ORIGINAL RESEARCH

Relations of Microvascular Function, Cardiovascular Disease Risk Factors, and Aortic Stiffness in Blacks: The Jackson Heart Study

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***Background*—**Blacks have more severe endothelial dysfunction and aortic stiffening as compared with whites. We aimed to investigate the association between aortic stiffness and microvascular function in the black community.

***Methods and Results*—**We assessed the association between forearm vascular reactive hyperemia (an indicator of microvascular function) and aortic stiffness in 1458 black participants (N=965 [66% women]; mean age: 66±11 years) in the Jackson Heart Study. We evaluated 2 measures of aortic stiffness: brachial pulse pressure and carotid-femoral pulse wave velocity. Using high-resolution ultrasound and Doppler, we evaluated brachial blood flow at baseline and during reactive hyperemia after 5 minutes of forearm ischemia. Multiple cardiovascular risk factors were significantly related to baseline and hyperemic brachial flow velocity. Women had lower baseline flow across the entire age spectrum. During hyperemia, we observed a significant age-sex interaction for flow velocity (P=0.02). Female sex was protective against microvascular dysfunction among younger participants, but older women exhibited a greater attenuation of the hyperemic flow reserve. In multivariable models that adjusted for cardiovascular disease risk factors and mean arterial pressure, higher carotid-femoral pulse wave velocity (β=−0.106±0.033; P=0.001 was related to lower baseline flow. However, during reactive hyperemia, elevated brachial pulse pressure (β=−0.070±0.031; P=0.03) and carotid-femoral pulse wave velocity (β=−0.128±0.030; P<0.001) were both related to attenuated brachial flow velocity.

***Conclusions*—**In a sample of blacks, higher aortic stiffness and pressure pulsatility were associated with lower flow reserve during reactive hyperemia, beyond changes attributable to traditional cardiovascular disease risk factors alone. **(*J Am Heart Assoc*. 2018;7:e009515. DOI: 10.1161/JAHA.118.009515.)**

Key Words: aortic stiffness • endothelium • health disparities • microvascular dysfunction • pulse wave velocity

Measures of vascular and microvascular function are powerful predictors of cardiovascular disease (CVD) risk and progression. Multiple studies have established that novel measures of hemodynamic load, including measures of aortic stiffness (eg, central pulse pressure and aortic pulse wave velocity), are predictive of incident CVD risk and disease progression.[1–10] In addition, subclinical microvascular dysfunction is prevalent in individuals with CVD and is associated with elevated aortic stiffness, which may stimulate small vessel damage or remodeling, leading to elevated peripheral resistance and attenuated flow.[11,12] Prior analyses from the Framingham Heart Study have shown that abnormal aortic stiffness and increased pressure pulsatility are associated with blunted microvascular reactivity to ischemic stress.[13] In addition, Framingham investigators have reported that associations between aortic stiffness and CVD events are mediated in part by pathways that include microvascular damage and remodeling.[14] Thus, microvascular dysfunction

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009515

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Clinical Perspective

What Is New?

- We assessed the association between microvascular function (brachial flow velocity) and aortic stiffness (brachial pulse pressure and carotid-femoral pulse wave velocity) in a sample of black participants.
- Multiple risk factors were related to baseline (age, sex, heart rate, body mass index, and smoking) and hyperemic (age, heart rate, prevalent cardiovascular disease, and use of statin medication) brachial flow velocity.
- We observed significant sex differences in relations between hyperemic flow velocity and age.
- Both elevated brachial pulse pressure and higher carotid-femoral pulse wave velocity were related to attenuated brachial flow velocity in black participants.

What Are the Clinical Implications?

- In a sample of blacks, higher measures of aortic stiffness and pressure pulsatility were associated with lower flow reserve during reactive hyperemia beyond changes attributable to traditional cardiovascular disease risk factors alone.
- Since black women have higher cardiovascular disease mortality rates as compared with white women, our data also suggest that differences in microvascular function may contribute to racial differences for heart disease in women.

may be an important contributing mechanism by which aortic stiffness leads to target organ damage and CVD events.[15–18]

Blacks are disproportionately affected by CVD. They have more severe endothelial dysfunction[19–21] and increased aortic stiffness[22,23] as compared with white Americans, which may contribute to the increased prevalence of CVD among this population. Since microvascular function varies among ethnic groups, it is important to establish the relation between aortic stiffness and microvascular reactivity within more diverse, community-based samples. Thus, we examined relations of microvascular function, CVD risk factors, and aortic stiffness in black participants in the JHS (Jackson Heart Study). We hypothesized that vascular risk factors are associated with alterations in microvascular function at baseline and during hyperemia and that measures of aortic stiffness are related to attenuated hyperemic flow and vasodilatory reserve after adjustment for other clinical correlates of vascular dysfunction.

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 Jackson Heart Study can be found at https://www.jacksonheartstudy.org/.

Participants

The details and design of the JHS have been described.[24,25] Established from the former participants of the ARIC (Atherosclerosis Risk in Communities) study, 5301 participants were recruited for the JHS baseline examination (2000–2004). Participants in the third examination cycle (2008–2013) who underwent arterial tonometry assessment were eligible for this investigation (n=2092). Participants were excluded for the following reasons: missing outcomes and vascular function data (n=470), and missing covariates (n=164). Written informed consent was obtained from all study participants, and the research protocol was approved by the Institutional Review Board of the University of Mississippi Medical Center.

Image Acquisition and Flow Velocity Analyses

Image and flow analyses were performed as described previously.[13,18] Brachial artery diameter and Doppler flow were measured at baseline and following 5 minutes of ischemia produced by inflating a cuff, which was positioned on the forearm, just distal to the antecubital fold, to ≈50 mm Hg above systolic pressure. The brachial artery images and Doppler flow were assessed 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 ≈60°. Ultrasound data were digitized during the primary acquisition and transferred to the core laboratory (Cardiovascular Engineering, Inc, Norwood, MA) for analyses that were performed masked to clinical data. Flows were analyzed from the digitized Doppler audio data by using a semi-automated signal-averaging technique as described previously.[18] During the examination for brachial flows, after cuff deflation, sonographers monitored and recorded flow (for up to 15 seconds after cuff release) until flow peaked. During secondary analysis, timing of peak flow was visually confirmed from a raw spectral analysis of individual beats; only 3 to 5 beats—representing the peak flow response—were marked for inclusion in the signal-averaged spectrum. Flow spectra were signal-averaged with the ECG as a fiducial point and corrected for actual insonation angle.

Measures of Aortic Stiffness and Microvascular Function

Aortic stiffness and microvascular function were assessed as described previously.[13] We measured brachial pulse pressure and CFPWV to assess 2 distinct but related measures of aortic stiffness. Brachial pulse pressure was examined as a measure

of the pressure pulsatility proximal to the vascular bed of interest. Pulse pressure amplification was calculated as the ratio of brachial pulse pressure to the central pulse pressure. CFPWV is related directly to aortic wall stiffness. In addition, using high-resolution ultrasound and Doppler flow, we assessed brachial flow velocity at baseline and during reactive hyperemia after 5 minutes of forearm cuff occlusion. Hyperemic flow velocity reflects the flow at near maximal dilation of forearm microvasculature in response to local shear stress and other ischemic stimuli. Baseline flow brachial flow velocity depends on forearm microvascular density, tone, and structure,[13,26] and hyperemic flow velocity reflects the near maximal microvessel dilation of the forearm produced by ischemia-induced vasodilator generation, including nitric oxide.[13,18,27,28]

Statistical Analyses

We assessed multivariable cross-sectional relations of various CVD risk factors with baseline and hyperemic brachial flow velocity using stepwise multivariable regression models that adjusted for age, sex, mean arterial pressure, and current antihypertensive medication use; the threshold value for inclusion and removal from the model was $P<0.1$. Other CVD risk factors considered in the stepwise model were selected a priori based on literature review and included heart rate, body mass index, active smoking, current statin use, prevalent CVD (defined as unstable angina, myocardial infarction, fatal coronary heart disease, heart failure, stroke, or intermittent claudication), pulse pressure amplification, alcohol consumption, hormone replacement therapy (in women), and fasting glucose. We considered non-linear relations for age, and since age and sex may differentially and synergistically affect aortic stiffness and microvascular function, we considered age-sex interaction by incorporating corresponding terms in the analysis. These stepwise models did not consider stiffness measures.

Furthermore, we assessed the relation between aortic stiffness measures (brachial pulse pressure and CFPWV) and microvascular function (brachial flow velocity) using multivariable regression after adjusting for other known or potential correlates of brachial flow velocity. Relations of each measure of aortic stiffness with brachial flow velocity (as the dependent variable) were considered separately. We also tested interactions of older age (using median age) and sex with stiffness variables by incorporating corresponding interaction terms in the analysis.

All analyses were performed with SAS version 9.3 for Windows (SAS Institute, Cary, NC). Two-tailed $P<0.05$ was considered statistically significant for the analysis.

Results

The final sample included 1458 participants (965 [66%] women). Characteristics and hemodynamic data of the study participants are presented in Table 1. This sample exhibited a high prevalence of anti-hypertension treatment. On average, brachial artery mean flow increased ≈ sevenfold during reactive hyperemia. A comparison of these characteristics between included and excluded participants is shown in Table S1. The included sample contained more female participants; however, the clinical characteristics between included and excluded groups were similar.

Multivariable cross-sectional correlates of baseline and hyperemic brachial flow velocity are presented in Table 2. Greater age was associated with lower baseline and hyperemic flows (Figure). Female sex was associated with lower baseline flow. In addition, during hyperemia, we observed a significant age-sex interaction ($\beta=-0.118\pm0.049$; $P=0.02$) for flow velocity. Higher heart rate was associated with elevated resting and hyperemic flows. Elevated body mass

Table 1. Demographic Characteristics and Hemodynamic Measures (n=1458)

Variable	Value*
Age, y†	66±11
Women, n (%)	965 (66)
Body mass index, kg/m^2	31±6
Fasting glucose, mg/dL	106±33
Medical history	
Anti-hypertension treatment, n (%)	1092 (75)
Prevalent cardiovascular disease, n (%)	225 (15)
Active smoking, n (%)	154 (10)
Current statin use, n (%)	473 (32)
Alcohol consumption in the past 12 mo, n (%)	635 (44)
Hormone replacement (women), n (%)	305 (21)
Tonometry and hemodynamic variables	
Heart rate, beats/min	65±10
Mean arterial pressure, mm Hg	98±12
Systolic blood pressure, mm Hg	137±19
Diastolic blood pressure, mm Hg	71±10
Brachial pulse pressure, mm Hg	66±18
Pulse pressure amplification‡	1.01±0.13
Carotid-femoral pulse wave velocity, m/s	11±4
Baseline mean brachial flow velocity, cm/s	5.3±3.3
Hyperemic brachial flow velocity, cm/s	44.9±17.8

*All values are mean±SD except as noted.
†Full age range for the participants is 33 to 93 years.
‡Calculated as the ratio of brachial pulse pressure to the central pulse pressure.

Table 2. Multivariable Relations Between Common Covariates and Brachial Flow Velocity (n=1458)

	Brachial Flow Velocity (SD)					
	Baseline			Hyperemia		
Variable	β	SE	*P* Value	β	SE	*P* Value
Age*	−0.162	0.027	<0.001	−0.314	0.040	<0.001
Female sex*	−0.148	0.055	0.007	0.016	0.050	0.8
Age×female sex	…	…	…	−0.118	0.024	0.02
Mean arterial pressure*	−0.034	0.025	0.2	−0.002	0.024	0.9
Antihypertensive medication	−0.006	0.062	0.9	−0.106	0.058	0.07
Heart rate	0.140	0.026	<0.001	0.064	0.024	0.007
Body mass index	0.073	0.026	0.006	…	…	…
Active smoking	0.176	0.084	0.04	…	…	…
Prevalent cardiovascular disease	…	…	…	−0.149	0.067	0.03
Antihypertensive medication	…	…	…	−0.102	0.052	0.05

*Forced into the model. All coefficients represent SD difference in flow per SD difference in continuous variables or presence of categorical variables. Baseline model adjusted R^2=0.07. Hyperemia model adjusted R^2=0.20.

index and active smoking were associated with higher resting flow but were not related to hyperemic flow. Prevalent CVD and statin medication use also were associated with a blunted flow response during hyperemia.

Relations between aortic stiffness measures and brachial flow velocity are presented in Table 3. In models adjusted for age, sex, mean arterial pressure, and heart rate, higher mean CFPWV was related to lower baseline flow, which persisted after further adjustment for additional CVD risk factors. In models adjusted for age, sex, mean arterial pressure, and heart rate, higher mean brachial pulse pressure and CFPWV were related to blunted hyperemic flow response. Upon further adjustment with additional correlates of brachial flow velocity and CVD risk factors, the relation between brachial pulse pressure and

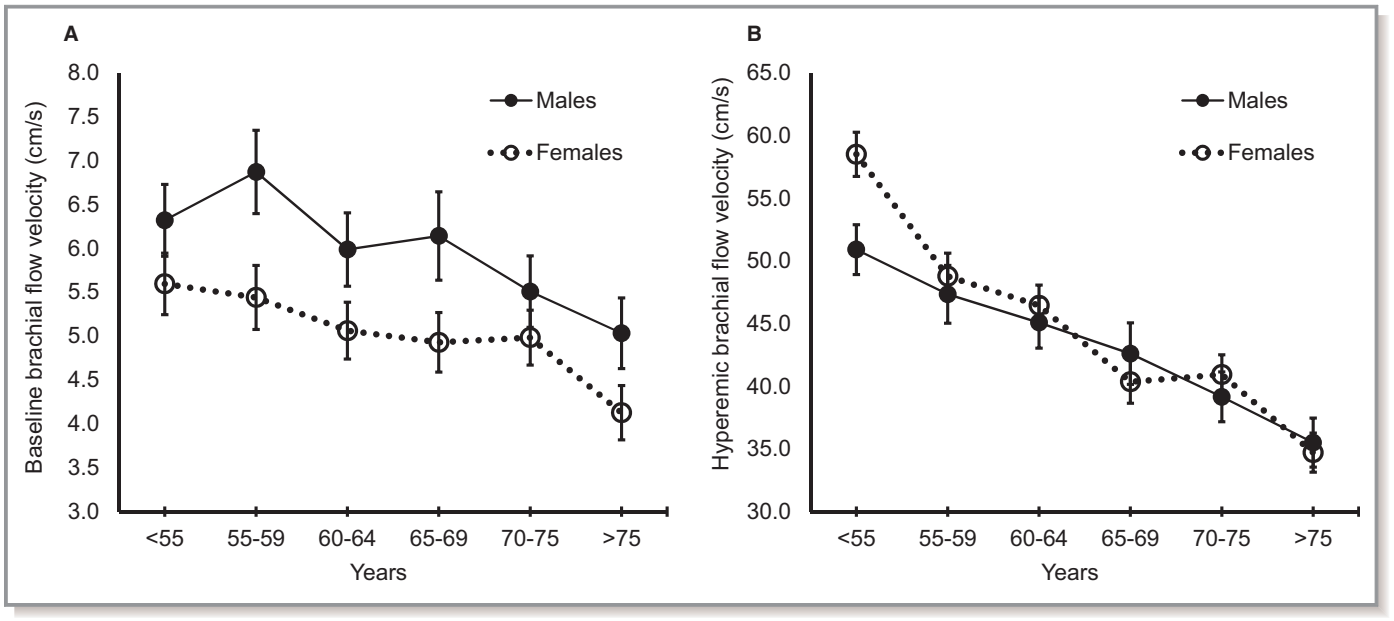

Figure. Adjusted mean brachial flow velocity across the age spectrum stratified by sex (n = 1458). The adjusted group means±SE (least squares means) of the (A) baseline brachial flow and (B) hyperemic brachial flow were plotted by age group and stratified by sex. Participants were grouped by 5-year age intervals. To prevent small groups on the extremes, participants aged <55 and ≥75 years were grouped together. Models were adjusted for age, sex, age-sex interaction, mean arterial pressure, heart rate, body mass index, active smoking, prevalent cardiovascular disease, statin medication, and antihypertensive medication.

Table 3. Relations Between Measures of Arterial Stiffness and Brachial Flow Velocity (n=1458)

Variable and Model	Brachial Flow Velocity (SD)					
	Baseline			Hyperemia		
	β±SE	*P* Value	Adjusted R^2	β±SE	*P* Value	Adjusted R^2
Brachial pulse pressure						
Minimally-adjusted model*	0.044±0.034	0.2	0.06	−0.086±0.031	0.006	0.19
Expanded model†	0.058±0.034	0.08	0.07	−0.070±0.031	0.03	0.20
CFPWV						
Minimally-adjusted model*	−0.111±0.033	<0.001	0.07	−0.135±0.030	<0.001	0.20
Expanded model†	−0.106±0.033	0.001	0.08	−0.128±0.030	<0.001	0.21

All coefficients represent SD difference in flow per SD difference in continuous variables. CFPWV indicates carotid-femoral pulse wave velocity.
*Adjusted for age, sex, mean arterial pressure, and heart rate.
†Adjusted for age, sex, age-sex interaction, mean arterial pressure, heart rate, body mass index, active smoking, prevalent cardiovascular disease, statin medication, and antihypertensive medication.

CFPWV persisted during hyperemia. We found no evidence of effect modification by median age or sex (all $P>0.05$) for the relations in Table 3.

Discussion

Principal Findings

Our community-based study evaluated cross-sectional relations between measures of aortic stiffness and microvascular function, as assessed by brachial flow velocity, in a sample of black participants. CFPWV, but not brachial pulse pressure, was associated with microvascular function at baseline. Baseline and hyperemic flows were lower with greater age. Women had significantly lower baseline flow velocity across the full age range examined; however, during hyperemia, age relations of flow velocity differed by sex. Furthermore, higher measures of aortic stiffness and pressure pulsatility were associated with lower mean brachial flow velocity during reactive hyperemia, indicating blunted flow reserve. The observed association of higher aortic stiffness or pressure pulsatility with lower hyperemic flow may be attributable to similar causal factors. However, the present study shows that these associations persisted in multivariable models that adjusted for contemporaneously measured shared risk factors, which is consistent with earlier findings by the Framingham Heart Study.[13] Thus, the present study suggests that aortic stiffening among blacks is accompanied by blunted reactivity of the peripheral microcirculation beyond that which is explained by CVD risk factor burden alone.

Comparisons to Previous Studies

Multiple risk factors were significantly related to baseline and hyperemic brachial flow velocities, which is similar to a prior Framingham study.[13] The Framingham study, however, additionally showed that total-to-high density lipoprotein cholesterol ratio (baseline), prevalent CVD (baseline), fasting glucose (hyperemic), antihypertensive medication (hyperemic), and hormone replacement in women (both baseline and hyperemic) were correlated to brachial flows. Although both studies were performed in middle-aged to older samples with similar techniques that measure brachial flow, our sample exhibited higher levels of CVD risk factors (compared with the Framingham sample),[13,18] which is consistent with previous studies of racial disparities.[29–32] Additionally, Howard et al observed that blacks have higher incidence of hypertension, diabetes mellitus, and dyslipidemia post-middle age,[33] which exacerbates disparities in risk factor prevalence later in life. Thus, disparities in the prevalence and incidence in clinical and subclinical risk factors likely contribute to racial discrepancies in correlates of vascular dysfunction.

In addition, although we observed that female sex was associated with lower baseline flow velocity, which may be protective in the setting of aortic stiffness, the relation of sex to hyperemic flow was more complex and varied across the age spectrum. Similar to Celermajer et al,[34] we observed that female sex was protective against microvascular dysfunction among the youngest group (aged <55 years), but older women exhibited a greater attenuation of the hyperemic flow reserve. Thus, we observed that the association of female sex with microvascular dysfunction reversed and was further exacerbated with advancing age (female sex-median age interaction, $P=0.02$), which was not observed in the prior Framingham sample. Our study is consistent with a few studies that suggest that this sex-related protection against microvascular damage is lost among black women as evidenced by reduced flow-mediated dilation. For example, Loehr et al observed that adjusted absolute and percentage change in brachial artery diameter was significantly reduced in African-American women compared with white women post menopause.[21] In addition, Perregaux et al showed that endothelium-dependent vasodilation was significantly impaired in blacks compared with whites,

and that while white women vasodilated significantly more than white men, the sex difference was not observed among black participants.[35] Neither of the 2 aforementioned studies adjusted for flow velocity, but a previous Framingham Heart Study showed that the sex difference in flow-mediated dilation was completely explained by differences in flow velocity.[18] Since black women have higher CVD mortality rates as compared with white women, perhaps differences in microvascular function may contribute to racial differences in rates of heart disease in women. However, additional studies among diverse cohorts of women across a broader age range are warranted to elucidate the putative mechanisms.

Link Between Stiffness Measures and Microvascular Dysfunction

At baseline, elevated pulse pressure was not associated with baseline flow, whereas elevated CFPWV was significantly associated with lower baseline flow. Although these are 2 well-known measures of aortic stiffness, they have varying relations with aortic wall stiffness and geometry. Brachial pulse pressure is affected by aortic flow, wave reflections, and local resistances; thus, apparent relations are influenced by parameters other than aortic stiffness.[13] On the contrary, CFPWV (the reference standard measure of aortic stiffness) is a more direct assessment of aortic wall stiffness and is less dependent on aortic diameter and local factors.[36] Yet, the combination of higher pulse pressure and higher baseline flow suggests a mismatch between basal flow and aortic diameter (assuming high aortic flow), which may have contributed to a trend toward a significant relation between elevated pulse pressure and higher baseline flow (P=0.08). However, higher aortic wall stiffness per se (as indicated by elevated CFPWV) may contribute to lower basal flow because of downstream microvascular damage and remodeling.

We observed that participants with higher CFPWV and brachial pulse pressure exhibited attenuated forearm brachial flow velocity during hyperemia (in models adjusted for potentially common CVD risk factors). This finding suggests that abnormal aortic stiffness and elevated arterial pressure pulsatility are associated with structural or functional abnormalities in peripheral small vessels. Thus, our data in this older black sample further contribute to the growing body of evidence that links elevated aortic stiffness and microvascular dysfunction. Beyond midlife, the aortic impedance increases disproportionately to the peripheral muscular arteries, leading to impedance matching between the aorta and first-generation arteries and a reduction in wave reflection.[37,38] This reduction in wave reflection eliminates the protective mechanism that normally buffers the peripheral microcirculation against excessive pressure and pulsatility.[37,38] For example, previous studies have shown that microvascular dysfunction may contribute to the progression of structural and functional damage to the brain and kidneys.[15–17] In addition, we recently showed that microvascular dysfunction may represent a partial mediator of the relations between aortic stiffness and CVD events, including myocardial infarction, unstable angina, heart failure, and ischemic stroke.[14] Thus, disparities in the extent and progression of microvascular dysfunction may contribute to ethnic differences in target organ diseases with microvascular etiologies. However, longitudinal studies that assess relative risks between blacks and other ethnic groups are warranted.

Limitations

Our study has limitations that should be considered. We employed a cross-sectional observational study design, which limits our ability to establish temporal relations between aortic stiffness measures and microvascular function. Cross-talk between small and large vessels has been described[39] and may represent bidirectional relations, which cannot be differentiated in our cross-sectional study. Thus, it is possible that alterations in peripheral blood flow and microvascular function affect aortic stiffness. We did not account for multiple testing; therefore, our investigation is more susceptible to type-1 error. In addition, the prevalence of antihypertensive medications was high; these medications affect vascular function, which may limit the external validity (generalizability) of the study's physiological insights. However, we adjusted for antihypertensive treatment in the primary analysis since it would be impractical to exclude these participants and unethical to request participants to suspend treatment. Furthermore, since blacks have a higher prevalence of hypertension (compared with white individuals), high prevalence of antihypertensive medications is an inherent characteristic of an aging black cohort. Thus, our findings may not be generalizable to other ethnic or racial groups and younger individuals. The consideration of these limitations should be balanced with the uniqueness of this study to investigate the relation of aortic stiffness to microvascular function in a large community-based cohort of blacks using novel vascular tonometry methods.

Conclusion

In our study, among a cross-section of black participants, elevated aortic stiffness and higher arterial pressure pulsatility were associated with microvascular dysfunction as assessed by brachial flow velocity during reactive hyperemia. Although various CVD risk factors are related to impaired microvascular function, they were unable to fully explain the relations between

measures of aortic stiffness and blunted hyperemic flow reserve. Thus, the effects of age-related, environmental, and genetic factors may impact microvascular function through alterations in aortic stiffness and pulsatile load. Because impairment in small and large vessel function is associated with worse long-term CVD outcomes, microvascular dysfunction, as a result of elevated aortic stiffness and pressure pulsatility, may represent an underlying mechanism for the increased CVD risk in blacks. However, further studies involving cohorts with more diverse participants are warranted.

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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 report no conflicts of interest related to this study. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the US Department of Health and Human Services. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Relations of Microvascular Function, Cardiovascular Disease Risk Factors, and Aortic Stiffness in Blacks: The Jackson Heart Study

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Supplemental Content:

Supplemental Table 1: Comparison of demographic characteristics and hemodynamic measures of excluded and included participants.

This supplementary material has been provided by the authors to give the readers additional information about their work.

Table S1: Comparison of demographic characteristics and hemodynamic measures of excluded and included participants.			
Variable	Included (N=1458)	Excluded* (N varies)	*P*-value†
Age, years	66±11	65±12	<0.001
Women, N (%)	965 (66)	318 (59)	0.004
Body mass index, kg/m^2	31±6	35±8	<0.001
Fasting glucose, mg/dL	106±33	105±32	0.39
Medical history			
Anti-hypertension treatment, N (%)	1092 (75)	327 (61)	0.05
Prevalent cardiovascular disease, N (%)	225 (15)	80 (15)	0.8
Active smoking, N (%)	154 (10)	51 (10)	1
Current statin use, N (%)	473 (32)	156 (29)	0.76
Alcohol consumption in the past 12 months, N (%)	635 (44)	238 (44)	1
Hormone replacement (women), N (%)	305 (21)	92 (17)	0.59
Tonometry and hemodynamic variables			
Heart rate, beats/min.	65±10	67±11	0.04
Mean arterial pressure, mm Hg	98±12	99±13	0.33
Systolic blood pressure, mm Hg	137±19	136±19	0.21
Diastolic blood pressure, mm Hg	71±10	73±11	0.002
Brachial pulse pressure, mm Hg	66±18	64±17	0.0007
Pulse pressure amplification	1.01±0.13	1.01±0.15	0.96
Carotid-femoral pulse wave velocity, m/s	11±4	12±6	0.24
Baseline mean brachial flow velocity, cm/s	5.3±3.3	5.5±3.8	0.14
Hyperemic brachial flow velocity, cm/s	44.9±17.8	46.7±20.1	0.004
All values are mean±standard deviation except as noted. *N varies (440–537) for excluded participants based on availability of data. †Differences between included and excluded participants were determined by *t*-tests for continuous variables and $\chi 2$ tests for categorical variables.			