Differences in Vascular Reactivity Between Men and Women

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The purpose of this study was to compare the gender- and age-related differences in vascular reactivity in healthy men and women across a wide age range. Fifty-seven men and 61 women between 20 and 89 years of age, free of cardiovascular disease and risk factors, were categorized into younger (20–39 years), middle-aged (40–59 years), and older (60–89 years) age groups. Subjects were characterized on body weight and height, body mass index (BMI), and calf blood flow under resting, postocclusive reactive hyperemic (PORH), and maximal hyperemic conditions in the lower extremity with use of venous occlusion mercury strain-gauge plethysmography. Similar baseline characteristics were observed among age groups, whereas men had greater body weight ($p < 0.05$), higher BMI values ($p < 0.05$), and a trend toward higher ankle-brachial index (ABI) values ($p = 0.054$) than women. While calf blood flow measurements were similar for men and women at rest and at maximal hyperemic conditions, women had a greater percentage change in calf blood flow from rest to PORH than men ($p = 0.046$). After adjusting for body weight, BMI, and ABI, the percentage change in calf blood flow from rest to PORH was no longer significantly higher in the women ($p > 0.05$). Furthermore, the percentage change in calf blood flow from rest to PORH was negatively related to body weight ($r = -0.30$, $p < 0.01$) and to BMI ($r = -0.26$, $p < 0.01$) in the men and women. No differences ($p > 0.05$) in the calf blood flow measures were observed among the age groups. In a healthy cohort free of cardiovascular disease, increased BMI accounted for poorer vascular reactivity in men compared to women regardless of age.

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Introduction

Advancing age has a profound effect on the structure and function of blood vessels and is a recognized risk factor for cardiovascular disease.[1] Many of the changes experienced by the vascular system with age affect the ability of the vessels to respond to changes in blood flow in response to stimuli or in the maintenance of homeostasis through endothelium-dependent vasodilation. It has been reported that reduced endothelial vasodilatory function occurs in atherogenesis before histologic and angiographic evidence of atherosclerosis.[2,3] In addition, impaired endothelium-dependent vasodilation is a common characteristic of several atherosclerotic risk factors including diabetes,[4] hypertension,[5] dyslipidemia,[6] and aging,[7] as well as all cardiovascular risk factors.[8] These conditions that occur with declining endothelial function increase the susceptibility for the development of vasospasm, thrombus formation, and myocardial infarction.[1]

Aging is also a risk factor for the development of cardiovascular disease due to structural and functional changes that occur in the vasculature.[1] It has been suggested that endothelial dysfunction begins before any detectable structural changes in the arterial wall during middle age.[9] The age-related decline in vascular function is different between men and women,[9] as men lose vasodilatory capacity gradually over time, while women experience rapid declines around the age of menopause.[5,7]

Numerous investigations have examined the declines in vascular reactivity with age,[1,7,10-15] but few have examined the effect of gender.[7,9] Furthermore, adiposity may partially explain differences in vascular reactivity between men and women of various age groups, as obesity and body fat distribution impair endothelium-dependent vasodilation.[16] However, little attention has focused on the interaction between age and gender on vascular reactivity, and whether this interaction is affected by adiposity. Therefore, the primary purpose of this study was to compare the gender-related differences in vascular reactivity in healthy men and women across a wide age range. In addition, the role of body mass index (BMI) on vascular reactivity was also assessed to provide insight on how fatness may affect vascular tone.

Methods

Subjects

A total of 57 men and 61 women between 20 and 89 years of age who were ambulatory with no functional limitations were categorized into younger (20–39 years), middle-aged (40–59 years), and older (60–89 years) age groups. All subjects were evaluated at the Department of Health and Exercise Sciences Vascular Laboratory at the University of Oklahoma, Norman campus. Subjects were recruited from local newspaper advertisements, flyers, and via a mass e-mail message to faculty and staff of the University of Oklahoma. Subjects were excluded for the following conditions: (1) cognitive dysfunction, measured by a score below 24 on the minimental state examination questionnaire; (2) cardiovascular disease risk factors and comorbid conditions that included diabetes, hypertension, hyperlipidemia, coronary artery disease, peripheral arterial disease, stroke, myocardial infarct, arterial revascularization, and current smoking; and (3) other mobility-limiting diseases or conditions. The procedures used in this study were approved by the Institutional Review Board at the University of Oklahoma. Written informed consent and a research privacy form were obtained from each subject before the investigation.

Measurements

Medical History. Demographic information, self-reported smoking habits, cardiovascular risk factors, and comorbid conditions were obtained by using a medical history questionnaire before collection of the vascular measurements. In addition, height was obtained by use of a stadiometer, weight was recorded from a physician scale, and BMI was calculated as: weight (kg)/height (m^2). Blood pressure and heart rate were measured with a Critikon automated Dinamap sphygmomanometer following 10 minutes of supine rest, and ankle/brachial index (ABI) was obtained by Doppler ultrasound.[17,18]

Calf Blood Flow. Calf blood flow was obtained under resting, reactive hyperemic, and maximal hyperemic conditions in the lower extremity by use of venous occlusion mercury strain-gauge plethysmography.[19] Subjects rested supine for 10 minutes, after which 5 measures were taken and averaged. Reactive hyperemia was then performed by inflating a thigh blood pressure cuff to at least 200 mm Hg to induce arterial occlusion for 3 minutes. Measurement of postocclusive reactive hyperemia (PORH) calf blood flow was obtained within the first minute following the 3-minute occlusion. Following the PORH calf blood flow measurement, a maximal hyperemic test was performed by inflating the thigh cuff to at least 200 mm Hg while subjects stood and performed heel raises for as long as they could tolerate. Maximal hyperemic calf blood flow was obtained within the first minute following the combined arterial occlusion and ischemic exercise. With use of these procedures, the test-retest intraclass reliability coefficient is $R = 0.86$ for calf blood flow.[19]

Statistical Analyses

Before statistical tests, data were analyzed for normality and to determine whether outlying data points existed. To determine the effects of age, gender, and the age by gender interaction on the clinical characteristics and the vascular measurements, a 2-factor (ie, age by gender) analysis of variance (ANOVA) was performed using the SPSS statistical package (version 11.5). A 2-factor analysis of covariance (ANCOVA) was performed to assess group differences in the vascular measurements after controlling for differences in clinical characteristics. Post-hoc independent t tests with Bonferroni adjustment to control for type 1 error rate were performed following the ANOVA and ANCOVA procedures to further evaluate mean differences between groups. Pearson correlation coefficients were also calculated to assess the relationships among weight, BMI, and hemodynamic measurements. Level of significance was set at $p < 0.05$. Measurements are presented as means ± standard deviations.

Results

Baseline characteristics (Table I) were similar across age and gender groups, with the exception that men had greater body weight ($p < 0.001$) and BMI ($p = 0.043$) than women. Pairwise comparisons found that men had greater body weight than women ($p < 0.017$) for the middle-aged and older age groups.

Calf blood flow measured at rest was similar ($p > 0.05$) between men and women, and among the 3 age groups (Table II). A trend was observed ($p = 0.072$) for women to have higher measured values of PORH calf blood flow compared to men of similar age. Women had a greater percentage change in calf blood flow from rest to PORH than men ($p = 0.046$). Maximal calf blood flow and the percentage change in calf blood flow from rest to maximal hyperemic conditions were similar ($p > 0.05$) between men and women and among the 3 age groups.

The vascular measurements adjusted for body weight, BMI, and ABI are shown in Table III. The percentage change in calf blood flow from rest to PORH was no longer significantly higher in the women ($p > 0.05$), and the trend for a higher absolute value of PORH calf blood flow in the women disappeared as well ($p > 0.05$). The adjusted PORH calf blood flow showed a tendency to decline with advancing age ($p = 0.075$). The adjusted maximal calf blood flow measurements remained similar ($p > 0.05$) between men and women and among the 3 age groups.

Table IV displays the correlation coefficients between clinical and hemodynamic variables. BMI and body weight were both negatively correlated with calf blood flow measured at rest, the percentage change in calf blood flow from rest to PORH, maximal calf blood flow, and the percentage change in calf blood flow from rest to maximal hyperemia. Neither BMI nor body weight was significantly correlated with PORH calf blood flow ($p > 0.05$), and age was not correlated with any of the calf blood flow measurements ($p > 0.05$).

Discussion

The major findings of this investigation were the following: (1) younger, middle-aged, and older women had a greater percentage change in calf blood flow from rest to PORH than men; (2) after adjustment for body weight, BMI, and ABI, the gender differences in the percentage change in calf blood flow from rest to PORH were no longer evident; and (3) BMI was negatively and significantly related to the percentage changes in calf blood flow from rest to PORH and maximal hyperemia, and to the absolute calf blood flow value obtained during maximal hyperemia

Our findings that men have impaired vascular reactivity compared to women do not agree with previous reports.[7,9] In these studies, men and women had similar vascular measurements at young and middle age,[9] suggesting that vascular reactivity is preserved through middle age in both men and women and that vascular reactivity does not decline with age in premenopausal women.[7] Both of these studies had large sample sizes and used techniques similar to the present investigation to measure vascular reactivity. Although BMI was shown to negatively correlate with the amount of vasodilation in men,[7] vascular reactivity measures were not adjusted for BMI and are difficult to compare with this study. By controlling for BMI, we found that the gender differences in vascular reactivity are no longer evident, suggesting that adiposity levels contribute to the variations in vascular reactivity seen between men and women at each age group.

Table I. Clinical characteristics of younger, middle-aged, and older men and women. Values are means ± standard deviations.

Variable	Men	Women	Significance From ANOVA
Age, yr			
Younger group	29 ±5	30 ±6	Age; p < 0.001
Middle-aged group	49 ±6	50 ±6	Gender; p = 0.894
Older group	71 ±7	70 ±7	Age × gender; p = 0.709
Weight, kg			
Younger group	82.5 ±13.0	72.3 ±23.8	Age; p = 0.854
Middle-aged group	91.5 ±16.6	67.0 ±11.3*	Gender; p < 0.001
Older group	84.3 ±14.6	71.2 ±14.7*	Age × gender; p = 0.102
BMI			
Younger group	26.8 ±4.2	25.9 ±6.2	Age; p = 0.451
Middle-aged group	29.4 ±5.2	26.1 ±4.0	Gender; p = 0.043
Older group	27.7 ±3.5	26.2 ±5.7	Age × gender; p = 0.534
Rest ABI			
Younger group	1.14 ±0.14	1.09 ±0.10	Age; p = 0.295
Middle-aged group	1.16 ±0.10	1.14 ±0.11	Gender; p = 0.054
Older group	1.18 ±0.10	1.13 ±0.08	Age × gender; p = 0.678

Sample sizes of the groups are as follows: younger men (n = 19), younger women (n = 15), middle-aged men (n = 21), middle-aged women (n = 23), older men (n = 17), older women (n = 23). *Significantly different from men (p < 0.017). ABI = ankle brachial index; ANOVA = analysis of variance; BMI = body mass index.

BMI appears to be an important factor explaining differences in vascular reactivity in healthy men and women across a wide age range. This notion is supported by our findings that (1) men had higher BMI values and reduced vascular reactivity than women, (2) BMI was indirectly related to vascular reactivity, and (3) no difference in vascular reactivity existed between men and women after adjusting for BMI, body weight, and ABI. These findings suggest that the poorer vascular reactivity observed in men may be due to their greater adipose tissue. Our finding agrees with a previous report showing that overweight and obese individuals have altered vascular reactivity, although the mechanisms are not clear.[20] Other studies have found that BMI is inversely related to blood flow measurements[20-23] and endothelium-dependent vasodilation,[9] whereas other studies have found that BMI is related to arterial stiffness,[20] elevated blood viscosity,[21] and increased platelet aggregation and arterial thrombosis.[22] One possible mechanism for the adipose-mediated endothelial dysfunction is that increased concentrations of leptin result in declines in endothelial nitric oxide production.[23]

Age did not influence vascular reactivity in men and women in the present study, as no differences were found among the 3 age groups. Our finding supports a previous report in which age did not affect vascular reactivity in men,[9] suggesting that factors associated with age, such as BMI, have greater impact on vascular reactivity than age per se. Furthermore, the lack of an age effect on vascular reactivity in women lends ad-

Table II. Blood flow measurements in younger, middle-aged, and older men and women. Values are means ± standard deviations.

Variable	Men	Women	Significance From ANOVA
Rest blood flow (mL/100 mL·min^{-1})			
Younger group	3.83 ±1.81	3.40 ±1.74	Age; p = 0.646
Middle-aged group	2.98 ±1.39	3.18 ±1.16	Gender; p = 0.632
Older group	2.96 ±1.37	3.88 ±4.83	Age × gender; p = 0.534
PORH blood flow (mL/100 mL·min^{-1})			
Younger group	9.80 ±5.38	10.55 ±6.32	Age; p = 0.128
Middle-aged group	6.55 ±5.42	10.18 ±7.04	Gender; p = 0.072
Older group	6.68 ±4.60	8.16 ±4.83	Age × gender; p = 0.514
PORH % Δ from rest			
Younger group	162 ±129	225 ±162	Age; p = 0.259
Middle-aged group	123 ±159	230 ±199	Gender; p = 0.046
Older group	130 ±153	139 ±119	Age × gender; p = 0.362
Maximal blood flow (mL/100 mL·min^{-1})			
Younger group	26.63 ±12.25	25.96 ±10.34	Age; p = 0.162
Middle-aged group	18.44 ±9.44	24.98 ±11.40	Gender; p = 0.515
Older group	23.41 ±12.77	21.53 ±7.44	Age × gender; p 0.167
Maximal % Δ from rest			
Younger group	669 ±609	843 ±640	Age; p = 0.709
Middle-aged group	560 ±326	792 ±612	Gender; p = 0.292
Older group	705 ±546	613 ±355	Age × gender; p = 0.347

Sample sizes of the groups are as follows: younger men (n = 19), younger women (n = 15), middle-aged men (n = 21), middle-aged women (n = 23), older men (n = 17), older women (n = 23). ANOVA = analysis of variance; PORH = postocclusive reactive hyperemia.

ditional support that women who have similar BMI values also have similar vascular reactivity regardless of their age.

Although the results of this study suggest that differences in vascular reactivity between men and women were related to differences in BMI and that age had minimal impact, several limitations exist. The cross-sectional design of this study does not imply a cause-and-effect relationship between vascular reactivity and BMI. Additional research is needed to further examine the relationship between vascular reactivity and adiposity by using more precise measurements of body fat than of BMI. Furthermore, a longitudinal research design examining change in vascular reactivity in men and women as they age would provide a more definitive assessment of the influence of age on vascular reactivity in men and women. Strengths of this study include recruiting men and women with a wide age range, as well as having sufficient sample size in the various groups. Based on the findings of this study, peripheral vascular reactivity is affected by BMI, suggesting that weight management

Table III. Adjusted blood flow measurements in younger, middle-aged, and other men and women. Values are means ± standard deviations.

Variable	Men	Women	Significance From ANCOVA
Rest blood flow (mL/100 mL·min^{-1})			
Younger group	3.94 ±2.61	3.72 ±2.53	Age; p = 0.331
Middle-aged group	2.68 ±2.74	3.24 ±2.83	Gender; p = 0.465
Older group	2.98 ±2.58	3.99 ±2.59	Age × gender; p = 0.598
PORH blood flow (mL/100 mL·min^{-1})			
Younger group	10.35 ±6.06	11.21 ±5.87	Age; p = 0.075
Middle-aged group	7.35 ±6.35	9.31 ±6.57	Gender; p = 0.454
Older group	7.35 ±5.98	7.75 ±5.98	Age × gender; p = 0.836
PORH % Δ from rest			
Younger group	167 ±164	226 ±158	Age; p = 0.269
Middle-aged group	150 ±172	212 ±177	Gender; p = 0.379
Older group	147 ±161	128 ±161	Age × gender; p = 0.458
Maximal blood flow (mL/100 mL·min^{-1})			
Younger group	26.78 ±11.10	24.88 ±10.53	Age; p = 0.302
Middle-aged group	19.98 ±11.48	23.98 ±11.88	Gender; p = 0.915
Older group	24.23 ±10.70	21.28 ±10.76	Age × gender; p = 0.305
Maximal % Δ from rest			
Younger group	635 ±498	711 ±482	Age; p = 0.934
Middle-aged group	597 ±522	799 ±540	Gender; p = 0.561
Older group	696 ±492	623 ±491	Age × gender; p = 0.452

Values were adjusted for body weight, body mass index, and ankle/brachial index.

Sample sizes of the groups are as follows: younger men (n = 19), younger women (n = 15), middle-aged men (n = 21), middle-aged women (n = 23), older men (n = 17), older women (n = 23). ANCOVA = analysis of covariance; PORH = postocclusive reactive hyperemia.

Table IV. Correlation coefficients between clinical and hemodynamic measurements.

	Rest Calf Blood Flow	PORH Blood Flow	% Increase From Rest	Max Blood Flow	% Increase From Rest
Age	–0.038	–0.151	–0.114	–0.164	–0.099
Weight	0.198*	–0.177	–0.300†	–0.265†	–0.265†
BMI	0.274†	–0.093	–0.261†	–0.276†	–0.316†

*Significant correlation coefficient ($p < 0.05$). †($p < 0.01$). BMI = body mass index; Max = maximal; PORH = postocclusive reactive hyperemia.

should be encouraged throughout young, middle, and old age.

Summary and Conclusion

In summary, the major findings of this investigation were the following: (1) younger, middle-aged, and older women had a greater percentage change in calf blood flow from rest to PORH than men; (2) after adjustment for body weight, BMI, and ABI, the gender differences in the percentage change in calf blood flow from rest to PORH were no longer evident; and (3) BMI was negatively and significantly related to the percentage changes in calf blood flow from rest to PORH and maximal hyperemia, and to the absolute value of calf blood flow obtained during maximal hyperemia. We conclude that in a healthy cohort free of cardiovascular disease, increased BMI accounted for poorer vascular reactivity in men compared to women regardless of age.

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