior studies suggest that aortic stiffness is modifiable and possibly preventable; therefore, it is a practical clinical target that may be relevant in addressing disparities for CVD. Further prospective studies including Black individuals and investigations involving more diverse samples are warranted.

ARTICLE INFORMATION

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Disclosures

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

Supplementary Materials

Tables S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of demographic characteristics and vascular measures between included and excluded participants.

Variable	Included (N=1749)	Excluded (N varies)*	*P*
Age, years	65±11	64±12	<0.001
Women, N (%)	1106 (63)	726 (64)	0.6
Body mass index, kg/m^2	31.0±6.1	33.8±7.6	<0.001
Ratio of total to HDL cholesterol	3.6±1.1	3.6±1.1	0.3
Medical history			
Active smoking, N (%)	183 (10)	122 (11)	0.6
Prevalent diabetes, N (%)	480 (27)	398 (35)	0.03
Antihypertensive medication use, N (%)	1276 (73)	826 (73)	0.9
Arterial tonometry measures			
Heart rate, beats/min.	65±10	67±11	<0.001
Mean arterial pressure, mm Hg	99±12	100±12	0.3
Central pulse pressure, mm Hg	66±21	64±20	0.04
Forward pressure wave amplitude, mm Hg	54±16	53±16	0.1
Augmentation index, %	16±12	16±16	0.4
Carotid-femoral pulse wave velocity, m/s	11.1±4.3	11.9±5.2	0.002
Carotid-brachial pulse wave velocity, m/s	9.4±2.2	8.9±2.4	<0.001
Pulse wave velocity ratio	1.1±0.4	1.2±0.5	<0.001
Doppler ultrasound measures†			
Baseline brachial flow velocity, cm/s	5.45±3.23	5.53±3.33	0.7
Hyperemic brachial flow velocity, cm/s	47.38±18.18	46.11±18.94	0.2

*Note that N varies (450–2111) for excluded participants based on availability of data. †Included, N=2429; Excluded N=450.

Table S2. Multivariable adjusted relations between individual vascular measures with their interaction terms and presence of cardiovascular disease.

Vascular measure	Odds Ratio (95% CI) Age interaction models*	*P*	Odds Ratio (95% CI) Sex interaction models†	*P*
Arterial tonometry measures‡				
Carotid-femoral PWV	1.47 (1.06, 2.25)	0.02	1.17 (0.86, 1.58)	0.31
Interaction term	**0.93 (0.63, 1.37)**	**0.71**	**1.08 (0.77, 1.52)**	**0.66**
Pulse wave ratio	1.34 (0.92, 1.95)	0.13	1.09 (0.85, 1.39)	0.51
Interaction term	**0.88 (0.59, 1.32)**	**0.54**	**1.00 (0.75, 1.33)**	**0.99**
Forward pressure wave amplitude	1.28 (0.93, 1.75)	0.13	1.00 (0.76, 1.32)	0.97
Interaction term	**0.98 (0.69, 1.38)**	**0.90**	**1.21 (0.89, 1.64)**	**0.23**
Central pulse pressure	1.27 (0.93, 1.72)	0.13	1.03 (0.77, 1.38)	0.86
Interaction term	**1.00 (0.72, 1.38)**	**0.98**	**1.16 (0.85, 1.59)**	**0.34**
Augmentation index	0.77 (0.60, 0.99)	0.04	0.78 (0.61, 0.99)	0.05
Interaction term	**1.12 (0.83, 1.52)**	**0.45**	**1.13 (0.83, 1.55)**	**0.44**
Doppler ultrasound measures§				
Baseline brachial flow velocity	0.97 (0.78, 1.21)	0.78	0.89 (0.71, 1.10)	0.28
Interaction term	**0.90 (0.68, 1.20)**	**0.47**	**1.13 (0.85, 1.50)**	**0.39**
Hyperemic brachial flow velocity	0.70 (0.54, 0.90)	0.005	0.78 (0.61, 0.99)	0.04
Interaction term	**1.08 (0.78, 1.50)**	**0.62**	**1.04 (0.76, 1.41)**	**0.83**

Odds ratios expressed per 1 standard deviation higher value. CI, confidence interval. PWV, pulse wave velocity. Corresponding interaction terms are presented in bold below each vascular measure. *Interaction term is vascular measure x median age; models adjusted for median age, sex, mean arterial pressure, heart rate, body mass index, cholesterol ratio, prevalent diabetes, and active smoking. †Interaction term is vascular measure x sex; models adjusted for age, sex, mean arterial pressure, heart rate, body mass index, cholesterol ratio, prevalent diabetes, active smoking, and antihypertensive treatment. ‡N=1749. §N=2429.

Table S3. Stepwise models for relations between measures of arterial stiffness and presence of cardiovascular disease (N=1749).

	CFPWV			Forward Wave Amplitude			Central pulse pressure		
Model Steps	**Added Variable**	**OR (95% CI)**	***P***	**Added Variable**	**OR (95% CI)**	***P***	**Added Variable**	**OR (95% CI)**	***P***
Minimal models (Step 0)*	age+sex	1.34 (1.11, 1.63)	0.003	age+sex	1.26 (1.09, 1.47)	0.002	age+sex	1.25 (1.08, 1.46)	0.004
Step 1	+HTNRx	1.30 (1.07, 1.57)	0.008	+HTNRx	1.24 (1.07, 1.44)	0.005	+DIA	1.23 (1.06, 1.44)	0.008
Step 2	+DIA	1.25 (1.03, 1.51)	0.02	+DIA	1.21 (1.04, 1.41)	0.02	+HTNRx	1.22 (1.04, 1.42)	0.01
Step 3	+SMK	1.25 (1.03, 1.51)	0.02	+SMK	1.21 (1.04, 1.41)	0.02	+SMK	1.21 (1.04, 1.41)	0.01
Step 4	+HR	1.29 (1.06, 1.58)	0.01	+MAP	1.16 (0.97, 1.37)	0.1	+BMI	1.22 (1.04, 1.42)	0.01
Step 5	+MAP	1.23 (1.00 1.52)	0.05	+BMI	1.16 (0.97, 1.37)	0.1	+MAP	1.17 (0.97, 1.40)	0.1
Step 6	+BMI	1.23 (1.00, 1.52)	0.05	+CHLR	1.16 (0.97, 1.37)	0.1	+CHLR	1.16 (0.97, 1.39)	0.11
Step 7	+CHLR	1.23 (0.99, 1.51)	0.06	+HR	1.14 (0.96, 1.36)	0.13	+HR	1.14 (0.94, 1.38)	0.18

Odds ratios (OR) expressed per 1 standard deviation higher value. CI, confidence interval. *Initial minimal models included age and sex that were forced into the models. CFPWV, carotid-femoral pulse wave velocity. HTNRx, antihypertensive treatment. DIA, prevalent diabetes. SMK, current smoking. HR, heart rate. MAP, mean arterial pressure. BMI, body mass index. CHLR, cholesterol ratio.

Table S4. Multivariable-adjusted relations between individual measures of arterial stiffness and wave reflection and history of stroke, heart failure, and myocardial infarction outcomes considered separately (N=1749).

Vascular measure	OR (95% CI) for history of stroke (n=52)	*P*	OR (95% CI) for history of heart failure (n=113)	*P*	OR (95% CI) for history of myocardial infarction (n=95)	*P*
Carotid-femoral PWV	1.40 (0.93, 2.10)	0.1	1.06 (0.82, 1.37)	0.6	0.97 (0.74, 1.28)	0.9
PWV ratio	1.20 (0.92, 1.57)	0.2	0.94 (0.75, 1.18)	0.6	0.89 (0.70, 1.12)	0.3
Forward pressure wave	1.02 (0.74, 1.41)	0.9	1.24 (0.99, 1.55)	0.06	1.17 (0.92, 1.48)	0.2
Central pulse pressure	1.06 (0.74, 1.50)	0.8	1.29 (1.01, 1.64	0.04	1.19 (0.92, 1.54)	0.2
Augmentation index	0.75 (0.55, 1.02)	0.07	0.99 (0.79, 1.24)	0.9	0.86 (0.67, 1.09)	0.2

Odds ratios (OR) expressed per 1 standard deviation higher value. CI, confidence interval. PWV, pulse wave velocity. Multivariable models adjusted for age, sex, mean arterial pressure, heart rate, body mass index, cholesterol ratio, prevalent diabetes, active smoking, and antihypertension treatment.

Table S5. Multivariable-adjusted relations between individual measures of microvascular function and history of stroke, heart failure, and myocardial infarction outcomes considered separately (N=2429).

Vascular measure	OR (95% CI) for history of stroke (n=63)	*P*	OR (95% CI) for history of heart failure (n=145)	*P*	OR (95% CI) for history of myocardial infarction (n=134)	*P*
Baseline flow velocity	0.93 (0.69, 1.25)	0.6	0.94 (0.78, 1.14)	0.5	0.97 (0.79, 1.18)	0.7
Hyperemic flow velocity	0.69 (0.49, 0.97)	0.03	0.75 (0.61, 0.93)	0.007	0.72 (0.57, 0.91)	0.006

Odds ratios (OR) expressed per 1 standard deviation higher value. CI, confidence interval. Multivariable models adjusted for age, sex, mean arterial pressure, heart rate, body mass index, cholesterol ratio, prevalent diabetes, active smoking, and antihypertension treatment.