Effects of Moderate Aerobic Exercise Training on Vascular Health and Blood Pressure in African Americans

Deborah L. Feairheller, PhD;[1,2] Keith M. Diaz, PhD;[3,2] Mohammed A. Kashem, MD;[4] Sunny R. Thakkar, MS;[2] Praveen Veerabhadrappa, PhD;[5] Kathleen M. Sturgeon, PhD;[6] Chenyi Ling, BS;[2,7] Sheara T. Williamson, PhD;[8] Jan Kretzschmar, BS;[2,7] Hojun Lee, BS;[2] Heather Grimm, MS;[2,7] Dianne M. Babbitt, MS;[2] Charmie Vin, MS;[2] Xiaoxuan Fan, PhD;[9] Deborah L. Crabbe, MD;[4] Michael D. Brown, PhD[2,7]

From the Hypertension and Endothelial Function with Aerobic and Resistance Training (HEART) Laboratory, Health & Exercise Physiology Department, Ursinus College, Collegeville, PA;[1] Hypertension, Molecular and Applied Physiology Laboratory, Department of Kinesiology, Temple University, Philadelphia, PA;[2] Center for Behavioral Cardiovascular Health, Department of Medicine, Columbia University Medical Center, New York, NY;[3] Division of Cardiology, Department of Medicine, School of Medicine, Temple University, Philadelphia, PA;[4] Department of Exercise Science, Shippensburg University, Shippensburg, PA;[5] School of Medicine, University of Pennsylvania, Philadelphia, PA;[6] Vascular Health Laboratory, Department of Kinesiology & Nutrition, University of Illinois at Chicago, Chicago, IL;[7] Department of Biology, Notre Dame of Maryland University, Baltimore, MD;[8] and Flow Cytometry Core Facility, School of Medicine, Temple University, Philadelphia ,PA[9]

As healthcare progresses toward individualized medicine, understanding how different racial groups respond to lifestyle interventions is valuable. It is established that African Americans have disproportionate levels of cardiovascular disease and impaired vascular health, and clinical practice guidelines suggest lifestyle interventions as the first line of treatment. Recently, the authors reported that 6 months of aerobic exercise improved inflammatory markers, flow-mediated dilation (FMD), and levels of circulating endothelial microparticles (EMPs) in African American adults. This study is a subgroup analysis of the aerobic exercise–induced changes in vascular health and blood pressure (BP) measures, including carotid artery intima-media thickness (IMT), nitroglycerin-mediated dilation (NMD), ambulatory BP, and office BP. Sedentary African American adults (53.4±6.2 years; 21 women and 5 men) showed improved vascular health but no change in BP. Carotid artery IMT decreased 6.4%, plasma nitric oxide levels increased 76.6%, plasma EMP levels decreased, percentage of FMD increased 59.6%, and FMD/NMD ratio increased 36.2% ($P<.05$ for all). Six months of aerobic exercise training is sufficient to elicit improvements in vascular structure and function in African Americans, even without improvements in BP measures or NMD (ie, smooth muscle function). To our knowledge, this is the first study to report such findings in African Americans. *J Clin Hypertens (Greenwich).* 2014;16:504–510. ©2014 Wiley Periodicals, Inc.

According to the 2013 American Heart Association (AHA) heart disease and stroke statistics, African Americans continue to have the highest prevalence of hypertension and obesity in the world.[1] Clinical and epidemiological studies report that African Americans have more cardiovascular disease (CVD) and impaired vascular health when compared with Caucasians.[2–4] Our research has previously demonstrated that differences exist at the endothelial cell layer as well. We have previously reported that endothelial cells of African Americans have higher oxidative stress and inflammation levels and respond differently to a laminar shear stress, compared with cells of Caucasians.[5–8] We have also reported differences between African American and Caucasian young adults in their responses to acute exercise.[9] These findings support a racial disparity in the pathophysiology of vascular function and health, which may have a significant impact in the extent of vascular damage that occurs in African Americans. Furthermore, limited information exists on the complex etiology of endothelial function/dysfunction, and on the effects that lifestyle interventions have on vascular health, in this population.

Vascular health is currently assessed through a number of clinical modalities, including flow-mediated dilation (FMD), nitroglycerin-mediated dilation (NMD), carotid artery intima-media thickness (IMT), plasma nitric oxide (NO) levels, and circulating levels of endothelial microparticles (EMPs). FMD is a noninvasive test, an index of NO-mediated endothelial-dependent function in humans.[10–12] NMD is a measure of endothelial-independent function, in particular smooth muscle function. Quantifying thickness of the smooth muscle layer (ie, IMT) assesses vascular remodeling.[13] Finally, recent studies have identified circulating EMPs, submicroscopic fragments of the blood vessel endothelial layer, as a novel direct marker of endothelial cell injury.[14–16] FMD, NMD, and IMT are established as reliable and valid markers of CVD and endothelial function, while EMPs are rapidly being accepted as an alternate surrogate marker. Importantly, exercise

Address for correspondence: Deborah L. Feairheller, PhD, The Hypertension and Endothelial Function with Aerobic and Resistance Training (HEART) Laboratory, Health & Exercise Physiology Department, Ursinus College, 601 East Main Street, Collegeville, PA 19426
E-mail: dfeairheller@ursinus.edu

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training has been shown to improve arterial function in adults with CVD risk factors.[17–19]

Recently, two well-designed randomized controlled trials showed that exercise training improves FMD in adults with prehypertension or CVD.[20,21] We previously reported that 6 months of aerobic exercise training improved inflammatory markers, FMD, and levels of circulating EMPs in African American adults with subclinical disease.[22] However, no examination of exercise-induced changes in carotid artery IMT, endothelial-independent dilation, office blood pressure (BP), or ambulatory BP (ABP) were included in these studies. To the best of our knowledge, there remains limited information in African Americans on the improvements in vascular health seen with exercise training. Thus, we tested the hypotheses that an aerobic exercise intervention would induce improvements in NMD, plasma NO levels, carotid artery IMT, clinical BP, and ABP measures in previously sedentary African Americans.

METHODS

Participants

Forty-two African Americans from the Philadelphia area were recruited by advertisements.[22] Due to scheduling issues and unavailability of hospital personnel, the first 16 participants did not undergo FMD testing before the exercise training program and were excluded from the current analysis. Thus, 26 adults, who underwent FMD testing pre-exercise and post-exercise training, were included in this subanalysis. Specific criteria for inclusion were: age 40 to 75 years, sedentary (<2 days of aerobic exercise per week), nondiabetic, nonsmoking, office BP <160/100 mm Hg, no medications that affect cardiovascular hemodynamics, no more than one antihypertensive medication, and no evidence or history of CVD, hypercholesterolemia, or renal disease. Both premenopausal and postmenopausal women were included in the study; postmenopausal women were not taking hormone replacement therapy. Each participant gave written informed consent. The protocol was approved by the institutional review board of Temple University, and all procedures were in accordance with the ethical standards of the Helsinki Declaration.

Study protocol

This was a single-group pre-post intervention study. All enrolled participants first completed a dietary stabilization period (ie, AHA diet). Participants on antihypertensive monotherapy (n=5: thiazides, 3; angiotensin II receptor antagonist, 1; angiotensin-converting enzyme inhibitor, 1) were then tapered off their medication under supervision of the study cardiologist. After a dietary stabilization period and medication taper were complete, researchers conducted baseline testing. Then laboratory personnel supervised a 6-month aerobic exercise training intervention, which was followed by a repeat of all baseline tests (ie, final testing). Methods for baseline/final testing, AHA diet, and the exercise training protocol have recently been described.[22,23] The exercise training protocol included, in brief, 6 months of supervised aerobic exercise training; 3 times a week, progressing from 20 minutes at 50% to 40 minutes at 65% of their maximal oxygen consumption (VO_{2max}). All final testing was performed at least 24 to 36 hours after the participant's last exercise session in order to prevent deconditioning and to control for the acute effects of exercise on hemodynamic and biochemical variables. Office BP measurements were obtained in accordance with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines.[24]

Twenty-four–hour ABP

Participants underwent 24-hour ABP using a noninvasive portable BP monitor (SpaceLabs, Redmond, WA) at baseline and at final testing, as described.[25] In brief, monitoring began in the morning of each participant's typical day. BP measures were obtained at 30-minute intervals during the day (6 AM–10 PM) and 60-minute intervals at night (10 PM–6 AM). Participant data were included in final analysis if >80% of the measurements were valid. Mean values were calculated for awake, sleep, and 24-hour time frames, for both systolic BP (SBP) and diastolic BP (DBP).

Forearm hemodynamics studies, FMD, and NMD

Brachial artery diameter was measured in response to increased flow (FMD) and to nitroglycerin (NMD) at baseline and final testing following published guidelines as previously described.[26,27] In brief, measurements were performed in the morning following an overnight fast in a quiet, temperature-controlled room. All measurements of brachial artery diameter were taken after 10 minutes of lying in the supine position, using a 7.5 MHz linear phase array transducer attached to a Sonos 5500 ultrasound machine (Philips Medical Systems, Bothell, WA). Reactive hyperemia was induced by distal forearm occlusion for 5 minutes. Brachial artery images were obtained 5 cm to 10 cm above the antecubital fossa. After at least 15 minutes of rest, new baseline images were obtained before a 0.4 mg nitroglycerin tablet was administered sublingually. Data analysis of FMD and NMD measures was conducted as previously described.[25,27]

Carotid artery IMT

On the same day as the FMD studies, the carotid arteries were evaluated with 2-dimensional high-resolution B-mode ultrasonography using an 8 MHz transducer. Images of the common carotid artery were obtained bilaterally. Three measures were collected for each artery, and the average was calculated. The maximal IMT of the common carotid artery was defined as the mean of the maximal IMT of the right and left sides. The same operator performed all FMD, NMD, and IMT measurements.

Plasma endothelial function markers

Blood samples were drawn into EDTA tubes in the morning following a 12-hour overnight fast. Samples were centrifuged at 2000 × *g* for 20 minutes at 4°C, and the isolated plasma was frozen at −80°C until the time of assay. Levels of NO end products were measured using a modified Griess assay (Assay Designs, Ann Arbor, MI) as previously described.[8] Circulating EMPs were quantified using a method we have previously described.[6,22] In brief, 100 μL of platelet poor plasma was incubated with fluorochrome-labeled antibodies (BD Biosciences, San Jose, CA) for 20 minutes at room temperature in the dark and then fixed with 10% formaldehyde. After incubation, samples were diluted with 500 mL of 0.22 μm phosphate buffered saline prior to flow cytometry. Two different fluorochrome-labeled antibody combinations were used to distinguish between EMP subpopulations: CD31-PE with CD42b-FITC and CD62E-PE alone. Samples were analyzed using BD LSRII flow cytometer (BD Biosciences) and BD FACSDIVA software (version 6.1.3; BD Biosciences). CD31+CD42− or CD62E+ events were defined as EMPs and were expressed as events per mL plasma.

Statistical analyses

Among the 26 African Americans who completed the 6-month exercise training program, the data reported for primary outcome variables in this paper include FMD (n=26), NMD (n=26), IMT (n=22), CD31+CD42− EMPs (n=18), CD62+EMPs (n=19), NO (n=14), clinic BP (n=25), 24-hour ABP (n=20), and awake and sleep ABP (n=19). The differences in sample size are related to issues with participant scheduling, acquiring blood samples, or assay procedure.

Data are expressed as mean± standard deviation (SD). Distribution of all variables was examined using the Shapiro-Wilk test of normality. Nonparametric tests were used when appropriate. Pre-exercise and post-exercise values were compared using the paired samples *t* test or the paired samples Wilcoxon signed-rank test. To examine the effect of prior antihypertensive medication, further analysis was conducted using repeated-measures analysis of variance adjusting for prior antihypertensive medication use. Statistical significance was set at $P<.05$. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc, Chicago, IL).

Power analyses

Power analyses were conducted using the PS software (Power and Sample Size Calculations, version 3.0.12; Vanderbilt University, Nashville, TN). Power calculations were based on the within-patient change in FMD and, separately, carotid artery IMT. The sample provided 80% power to detect a within-patient change in FMD ≥2.2% (α level 0.05, two-sided) and a within-patient change in carotid artery IMT ≥0.045 (α level 0.05, two-sided).

RESULTS

The Table presents the clinical characteristics of the study population before and after the exercise training program.

Demographics of the cohort

The study population consisted of 21 female and 5 male African Americans (aged 53.4±6.2 years) with a baseline VO_{2max} of 27.0±6.3 mL/kg/min. Among the female participants, 10 were premenopausal and 11 were postmenopausal. After dietary stabilization and medication taper (baseline), 10 participants were normotensive, 9 were prehypertensive, and 7 were hypertensive. The average baseline body mass index (BMI) was 31.4±5.9 kg/m^2. In the group, 5 were normal weight, 6 were overweight, and 15 were obese, according to obesity classifications.[28]

After 6 months of aerobic exercise, VO_{2max} increased 7.9%. Within the group, 88% of the participants had >70% adherence and 62% had >80% adherence to the exercise training program, which is comparable to other studies in older adults.[29] Also after exercise training, body weight decreased by 2.6%, BMI by 2.3%, triglyceride levels by 18.1%, and fasting plasma glucose by 5.6% ($P<.05$ for all). The 6-month aerobic exercise program did not alter body fat, total cholesterol, or HDL and LDL levels.

Blood pressure

Office and ABP measurements are presented in the Table. The average office BP, after dietary stabilization, at baseline was 123.3±13.7 mm Hg SBP and 79.1±7.6 mm Hg DBP. From the ABP test data, the mean 24-hour SBP and DBP at baseline were 125.7±13.4 mm Hg and 77.6±10.6 mm Hg, respectively. The 6-month aerobic exercise program did not alter clinic SBP, DBP, awake SBP or DBP, sleep SBP or DBP, or average 24-hour SBP or DBP.

Vascular health measures

Vascular health measures are presented in the Table, and individual changes are shown in the Figure. Significant improvements ($P<.05$) were seen in all measures, except for percentage of NMD, with exercise training. There was a 59.6% increase in percentage of FMD and a 36.2% increase in FMD normalized for smooth muscle function (FMD/NMD ratio). We found that common carotid IMT decreased 6.4% with 6 months of aerobic exercise training. For circulating measures of vascular health, levels of CD31+/CD42− EMPs and CD62+ EMPs were decreased 50.6% and 39.5%, respectively. In addition, levels of plasma NO end products increased 76.6%.

DISCUSSION

The main finding of this substudy is that African American adults showed improvements in vascular health measures with 6 months of aerobic exercise training. We found a significant improvement in carotid

TABLE. Changes With Exercise Training

Variable	No.	Baseline	Final	% Change	*P* Value
Age, y	26	53.4±1.2	–	–	–
Male/female	26	5/21	–	–	–
Body weight, kg	25	89.1±19.7	87.0±19.2	−2.4	.02
BMI, kg/m^2	26	31.4±5.9	30.7±6.0	−2.2	.016
Body fat, %	24	42.2±9.4	42.1±7.7	−0.2	.77
Total cholesterol, mg/dL	22	190.7±22.5	187.5±27.4	−1.7	.45
Triglycerides, mg/dL	22	82.6±34.2	66.5±18.4	−19.5	.008
HDL-C, mg/dL	22	68.9±23.4	67.2±24.4	−2.5	.82
LDL-C, mg/dL	22	105.2±18.4	107.1±21.9	1.8	.50
Fasting glucose, mg/dL	20	93.7±10.4	87.5±10.7	−6.6	.04
VO_{2max}, mL/kg/min	25	27.2±6.3	28.9±7.1	6.3	.04
Office BP measures					
SBP, mm Hg	25	123.2±14.0	124.5±16.5	1.1	.55
DBP, mm Hg	25	78.6±7.3	79.0±8.3	0.5	.78
ABPM measures					
Awake SBP, mm Hg	19	125.9±14.2	127.9±13.8	1.6	.12
Sleep SBP, mm Hg	19	113.0±13.5	116.2±11.9	2.8	.11
24-h SBP, mm Hg	20	124.4±13.9	126.5±13.3	1.7	.07
Awake DBP, mm Hg	19	78.6±9.0	77.8±9.6	−1.0	.39
Sleep DBP, mm Hg	19	66.2±10.5	67.4±7.6	1.8	.53
24-h DBP, mm Hg	20	77.1±9.6	76.8±9.9	−0.4	.68
Vascular measures					
Baseline BA diameter – FMD, mm	26	0.34±0.05	0.35±0.05	2.9	.15
FMD, %	26	6.0±2.9	9.6±2.1	60.0	<.001
Baseline BA diameter – NMD, mm	26	0.34±0.04	0.36±0.04	5.9	.10
NMD, %	26	17.7±8.0	19.5±8.5	10.2	.37
FMD/NMD ratio	26	0.38±0.06	0.51±0.03	36.2	.036
CCIMT, mm	22	0.64±0.1	0.59±0.07	−7.8	.007
CD31 + CD42- EMPs/μL plasma	18	3.2±0.5	1.4±0.1	−56.3	.001
CD62 + EMPs/μL plasma	19	31.3±15.3	20.4±23.4	−34.8	.127
NOx, μmol/L	14	23.8±8.6	43.3±15.8	81.9	.001

Abbreviations: BA, brachial artery; BMI, body mass index; DBP, diastolic blood pressure; EMPs, endothelial microparticles; FMD, forearm mediated dilation; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; NMD, nitroglycerin mediated dilation; NOx, nitric oxide end products; SBP, systolic blood pressure. Data are presented as mean±standard deviation. Significance set at $P<.05$.

artery IMT, along with improvements in brachial artery FMD, circulating EMP levels, and plasma NO, even without improvements in office BP, ABP, or NMD.

Other studies have reported similar findings, in adults with obesity[30] and coronary artery disease (CAD)[18] after 8 weeks of aerobic exercise, and in adults with diabetes after 3 months of aerobic and anaerobic exercise (ie, resistance training).[17] However, patient race was not controlled for in these studies. For example, Beck and colleagues[20] reported that both aerobic and resistance training improved FMD, BP, and NO levels in young prehypertensive adults. Ades and colleagues[21] found, with 4 months of aerobic exercise training, significant improvements in FMD, body weight, triglycerides, and fasting plasma glucose, but observed no changes in NMD or BP. However, the patients in the study by Ades and colleagues[21] had diagnosed CAD and were all taking medication (aspirin, 100%; statins, 90%; β-blockers, 76%; angiotensin inhibitors, 29%; clopidogrel, 61%), so it is unclear to what extent medication usage may have confounded their study findings. In our study, African Americans were either not taking regular antihypertensive medication or had been tapered off their medication. To assess for confounding effects of medication usage we conducted additional analyses and found that medication usage did not have an effect on FMD but may have had an effect on IMT, EMP, and NO measures. Thus, future research should examine whether antihypertensive medication may have an effect on changes or improvements in vascular health with physical activity interventions. Studies generally report medication usage of patients, but this has not been examined in relation to exercise training.

As mentioned, it is established that African Americans have more CVD and endothelial dysfunction compared with other racial groups.[2,3,31] Exercise training studies in adults with different types of CVD, and no mention of racial group, suggest that exercise could contribute to

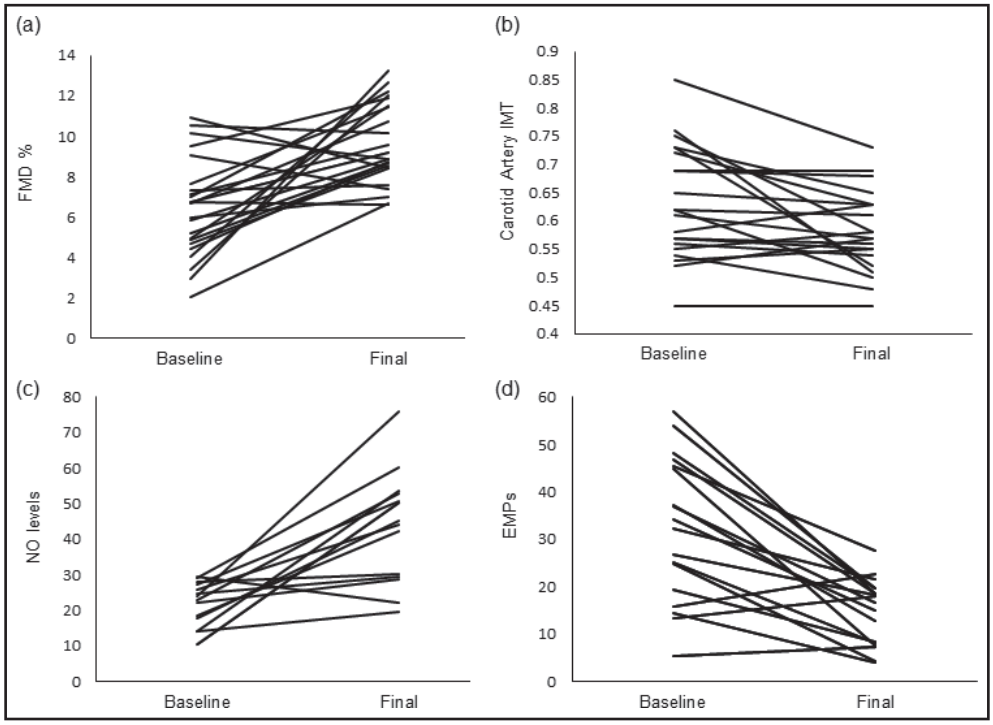

FIGURE. Individual exercise training responses in vascular health measures: (a) flow-mediated dilation (FMD), (b) carotid artery intima-media thickness (IMT), (c) nitric oxide end products (NO), and (d) endothelial microparticles (EMPs)

changes along the endothelial layer (FMD) but not along the smooth muscle layer (NMD).[17,18,21,29] Likewise, we found that with 6 months of exercise, African American adults had improved FMD yet preserved NMD responses. FMD depends on the production of, and the inactivation of, NO within the vasculature.[12] NMD methods use an exogenous NO donor (nitroglycerin) to determine endothelial-independent response. The FMD/NMD ratio is an aggregate measure of NO vasodilator function. In our study, this ratio was significantly improved and is most likely related to the increase in FMD. Since we found increased NO and decreased EMPs, the improvement in FMD, without a change in NMD, points to improved endothelial function only. Our findings strengthen the existing conclusion that aerobic exercise training improves endothelial function and provide evidence for one of the first times that aerobic exercise is beneficial to vascular health in the African American population as well. Future research should compare responses between racial groups and should also examine exercise-induced changes in vascular health in a variety of ethnic populations.

Age and overall health may also mitigate exercise-induced adaptations to vascular health. It has been suggested that exercise in "healthy" older adults may not elicit improvements in either NMD or FMD.[32] Recently, Black and colleagues[32] measured both FMD and NMD in healthy (no CVD or diabetes) sedentary older adults (no mention of ethnicity) who underwent 6 months of aerobic exercise training at a similar intensity to our program. Like us, Black and colleagues reported no change in NMD; however, they also reported no change in FMD with exercise training. Taken together, the studies in adults with impaired vascular health (eg, CVD, African Americans) suggest that smooth muscle function is preserved while endothelial function improves with exercise. However, the study by Black and colleagues suggests that changes may not occur in either smooth muscle or endothelial function in older adults. Thus, mechanistic studies are needed to elucidate how the arterial adaptations to lifestyle interventions differ for healthy and diseased populations of varying ethnicity and age.

To the best of our knowledge exercise-induced changes in carotid artery IMT in African Americans has yet to be examined. Thus, an important finding from this study is the decrease in IMT seen with aerobic exercise training. Previous studies have reported that African Americans have greater carotid artery IMT compared with their Caucasian counterparts after adjustment for a wide range of risk factors. This suggests that African Americans are predisposed to greater vascular structure abnormalities.[33–35] Thus, treatment modalities that attenuate carotid artery IMT may be particularly relevant for the high-risk populations. Studies on carotid artery IMT and exercise have reported mixed results, and none have included a solely

African American population.[36–38] Here we report that 6 months of aerobic exercise training elicited a significant decrease in IMT. Coupled with the improvement in FMD, this suggests that aerobic exercise elicited an improvement in vascular structure as well as function.

STUDY LIMITATIONS

This study has several limitations. First, the population used in our study was small and predominately female, limiting its generalizability to other populations. Future studies with larger sample sizes and greater sex distributions are needed to corroborate our findings. Second, studies recommend that FMD percentages are normalized to the individual shear flow rate to account for blood flow response heterogeneity, but we did not normalize FMD. Thus, our results could have been confounded by inter-patient variability in hyperemic shear stress. It should be noted, however, that this shear stress normalization approach has recently been brought into question as some have argued that it may be an imprecise measure subject to violation of statistical assumptions. At present, no real consensus exists as to how to appropriately control for differences in the magnitude of reactive hyperemia induced by FMD. However, we use the FMD/NMD ratio, which is predicated off the assumption that NMD values represent the maximal achievable diameter of the brachial artery, thus representing a normalized measure of vasodilatory capacity. Third, the technique for measurement of EMPs has yet to be standardized, so comparisons across studies should be done with caution. Finally, our study lacked a control group, making it difficult to provide a causal relationship between the changes seen and aerobic exercise. However, despite these limitations, our study may have scientific and clinical importance as the vascular responses to exercise training have not been well established in African Americans.

CONCLUSIONS

Our study findings show that aerobic exercise training for 6 months is sufficient to elicit improvements in vascular structure and function in African Americans. This study is important because as healthcare progresses toward the use of individualized clinical practice guidelines, understanding how populations of different racial groups, along with different diseased populations, respond to lifestyle interventions (ie, exercise, diet) is valuable and may help direct clinical trials for these populations.

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