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GENDER AND ETHNIC DIFFERENCES IN ARTERIAL COMPLIANCE IN PATIENTS WITH INTERMITTENT CLAUDICATION

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Abstract

Purposes—To assess the gender and ethnic differences in arterial compliance in patients with intermittent claudication.

Methods—A total of 114 patients participated, including 38 Caucasian men, 32 Caucasian women, 16 African-American men, and 28 African-American women. Patients were assessed on large artery elasticity index (LAEI), small artery elasticity index (SAEI), age, weight, body mass index, ankle-brachial index (ABI), smoking status, and metabolic syndrome components.

Results—Group differences were found for LAEI (p = 0.042), SAEI (p = 0.019), body mass index (p = 0.020), prevalence of elevated fasting glucose (p = 0.001), and prevalence of abdominal obesity (p = 0.025). Significant covariates for LAEI included age (p = 0.0002) and elevated triglycerides (p = 0.0719). LAEI (units = 10 ml × mmHg) adjusted for age and triglycerides was 39% lower (p = 0.0005) in African-Americans (11.4 ± 0.90; mean ± SE) than in Caucasians (15.8 ± 0.72), whereas no significant difference (p = 0.7904) existed between men (13.8 ± 0.81) and women (13.5 ± 0.79). Significant covariates for SAEI included age (p = 0.0001), abdominal obesity (p = 0.0030), and elevated blood pressure (p = 0.0067). SAEI (units = 100 ml × mmHg) adjusted for age, abdominal obesity, and elevated blood pressure was 32% lower (p = 0.0007) in African-Americans (2.8 ± 0.3) than in Caucasians 4.1 ± 0.2), and was 18% lower (p = 0.0442) in women (3.1 ± 0.2) than in men (3.8 ± 0.2).

Conclusion—African-American patients with intermittent claudication have more impaired macrovacular and microvascular function than Caucasian patients, and women have more impaired microvascular function than men. These ethnic and gender differences in arterial compliance are evident even though ABI was similar among groups, suggesting that arterial compliance provides unique information to quantify vascular impairment in patients with intermittent claudication.

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INTRODUCTION

Intermittent claudication is a symptom of peripheral arterial disease (PAD), and is associated with elevated rates of mortality,(1–4) and morbidity.(5) Intermittent claudication afflicts 5% of the US population older than 55 years of age,(6) and occurs during ambulation when the peripheral circulation is inadequate to meet the metabolic demand of the active leg musculature.

Gender and ethnic differences exist in the prevalence and manifestation of PAD. The prevalence of PAD is less in women at younger ages, but is similar to that of men at older ages.(7) Women are more likely to have asymptomatic PAD,(8) and less likely to report classic symptoms of intermittent claudication than men at all age groups.(9;10) Women with intermittent claudication have shorter walking distances to the onset of claudication pain, and to maximal claudication pain during standardized treadmill exercise than men.(11;12) With regards to ethnicity, African-Americans have more than a two-fold greater risk of developing PAD,(13) which may not be explained by a greater burden of atherosclerotic risk factors such as diabetes, hypertension, and obesity.(13;14) African-Americans have greater ambulatory dysfunction, as measured by self-paced walking tasks, than compared to Caucasians.(15)

Although differences in vascular function may contribute to gender and ethnic differences in symptomatology, limited data is available. Arterial compliance is a clinically important outcome measure because it is associated with functional and structural characteristics of the vasculature,(16;17) and is a predictor of cardiovascular events.(18) PAD patients have reduced arterial compliance of the large and small arteries compared to age-matched controls,(19;20) indicating that PAD patients have impaired arterial compliance of both the macrovasculature and microvasculature. However, the characteristics associated with arterial compliance in PAD patients are not well described. Therefore, the purpose of this study was to assess the gender and ethnic differences in arterial compliance in PAD patients with intermittent claudication.

METHODS

SUBJECTS

Recruitment—Patients participated in this study at the General Clinical Research Center (GCRC), at the University of Oklahoma Health Sciences Center (HSC). Patients were recruited by referrals from the HSC vascular clinic, as well as by newspaper advertisements. The procedures used in this study were approved by the Institutional Review Board at the University of Oklahoma HSC. Written informed consent was obtained from each patient prior to investigation.

Screening—Patients with intermittent claudication secondary to vascular insufficiency were included in this study if they met the following criteria: (a) a history of intermittent claudication, (b) ambulation during a graded treadmill test limited by intermittent claudication,(21) and (c) an ABI ≤ 0.90 at rest(22) or an ABI ≤ 0.73 after exercise.(23) Patients were excluded from this study for the following conditions: (a) absence of PAD (ABI > 0.90 at rest and ABI > 0.73 after exercise), (b) inability to obtain an ABI measure due to non-compressible vessels, (c) asymptomatic PAD determined from the medical history and verified during the graded treadmill test, (d) use of medications indicated for the treatment of intermittent claudication (cilostazol and pentoxifylline) initiated within three months prior to investigation, (e) exercise tolerance limited by factors other than leg pain (e.g., severe coronary artery disease, dyspnea, poorly controlled blood pressure), and (g) active cancer, renal disease, or liver disease.

MEASUREMENTS

Medical History, Physical Examination, and Anthropometry—Patients arrived at the GCRC in the morning fasted, but were permitted to take their usual morning medication regimen. Demographic information, height, weight, body mass index (BMI), waist and hip circumferences,(24) cardiovascular risk factors, co-morbid conditions, claudication history, blood samples, and a list of current medications were obtained from a medical history and physical examination at the beginning of the study.

Metabolic Syndrome—Patients were evaluated for each component of metabolic syndrome according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III.(25) Metabolic syndrome is defined as having three or more of the following components: (1) abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women), (2) elevated triglycerides (≥ 150 mg/dl), (3) reduced HDL cholesterol (< 40 mg/dl in men and < 50 mg/dl in women), (4) elevated blood pressure (≥ 130/85 mmHg), and (5) elevated fasting glucose (≥ 110 mg/dl) as well as those with diabetes. In addition, treatment with medications for dyslipidemia, hypertension, and diabetes were used to define presence of metabolic syndrome components. All of the women were post-menopausal, and none were on hormonal therapy. Although several definitions of metabolic syndrome exist, the NCEP ATP III definition was used in this investigation because it was specifically established on a population from the United States.

ABI—After 10 minutes of supine rest, the ankle and brachial systolic blood pressures were obtained as previously described.(26) Briefly, ankle systolic pressure was measured by Doppler technique in the posterior tibial and dorsalis pedis arteries of both legs. The higher of the two arterial pressures from the symptomatic leg was recorded as the resting ankle systolic pressure. Similarly, brachial blood pressure was taken from both arms, and the arm yielding the higher systolic pressure was recorded as the brachial systolic pressure. The ABI was then calculated as ankle systolic pressure / brachial systolic pressure. The test-retest intraclass reliability coefficient for the measurement of ABI in our laboratory is R = 0.96 for ABI.(21)

Diastolic Pulse Contour Analysis (PCA)—Arterial compliance measurements were obtained in the morning following an overnight fast of at least eight hours, and prior to engaging in any strenuous physical activity. The large artery elasticity index (LAEI) and small artery elasticity index (SAEI) were obtained by an HDI/Pulsewave™ CR-2000 Cardiovascular Profiling System (Hypertension Diagnostic, Inc., Eagan, Minnesota, USA) following 5 to 10 minutes of rest in the supine position as previously described.(27–30) To convert values to whole numbers, the units for LAEI (ml × $mmHg^{-1}$) were multiplied by 10 and the units for SAEI (ml × $mmHg^{-1}$) were multiplied by 100. An appropriately sized blood pressure cuff was placed around the subject’s left upper-arm, and a rigid plastic wrist stabilizer was placed on the subject’s right wrist to minimize wrist movement and stabilize the radial artery during the measurement. An Arterial Pulsewave™ Sensor was placed on the skin directly over the radial artery at the point of the strongest pulse, while the arm rested in a supine position. The non-invasive acoustic sensor was adjusted to the highest relative signal strength, and arterial waveforms were recorded for 30 seconds and the diastolic portion was digitized at 200 samples per second to determine large artery and small artery elasticity indices.(31) Both LAEI and SAEI are measures of arterial compliance throughout the entire arterial tree. LAEI is determined from the decay in diastolic pressure, and SAEI is determined from the decay in arterial waves reflected from resistance vessels and the microvasculature.(29) Measurements were averaged over three continuous 30-second trials. The test-retest intraclass reliability coefficient is R = 0.87 for large artery compliance and R = 0.83 for small artery compliance.(28)

STATISTICAL ANALYSES

Measurement variables were summarized by presenting means and standard deviations within each of the four race by gender groups. Equality of the four means for each variable was tested using a one way ANOVA procedure. The Kruskal-Wallis procedure was used for the ranking scale metabolic syndrome components variable. Dichotomous variables were summarized by presenting percent “yes” within groups and equality of proportions tested using 2 by 4 Chi Square.

For the two primary response variables, LAEI and SAEI, an ANCOVA was used to test for possible gender, ethnic, and their interaction effects. For each of these responses, selection of appropriate covariates from all the other variables was made by first using a stepwise forward selection method to obtain best linear model constrained to include gender and ethnicity, then using as covariates those variable contained in the set of selected variables for which all covariates were significant at the 0.1 level in the ANCOVA. The 0.1 inclusion criteria was chosen as a conservative measure to guard against omitting pertinent variables while still avoiding over parameterization of model. Since age was the most prominent covariate selected, the association of other variables with primary responses was examined by obtaining partial correlations after adjustment for age, ethnicity, and gender.

RESULTS

The clinical characteristics of the Caucasian and African-American men and women are displayed in Table I. A total of 114 patients participated, including 38 Caucasian men, 32 Caucasian women, 16 African-American men, and 28 African-American women. Overall group differences were found for BMI ($p = 0.020$), prevalence of elevated fasting glucose ($p = 0.001$), medication usage for diabetes ($p = 0.001$), prevalence of abdominal obesity ($p = 0.025$), LAEI ($p = 0.042$), and SAEI ($p = 0.019$). Women had higher values for BMI and abdominal obesity than men, and African-Americans had higher prevalence of elevated fasting glucose, greater usage of diabetes medication, and lower LAEI and SAEI than Caucasians. All of the remaining variables were similar among groups ($p > 0.05$), including ABI ($p = 0.894$).

The association between clinical characteristics and arterial compliance adjusted for age, gender, and ethnicity are shown in Table II. SAEI was negatively correlated with current smoking ($p < 0.05$) and elevated blood pressure ($p < 0.05$), and positively associated with weight ($p < 0.01$), BMI ($p < 0.05$), abdominal obesity ($p < 0.05$), and obesity ($p < 0.05$). The significant covariates in the ANCOVA model for SAEI (Table III) included age ($p = 0.0001$), abdominal obesity ($p = 0.0030$), and elevated blood pressure ($p = 0.0067$). The significant covariates for LAEI included age ($p = 0.0002$) and elevated triglycerides ($p = 0.0719$). Use of medications to control blood pressure, cholesterol, diabetes, and PAD were not significant covariates in the ANCOVA models for SAEI and LAEI.

The LAEI of the Caucasian and African-American men and women adjusted for age and triglycerides is shown in Table IV. LAEI was 39% lower in African-Americans than in Caucasians ($p = 0.0005$), whereas no difference existed between men and women ($p = 0.7904$). The SAEI adjusted for age, abdominal obesity, and elevated blood pressure is shown in Table V. SAEI was 32% lower in African-Americans than in Caucasians ($p = 0.0007$), and was 18% lower in women than in men ($p = 0.0442$).

DISCUSSION

The primary finding of this investigation was that African-American patients had impaired large and small arterial compliance compared to Caucasian patients, even after adjusting for covariates such as age, abdominal obesity, and elevations in blood pressure and triglycerides. This finding supports a previous observation that in young, asymptomatic adults between 18 and 44 years of age, African-Americans had lower large and small arterial compliance than Caucasians.(32) However, this is the first study to compare ethnic differences in arterial compliance in PAD patients, and supports the notion of African-Americans having a greater atherosclerotic burden than Caucasians.(13) Thus, less compliant large and small arteries of African-Americans may be one factor contributing to their higher risk for PAD,(13) and to their shorter 6-minute walk distance, slower velocity while walking four meters, and lower summary performance score.(15)

A second key observation in this report was that women had similar large artery compliance to men, but lower small artery compliance adjusted for age, abdominal obesity, and elevated blood pressure. Thus, the macrovasculature was similar between men and women, both from the standpoint of having similar large artery compliance as well as having similar ABI. However, the lower small artery compliance of women indicates that they have impaired microvasculature function compared to men. This finding supports a recent study from our laboratory that measured calf muscle hemoglobin oxygen saturation (StO_2) during treadmill exercise in men and women.(12) Calf muscle StO_2, a measure of the local circulation, was impaired in women and was predictive of their lower exercise performance. Less compliant small arteries of women with intermittent claudication observed in this investigation may contribute to their impaired calf muscle StO_2 and shorter walking distances. The lower small artery compliance in women in our study also is in agreement with the finding that young, asymptomatic adult women have lower small artery compliance than their male counterparts.(32)

Age was the most significant single covariate for both large and small artery compliance, indicating that age has a deleterious effect on arterial compliance in older patients with PAD and intermittent claudication. This observation is supported by previous studies reporting a decrease in large and small artery compliance in PAD patients with either intermittent claudication or critical limb ischemia,(20) in patients solely with intermittent claudication, (19) and in asymptomatic adults.(27;31;32) The age-related decrease in arterial compliance occurs due to structural changes within the arterial wall, such as increased fragmentation and decreased density of elastin,(33) increased concentration of collagen,(34) and hypertrophy of vascular smooth muscle.(34)

Elevated blood pressure was another significant covariate for small artery compliance, indicating that hypertension impairs microvascular function. This finding is supported by previous reports in patients with intermittent claudication(19) and in asymptomatic adults. (29;31;32) The clinical implication is that management to lower blood pressure not only lowers cardiovascular risk of patients with intermittent claudication,(7) but it may also increase small artery compliance, a marker of endothelial function,(31) and thus improve microcirculation. Abdominal obesity was another covariate of small artery compliance, as those with abdominal obesity had higher compliance. This finding agrees with previous studies,(20;31) and suggests that obesity may reflect a state of chronic vasodilatation, perhaps secondary to relative hyperinsulinemia frequently associated with obesity.(35) Elevated triglyerides, a component of metabolic syndrome, was a final covariate for arterial compliance, as it was a significant covariate for large artery compliance after adjusting for age.

There are several limitations to this study. The cross-sectional research design of this study does not allow causality to be established when examining the relationship between arterial compliance and covariates, such as age, blood pressure, body fatness, and metabolic syndrome components. Another limitation is that diastolic PCA is a non-invasive technique

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to determine large and small artery compliance.(31;36;37) However, this technique has been validated with invasive measures of arterial compliance,(36) and provides reliable measurement of arterial compliance.(28) The present findings are also limited to PAD patients who have intermittent claudication, and may not be generalized to patients with less severe or more severe PAD. However, the patients in the current study are typical of patients with intermittent claudication, as there was a high prevalence of cardiovascular risk factors for PAD, including smoking, diabetes, hypertension, dyslipidemia, and obesity. Thus, the findings of the present study are generalizable to the majority of patients with intermittent claudication who typically have numerous co-morbid conditions.

Conclusions and implications

African-American patients with intermittent claudication have more impaired macrovacular and microvascular function than Caucasian patients, and women have more impaired microvascular function than men. These ethnic and gender differences in arterial compliance are evident even though ABI was similar among groups, suggesting that arterial compliance provides unique information to quantify vascular impairment in patients with intermittent claudication. Future investigations should examine whether arterial compliance is associated with symptomatology and exercise performance, and whether it is modifiable with interventions such as exercise and medication therapies.

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Table I

Clinical characteristics of peripheral arterial disease patients with intermittent claudication. Values are means (SD) and percentages.

Variables	Caucasian Men (N = 38)	African-American Men (N = 16)	Caucasian Women (N = 32)	African-American Women (N = 28)	P Value
Age (years)	68 (12)	60 (7)	67 (12)	64 (9)	0.098
Weight (kg)	84.6 (16.3)	93.7 (25.0)	77.9 (17.9)	85.9 (18.7)	0.050
Body Mass Index (kg / m^2)	27.4 (4.4)	30.9 (8.0)	29.7 (6.7)	32.3 (6.9)	0.020
Ankle/Brachial Index	0.72 (0.21)	0.78 (0.20)	0.74 (0.27)	0.73 (0.29)	0.894
Current Smoking (% yes)	24	50	34	41	0.247
Elevated Fasting Glucose (% yes)	26	56	23	64	0.001
Elevated Blood Pressure (% yes)	81	100	77	93	0.101
Elevated triglycerides (% yes)	76	75	74	64	0.748
Reduced HDL Cholesterol (% yes)	87	81	87	82	0.915
Abdominal Obesity (% yes)	35	38	61	68	0.025
Metabolic Syndrome Components (n)	3.0 (1.2)	3.5 (1.2)	3.2 (1.2)	3.7 (1.4)	0.119
Metabolic Syndrome (% yes)	70	81	74	79	0.807
Obesity (%)	32	44	47	61	0.132
Medication for blood pressure (% yes)	74	88	69	86	0.298
Medication for dyslipidemia (% yes)	63	56	72	61	0.700
Medication for diabetes (% yes)	26	50	16	61	0.001
Medication for PAD (% yes)	71	81	72	64	0.696
Large Artery Elasticity Index (ml × $mmHg^{-1}$) × 10	15.7 (5.8)	12.6 (3.9)	15.2 (9.1)	11.5 (4.3)	0.042
Small Artery Elasticity Index (ml × $mmHg^{-1}$) × 100	4.3 (2.3)	3.0 (1.8)	3.7 (2.2)	2.8 (1.3)	0.019

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Table II

Association between clinical characteristics and measures of arterial compliance in 110 peripheral arterial disease patients with intermittent claudication.

Variables	Large Artery Elasticity Index	Small Artery Elasticity Index
Weight	0.152	0.251**
Body Mass Index	0.114	0.220*
Ankle/Brachial Index	0.044	0.156
Current Smoking	−0.044	−0.214*
Elevated Fasting Glucose	−0.060	0.014
Elevated Blood Pressure	0.007	−0.191*
Elevated triglycerides	0.176	0.023
Reduced HDL Cholesterol	0.154	0.141
Abdominal Obesity	0.022	0.213*
Metabolic Syndrome	0.146	0.042
Obesity	0.140	0.210*

Values are Pearson partial correlation coefficients adjusted for gender, ethnicity, and age.

* $p < 0.05$,

** $p < 0.01$.

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Table III

Regression coefficient summary for covariates used in ANCOV models for large artery elasticity index (LAEI) and small artery elasticity index (SAEI) of peripheral arterial disease patients with intermittent claudication.

Variables	Predictors	Regression Coefficient	95% CI	R^2	P Value
LAEI	Age	−0.2000 per year	−0.3027 to −0.0972	0.1110	0.0002
	Elevated Triglycerides	2.3188 condition present	−0.2097 to 4.8474	0.0246	0.0719
SAEI	Age	−0.0649 per year	−0.0965 to −0.0333	0.0961	0.0001
	Abdominal Obesity	1.0519 condition present	0.3657 to 1.7380	0.0535	0.0030
	Elevated Blood Pressure	−1.3708 condition present	−2.3535 to −0.3882	0.0443	0.0067

Table IV

Large artery elasticity index (LAEI) of peripheral arterial disease patients with intermittent claudication. Values are means (SE) adjusted for age and elevated triglycerides.

Ethnicity	Male	Female	Ethnic Means	P Value
Caucasian	16.2(1.0)	15.5(1.1)	15.8 (0.72)	G = 0.7904
African-American	11.5(1.5)	11.5(1.1)	11.4 (0.90)	E = 0.0005
Gender Means	13.8 (0.81)	13.5 (0.79)	13.7	GxE = 0.7915

G = gender effect, E = ethnicity effect, GxE = gender by ethnicity interaction.

Table V

Small artery elasticity index (SAEI) of peripheral arterial disease patients with intermittent claudication. Values are means (SE) adjusted for age, abdominal obesity, and elevated blood pressure.

Ethnicity	Male	Female	Ethnic Means	P Value
Caucasian	4.6(0.3)	3.5 (0.3)	4.1 (0.2)	G = 0.0442
African-American	3.0 (0.4)	2.6 (0.3)	2.8 (0.3)	E = 0.0007
Gender Means	3.8 (0.2)	3.1 (0.2)	3.4	GxE = 0.2716

G = gender effect, E = ethnicity effect, GxE = gender by ethnicity interaction.