RACIAL DIFFERENCES IN CENTRAL HEMODYNAMIC BURDEN IN MEN WITH HIV: PRELIMINARY FINDINGS

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Objectives: African Americans infected with HIV are almost 3 times more likely to die from cardiovascular disease (CVD) than their White HIV-infected counterparts. The purpose of this study was to examine racial differences in novel measures of vascular function and CVD risk in African American and White men infected with HIV.

Design: Our study uses a cross-sectional approach.

Setting: Participants were recruited from the nutrition/infectious disease clinic at a large metropolitan hospital.

Participants: African American men ($n=21$) and White men ($n=21$) with HIV on stable anti-retroviral therapy were included in this study.

Main Outcome Measures: High resolution ultrasound was used to assess brachial artery flow mediated dilation (FMD). Applanation tonometry was used to measure carotid-femoral and carotid-radial pulse wave velocity (PWV), carotid augmentation index (AIx) and carotid-brachial pulse pressure (PP) amplification. Left ventricular (LV) pressure effort was derived from the contour of the central BP waveform.

Results: There were no racial differences in brachial FMD (African American: 4.9 ± 1.1 vs White: 5.4 ± 1.0%; $P>.05$) or carotid-femoral PWV (African American: 8.9 ± .6 vs White: 8.7 ± .4 m/s; $P>.05$). African American men with HIV had significantly higher carotid-radial PWV (11.3 ± .4 vs 9.8 ± .3 m/s; $P<.05$), higher carotid AIx (6 ± 3 vs −1 ± 2%; $P<.05$), higher LV pressure effort (2262 ± 369 vs 1030±140 dyne sec/cm^2; $P<.05$) and lower PP amplification (1.10 ± .03 vs 1.24 ± .03; $P<.05$) compared to White men with HIV.

Conclusion: Elevated CVD risk in African American men with HIV may be partially mediated by increased central hemodynamic burden and not endothelial dysfunction or increased aortic stiffness. (*Ethn Dis.* 2013; 23[2]:217–222)

Key Words: African American, Human Immunodeficiency Virus, Arterial Stiffness, Blood Pressure, Wave Reflection

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INTRODUCTION

Human immunodeficiency virus (HIV) and cardiovascular disease (CVD) are the two most significant determinants of overall shorter life expectancy in African Americans living in the United States.[1] More than 50% of persons infected with HIV in the United States are African American.[2] Mortality rates are disproportionately higher in African Americans infected with HIV compared to Whites infected with HIV[3] and African Americans infected with HIV are almost 3 times more likely to die from CVD than their White HIV-infected counterparts.[4] The reason for increased CVD mortality in HIV-infected African Americans remains unknown but may be related to racial differences in vascular function and central hemodynamics. Compared to non-HIV infected Whites, African Americans have endothelial dysfunction, increased arterial stiffness, higher augmentation index and lower pulse pressure (PP) amplification.[5–7] This vascular and hemodynamic sequela is linked to atherosclerotic CVD, target organ damage (ie, left ventricular hypertrophy and renal dysfunction-clinically relevant facets of HIV pathology and significant contributors to morbidity/mortality in African Americans) and future CVD events.[8–10]

It is well-established that persons living with HIV have vascular dysfunction made worse by use of anti-retroviral therapy (ART).[11,12] African Americans may be particularly susceptible to the untoward vascular effects of HIV and

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ART given an underlying predisposition to vascular dysfunction. The purpose of our study was to test the hypothesis that African American men infected with HIV will have reduced brachial artery flow mediated dilation (FMD), increased aortic pulse wave velocity (PWV) and altered central hemodynamic burden (higher augmentation index and lower PP amplification) compared to White men infected with HIV.

METHODS

Twenty-one African American and thirty-one White men with HIV on stable ART were recruited for our study. From the 31 White participants, 21 were selected to ensure that groups did not statistically differ in important confounders of central hemodynamics and vascular function. These included: age, blood lipids, fasting glucose, renal function, brachial systolic and diastolic blood pressure (BP), viral load, ART (similar self-reported use of non-nucleosides and protease inhibitors), height, body mass, heart rate, CVD medication use (particularly anti-hypertensive therapies) and daily physical activity. Participants were recruited from the Nutrition/Infectious Disease clinic at Tufts Medical Center and the greater Boston community. Exclusion criteria included: 1) plasma HIV-1 RNA≥10,000 copies/mL; 2) change in ART regimen over two months prior to study entry; 3) evidence of liver or renal disease with values of liver enzymes >5 times upper limit of normal or creatinine >1.5 times upper limit of normal; 4) presence of active opportunistic infection or malignancy. Written informed consent was obtained from all study participants and the study protocol was approved by the Tufts Medical Center/Tufts University Institutional Review Board.

Laboratory Measurements

Glucose, blood lipids, CD4+ cell counts and HIV RNA levels were conducted in the Tufts Medical Center Clinical Laboratory using standard procedures. Measures of systemic inflammation included white blood cell count and neutrophil/lymphocyte ratio.[13,14] Glomerular filtration rate (GFR) was estimated from serum creatinine (sCR) measurements using the MDRD equation: eGFR ($ml \cdot min^{-1} \times [1.73\ m^2]$) = $186 \times (sCR)^{-1.154} \times (age)^{-.203} \times$ (1.210 if African American).

Pulse Wave Velocity and Augmentation Index

Patients were asked to refrain from caffeine, smoking and activity the day of testing and were at least 12 hours postprandial (overnight fast). Moreover, participants were instructed to withhold all vasoactive medications. With subjects in the supine position and following 15-min of quiet supine rest, BP was measured in triplicate (average used for subsequent analyses) as previously described.[15] A high-fidelity strain gauge transducer (Noninvasive hemodynamic monitor, Cardiovascular Engineering, Norwood Mass, USA) was then used to obtain pressure waveforms from the right radial, femoral and common carotid arteries. PWV was calculated from the distances between measurement points and the measured time delay between proximal and distal foot waveforms: PWV = D / δt (m/s^{-1}); where D is distance in meters and δt is the time interval in seconds. Carotid pressure waves, calibrated against brachial diastolic and mean arterial pressure as previously described[15] were used to obtain: 1) augmented pressure (AP), defined as the difference between maximal carotid BP (SBP) and the pressure at the forward wave peak (P_1); 2) time to inflection (Ti), determined from the time from the initial upstroke of the pressure wave to the foot of the reflection wave and taken as a measure of wave travel time; 3) the augmentation index (AIx), calculated as AP/PP and expressed as a percentage. Left ventricular (LV) pressure effort (ΔE_w) was calculated as 2.09 × AP(ED-Ti), where ED is left ventricular ejection duration and Ti is time to the inflection point.[16] Pulse pressure amplification was defined as the ratio of brachial PP to carotid PP (where PP is calculated as SBP – DBP). Effective reflecting distance was calculated as (aortic PWV × Ti)/2.[17]

Brachial Artery Reactivity

The brachial artery was longitudinally imaged 2 cm above the antecubital fossa using a 10mHz linear array vascular ultrasound transducer. Diameters were measured during end-diastole (gated with ECG R-waves) using ultrasonic calipers at baseline and 60 seconds after the introduction of an ischemic stimulus (inflation of a BP cuff around the upper arm to 200 mm Hg for 5 minutes). Responses were calculated as percentage change in brachial artery diameter from baseline (flow mediated dilation [FMD]).[18]

Statistical Analyses

Power analyses on existing data were used to estimate a sample size for select main outcome measures.[5] A priori significance was set at $P<.05$. Normality of distribution was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Group comparisons were made using analysis of variance. Chi-square tests were used to compare categorical variables. Correlations of interest were examined using Pearson's correlation coefficients. All data analysis was carried out using Statistical Package for the Social Sciences (SPSS, v 16.0, SPSS, Inc., Chicago, IL).

RESULTS

By design there were no group differences in potential confounders of vascular and central hemodynamic burden (Table 1, $P>.05$). There were significant group differences in carotid AIx, Ti, PP amplification, LV pressure

Table 1. Clinical and descriptive characteristics

Variable	White $n = 21$	African American $n = 21$	*P*
Age, yrs	52 ± 2	53 ± 1	.88
Body mass index, kg/m^2	27 ± 1	29 ± 1	.44
Waist circumference, cm	99 ± 2	102 ± 4	.49
Total cholesterol, mg/dL	188 ± 8	177 ± 8	.29
HDL-cholesterol, mg/dL	37 ± 2	42 ± 3	.13
LDL-cholesterol, mg/dL	108 ± 8	91 ± 8	.13
Triglycerides, mg/dL	216 ± 22	239 ± 33	.56
Glucose, mg/dL	103 ± 9	102 ± 12	.96
Smoking, n, %	6, 29	9, 43	.35
eGFR, mL/min/1.73 m^2	88 ± 5	92 ± 5	.69
CD4+ count, k/uL	645 ± 65	685 ± 80	.94
Hemoglobin, g/dL	14.6 ± .3	14.4 ± .3	.66
Hematocrit, %	42.6 ± .7	42.4 ± .9	.87
WBC Count, k/uL	5.4 ± .5	6.2 ± .5	.19
Neutrophil/lymphocyte ratio	1.5 ± .1	1.5 ± .3	.88
Medications, %			
Dyslipidemics	48	43	.99
Hypoglycemics	14	14	.99
Antihypertensives	52	61	.76
β-blockers	29	33	.99
ACE/ARB	19	33	.48
Ca^{2+} channel blockers	14	10	.99
Diuretics	19	33	.48
Anti-retrovirals	100	100	.99
Protease inhibitors	29	14	.45
Non-nucleosides	71	86	.45

Data are mean ± SEM unless noted otherwise.

HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate; WBC, white blood cell; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ca^{2+}, calcium.

Table 2. Vascular and hemodynamic parameters

Variable	White $n = 21$	African American $n = 21$	*P*
Brachial SBP, mm Hg	124 ± 2	125 ± 2	.77
Brachial DBP, mm Hg	74 ± 1	75 ± 2	.47
Brachial PP, mm Hg	51 ± 2	50 ± 2	.71
Mean arterial pressure, mm Hg	93 ± 1	94 ± 2	.47
Brachial FMD, %	5.4 ± 1.0	4.9 ± 1.1	.87
Carotid SBP, mm Hg	117 ± 2	121 ± 3	.19
Carotid DBP, mm Hg	76 ± 1	76 ± 2	.62
Carotid PP, mm Hg	41 ± 2	45 ± 3	.27
Carotid augmented pressure, mm Hg	3 ± 1	6 ± 1	.004
Carotid primary wave pressure, mm Hg	38 ± 2	38 ± 2	.91
Carotid-femoral PWV, m/s	8.7 ± .4	8.9 ± .6	.66
Carotid-radial PWV, m/s	9.8 ± .3	11.3 ± .4	.03
Carotid augmentation index, %	−1 ± 2	6 ± 3	.04
Pulse pressure amplification	1.24 ± .03	1.10 ± .03	.02
Time to inflection, ms	148 ± 3	130 ± 4	.004
Effective reflection distance, mm	657 ± 38	554 ± 21	.02
LV pressure effort, dyne sec/cm^2	1030 ± 140	2262 ± 369	.003
Heart rate, bpm	54 ± 2	55 ± 2	.68

Data are mean ± SEM.

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; FMD, flow mediated dilation; PWV, pulse wave velocity.

effort, effective reflection distance and carotid-radial PWV (Table 2, $P<.05$). There were no racial differences in self-reported physical activity. Approximately 33% of African American and 50% of White participants reported engaging in regular strength training (~3 days per week; $P>.05$); 50% of African American and 65% of White participants reported engaging in regular aerobic exercise training (~3 days per week; $P>.05$). There were no racial differences in aortic PWV or brachial artery FMD (Table 2, $P>.05$).

In African American men with HIV, carotid AIx was inversely associated with PP amplification ($r=-.63$, $P<.05$), eGFR ($r=-.52$, $P<.05$) and positively associated with LV pressure effort ($r=.69$, $P<.05$). In African American men with HIV, PP amplification was also inversely associated with LV pressure effort ($r=-.77$, $P<.05$). In African American men with HIV, carotid-radial PWV was inversely associated with Ti ($r=-.46$, $P<.05$) and positively associated with effective reflection distance ($r=.37$, $P<.05$). None of these associations were seen in White men with HIV ($P>.05$ for all).

DISCUSSION

African American men with HIV had higher carotid AIx and lower PP amplification compared to White men with HIV suggesting racial differences in central hemodynamic burden in men with HIV. This increased central hemodynamic burden was associated with reduced renal function and increased LV pressure effort (an important determinant of LV hypertrophy) in African American men. While there were no racial differences in brachial FMD or aortic stiffness in men with HIV, racial differences in peripheral artery stiffness were detected and this was associated with central hemodynamic burden in African American men. Elevated CVD risk in African American men with HIV may in part be mediated by heightened central hemodynamic burden and not endothelial dysfunction or increased aortic stiffness.

We noted prominent racial differences in AIx in men with HIV and this is consistent with recent reports in men without HIV.[5,6] Compared to other larger studies that measured AIx using the same approach (carotid applanation tonometry), values obtained in our study were similar to those seen in men of similar age without HIV.[15,19] With each cardiac contraction a forward pressure wave is generated. This forward traveling wave traverses the aorta arriving at areas of impedance mismatch (smaller arteries/arterioles, bifurcations). Upon encountering these sites, part of that forward wave is reflected back toward the heart. This backward travelling wave will eventually collide with a newly generated forward wave. The confluence of these forward and reflected pressure waves is encapsulated with a single measure, the augmentation index. Elevated AIx is associated with CV risk factor burden, target organ damage and is an independent predictor of future CV morbidity and mortality.[20,21] Indeed in the present study AIx was associated with eGFR and LV pressure effort, two surrogate measures of target organ damage. Given that there were no racial differences in forward wave pressure (P_1) but differences in augmented pressure (pressure due to wave reflection), our findings suggest that elevated AIx in African American men with HIV is mediated by elevated pressure from wave reflections.

We also noted prominent racial differences in PP amplification in men with HIV and this too is consistent with recent reports in adults without HIV.[5] Compared to other larger studies that have used a similar approach to obtain PP amplification, values seen in African American men with HIV are significantly lower than previously reported in White European men of similar age without HIV.[27] Pulse pressure amplification describes the increase in amplitude of the blood pressure wave as it travels distally away from the heart.[22] This amplification is determined by a combination of factors including arterial stiffness, timing and/or magnitude of wave reflections, and arteriolar tone/vascular resistance.[22] Reduced pulse pressure amplification occurs with aging[23] and disease (hypertension, diabetes, hypercholesterolemia, coronary artery disease) and is associated with traditional cardiovascular risk factors[24,25] and overall vascular burden.[26] Moreover, reduced pulse pressure amplification independently predicts future cardiovascular mortality.[27,28] Thus, pulse pressure amplification has been proposed as a potential mechanical biomarker of cardiovascular risk and global arterial function.[27] Our findings suggest that racial differences in AIx and PP amplification may contribute to heightened CVD risk in African American men with HIV.

Carotid-radial PWV was also higher in African American men with HIV suggesting increased stiffness of peripheral vascular beds. Values seen in African American men with HIV are significantly higher than previously reported in White men without HIV of similar age.[19] Peripheral artery stiffness is associated with CVD risk,[29] albeit to a lesser degree than central artery stiffness, and provides useful physiologic insight into our findings. Altered peripheral artery stiffness may affect conduit-resistance vessel impedance matching, shifting peripheral reflection sites closer to the heart. This in turn could shorten the distance to reflection, reduce transit time of the BP wave and increase AIx. Indeed, in our study, there were noted associations between peripheral PWV, effective reflection distance and time to reflection in the African American men only. Thus peripheral artery stiffness may be an important effector of central hemodynamic burden in African American men with HIV.

Left ventricular hypertrophy is not only common, but epidemic in African

Contrary to our hypothesis, we did not detect any racial differences in aortic PWV or brachial FMD in men with HIV.

American men, irrespective of the presence or absence of hypertension.[30] It is also considered part of the HIV phenotype as extent and prevalence of subclinical functional and structural cardiac abnormalities is far greater in patients with HIV than the general population.[31] Left ventricular pressure effort (ΔE_w) is defined as the energy/work required by the LV to overcome pressure from wave reflections. Rather than contributing to aortic outflow, a greater proportion of LV energy is wasted in an attempt to overcome pressure from wave reflection. LV pressure effort increases with age and hypertension and is associated with pathologic LV hypertrophy.[16] Left ventricular pressure effort was significantly higher in African American men with HIV and both AIx and PP amplification were associated with LV pressure effort in African American men only. Direct comparison of values to other studies is challenging given that previous studies have derived LV pressure effort from synthesized aortic pressures wave while our study used directly measured carotid pressure waves. Based on previous studies, values obtained in African American men with HIV are comparable to much older adults.[32] Our findings suggest that heightened central hemodynamic burden in African American men with HIV may contribute to previously well characterized racial differences in LV hypertrophy.

Contrary to our hypothesis, we did not detect any racial differences in aortic PWV or brachial FMD in men with HIV. It is possible that endothelial dysfunction and aortic stiffening are so profound in HIV (due to infection and/or use of ART) that this obscures any potential for detection of racial differences. Indeed aortic PWV was inversely associated with CD4+ count ($r = -.34$, $P < .05$) and FMD positively associated with CD4+ count ($r = .28$, $P < .05$) and this is consistent with previous findings.[33] Values of aortic PWV and FMD obtained in our investigation were similar to those previously reported in slightly older adults[19] with substantial coronary artery disease.[34] When examining the interaction of race, HIV and CVD risk, AIx and PP amplification may have more clinical utility than FMD and/or PWV.

We did not examine vascular function in African American and White women with HIV, thus our findings may not be extrapolated to both sexes and this is a limitation. In conclusion, we noted racial differences in peripheral artery stiffness, AIx and pulse pressure amplification; important biomarkers of systemic vascular function and CVD risk. Elevated CVD risk in African American men with HIV may in part be mediated by these differences in central hemodynamic burden. Future research is needed to examine if specifically targeting pressure from wave reflections may reduce CVD risk in African Americans infected with HIV.

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