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Peripheral Vascular Endothelial Function Correlates with Exercise Capacity in Women

AYAN R. PATEL, M.D., JEFFREY T. KUVIN, M.D., KATHLEEN A. SLINEY, R.N., WILLIAM M. RAND, PH.D.,* NATESA G. PANDIAN, M.D., RICHARD H. KARAS, M.D., PH.D.†

Division of Cardiology/Department of Medicine, *Department of Biostatistics, and †the Molecular Cardiology Research Institute, Tufts-New England Medical Center, Boston, Massachusetts, USA

Summary

Background: Vascular endothelial function has been observed to correlate with exercise capacity in predominantly male populations. Gender-based differences exist in the clinical course of coronary artery disease, and previous studies indicate that estrogen may influence endothelial function. These observations raise the possibility that the relationship between endothelial function and exercise capacity in women may differ from that in men.

Hypothesis: This study aimed to determine whether peripheral vascular endothelial function correlates with exercise capacity in women.

Methods: Women who were referred for clinically indicated exercise testing with technetium-99 myocardial perfusion imaging were consecutively recruited. To ensure a population free of exercise limitation due to ischemic heart disease, women without myocardial perfusion defects were included for analysis in this study (n = 105). Endothelial function was assessed by brachial artery ultrasound flow-mediated vasodilation (FMD). Exercise capacity was defined as the duration of exercise on a symptom-limited Bruce protocol.

Results: Mean FMD was 11.8 ± 0.6%, and median FMD was 12%. Subjects with an FMD less than the median of 12% had a significantly shorter exercise time than those with FMD ≥ 12% (411 ± 17 vs. 482 ± 24 s, p = 0.014). There was a significant correlation between FMD and exercise time (r = 0.34, p < 0.001). Age and body mass index were additional predictors of exercise time; however, the relationship between FMD and exercise time was independent of these variables.

Conclusion: Brachial artery FMD correlates with exercise capacity in women, even in the absence of ischemic heart disease.

Key words: endothelium, exercise capacity, women

Introduction

Vascular endothelial dysfunction is present in individuals with atherosclerosis and is a predictor of cardiac events in these patients.[1–5] It has been observed that peripheral vascular endothelial function is also abnormal in individuals with heart failure and correlates with exercise capacity in these patients.[6,7] In addition, one prior study, conducted in a predominantly male population, has observed a correlation between endothelial function and exercise capacity in subjects without heart failure or coronary artery disease (CAD).[8] These observations suggest that endothelium-dependent vasodilation and exercise capacity are interrelated. However, most of the currently available data are predominantly from male subjects, and whether peripheral vascular endothelial function correlates with exercise capacity in women is unknown. It has been observed that gender-based differences exist in the clinical course of CAD, suggesting that the pathogenesis of atherosclerosis in women may differ from that in men.[9] In addition, several studies have indicated that estrogen has acute and chronic effects on vascular endothelial function.[10–14] These observations raise the possibility that the relationship between endothelial function and exercise capacity in women may differ from that in men. The purpose of this study was to determine whether brachial artery flow-mediated vasodilation correlates with exercise capacity in women.

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Address for reprints:

Ayan R. Patel, M.D.
Division of Cardiology
Tufts-New England Medical Center
750 Washington Street, Box 32
Boston, MA 02111, USA
e-mail: apatel@tufts-nemc.org

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Methods

Female subjects were recruited from a population of consecutive outpatients who had been referred for clinically indicated exercise myocardial perfusion testing. Reasons for referral for stress testing included chest pain (76%), dyspnea (9%), palpitations (5%), preoperative evaluation (4%), abnormal electrocardiogram (ECG) (2%), dizziness/syncope (2%), and screening for ischemia in patients with cardiac risk factors (2%). Exclusion criteria included inability to exercise, history of coronary artery disease, heart failure, significant valvular disease, or refusal to participate in the study. All subjects underwent symptom-limited exercise treadmill testing on a Bruce protocol, with technetium-99 myocardial perfusion imaging. To avoid potential confounding effects of the presence of ischemic heart disease on exercise time, women who were found to have fixed or reversible perfusion defects on stress testing were excluded from the analysis. Subjects were considered to be free of ischemic heart disease if they had no perfusion defects on stress testing. Left ventricular ejection fraction was determined from gated single-photon emission tomography. Exercise treadmill time was measured in seconds. The protocol was approved by the Tufts-New England Medical Center Institutional Review Board, and written informed consent was obtained for all study subjects.

As described in prior studies,[6, 8, 15] peripheral vasomotor function was assessed by brachial artery ultrasound testing, which was performed according to standard techniques.[16, 17] Subjects fasted overnight prior to testing and abstained from smoking on the day of testing. Longitudinal axis images of the brachial artery were obtained above the antecubital fossa using a 10-MHz linear array vascular transducer (General Electric, Vingmed, System Five, Horten, Norway). A sphygmomanometer cuff (Hokanson, Bellevue, Wash., USA) was placed proximal to the transducer and inflated to suprasystolic pressure for 5 min. Pulsed-wave Doppler recording was obtained immediately after cuff deflation to confirm the presence of reactive hyperemia. The brachial artery was imaged continuously for the first minute after cuff deflation, and the peak hyperemic brachial artery diameter was measured 1 min after cuff deflation. Endothelium-dependent vasodilation was assessed by measuring brachial artery flow-mediated vasodilation (FMD), calculated as [100 × (reactive hyperemia diameter-baseline diameter)/baseline diameter].

After 10 min, repeat baseline arterial diameter measurements were obtained. Sublingual nitroglycerin (400 mcg) was administered, and brachial artery diameter measurements were made 5 min after administration of nitroglycerin. Nitroglycerin was not administered to subjects whose systolic blood pressure was < 90 mmHg or those with a history of nitroglycerin intolerance. Endothelium-independent vasodilation was determined by calculating the percent increase in arterial diameter after nitroglycerin, compared with prenitroglycerin baseline diameter.

Mean values for intra- and interobserver variability of FMD measurements in our laboratory are 1.9 and 2.8%, respectively.

Statistical analysis was performed using Statistical Package for Social Sciences SigmaStat software, version 2.0 (SPSS, Chicago, Ill., USA). Data were assessed for normal distribution, and differences between groups were compared using the Student's *t*-test. Linear regression analysis was performed to assess associations between baseline variables and exercise treadmill time. Multivariate analysis was used to determine the relationship between FMD and exercise treadmill time, and to evaluate for any potential confounding variables. Data are presented as mean values ± standard error of the mean (SEM). A probability value < 0.05 was considered to be statistically significant.

Results

In all, 123 women were enrolled in this study. Eighteen women (15%) were found to have myocardial perfusion defects; these were excluded from analysis to avoid the confounding effects of ischemic heart disease on exercise time. The baseline characteristics of the group of women without ischemic heart disease (n = 105) are shown in Table I. The maximal heart rate achieved was 151 ± 1 beats/min, and percent of age-predicted maximal heart rate was 92 ± 1%. Reasons for termination included fatigue (69%), dyspnea (25%), chest pain (6%), and leg discomfort (2%). Mean baseline brachial artery diameter was 3.2 ± 0.1 mm, hyperemic diameter was 3.6 ± 0.1 mm, and mean FMD was 11.8 ± 0.6%. The median FMD was 12%. The mean nitroglycerin-mediated vasodilation was 23.3 ± 1% (prenitroglycerin diameter = 3.3 ± 0.1 mm, postnitroglycerin diameter = 4.1 ± 0.1 mm). Among premenopausal women (n = 30), mean FMD was

TABLE I Baseline characteristics

	Subjects (n=105)
Age, years (range)	55 ± 1 (34–79)
LVEF, % (range)	65 ± 1 (46–78)
Exercise time (s)	447 ± 14
Diabetes mellitus, n (%)	6 (6)
Hypertension, n (%)	44 (42)
Smoker, n (%)	8 (8)
Hypercholesterolemia, n (%)	46 (44)
Family history CAD, n (%)	61 (58)
Postmenopausal, n (%)	75 (71)
Total cholesterol, mg/dl	211 ± 4
LDL cholesterol, mg/dl	127 ± 5
HDL cholesterol, mg/dl	58 ± 2
ACE inhibitor, n (%)	15 (14)
Nitrates, n (%)	8 (8)
Statin, n (%)	18 (17)
Other lipid Rx, n (%)	8 (8)

Abbreviations: ACE = angiotensin-converting enzyme, CAD = coronary artery disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction.

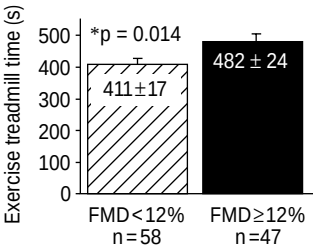

FIG. 1 Exercise treadmill time in women without ischemic heart disease who had flow-mediated vasodilation (FMD) < the median value of 12% (n = 58) and those with FMD ≥ 12% (n = 47).

12.9 ± 1.1%, compared with an FMD of 11.4 ± 0.8% in postmenopausal women (n = 75, p = 0.289). Among the postmenopausal women, there was no significant difference in FMD between those on (n = 17, 11.8 ± 1.6%) and those not on hormone replacement therapy (n = 58, 11.2 ± 0.9, p = NS).

Using the median FMD of 12% as a cut-point, subjects with an FMD ≥ 12% had a significantly longer exercise time than those with FMD < 12% (Fig. 1). Univariate linear regression analysis demonstrated that FMD predicted exercise time ($r = 0.34$, $p < 0.001$). There were insufficient numbers of premenopausal women to perform an analysis of the association between FMD and exercise time in this subgroup. However, in the subgroup of postmenopausal women (n = 75), the relationship between FMD and exercise time remained significant ($r = 0.375$, $p < 0.001$). There was no association between exercise time and the presence of hypertension, diabetes, hypercholesterolemia, or smoking. Linear regression analysis was also used to examine the associations between exercise time and age, left ventricular ejection fraction, and body mass index. Of these variables, age ($r = 0.44$, $p < 0.001$) and body mass index ($r = -0.313$, $p < 0.001$) were additional predictors of exercise time. Multivariate analysis demonstrated that the relationship between FMD and exercise time remained significant ($p = 0.022$) independent of age and body mass index.

Discussion

The results of this study demonstrate that brachial artery FMD correlates with exercise treadmill time in women. Though age and body mass index were additional predictors of exercise capacity, the relationship between endothelial function and exercise capacity was independent of these variables. Previous studies have observed a correlation between peripheral vascular endothelial function and exercise capacity in predominantly male populations in the setting of coronary artery disease, heart failure, and following cardiac transplantation.[7–9, 18] The correlation observed between vasomotor function and exercise capacity in women did not result from the presence of ischemia or left ventricular dysfunction in the current study, as this finding was noted in a population of women free of these disorders.

Previous studies support the concept that there is a complex interaction between exercise capacity and vascular function. For example, existing data indicate that interventions that improve endothelial function may improve exercise capacity.[19–21] Maxwell *et al.* have previously reported that treatment with arginine improves flow-mediated vasodilation and the duration of exercise prior to developing ischemia in subjects with coronary artery disease.[19] In addition, several studies have demonstrated that exercise training improves endothelial function.[8, 20] While the mechanisms of the relationship between endothelial function and exercise have not been fully elucidated, these prior data suggest that vascular function and exercise are interdependent and may influence each other. Thus, while exercise can ameliorate endothelial dysfunction, the resultant improved vascular function may subsequently improve exercise tolerance and cardiac risk. It is interesting that, in addition to its effects on endothelial function, exercise training has also been reported to reduce cardiac events,[22] supporting the link between exercise, endothelial function, and prognosis.

The association between endothelial function and exercise has been most extensively studied in the heart failure population, in whom endothelial function is often impaired.[6, 7, 20, 21, 23] Katz *et al.* observed that nitric oxide synthase inhibition reduced exercise-induced blood flow in normal subjects, but not in patients with heart failure, suggesting that nitric oxide-mediated vasodilation during exercise is impaired in individuals with heart failure.[23] In addition, Hirai *et al.* have reported that inhibition of nitric oxide synthase resulted in reduced blood flow to exercising skeletal muscle in rats.[24] In a small human study, Gilligan *et al.* observed that inhibition of nitric oxide synthase resulted in decreased forearm blood flow during hand-grip exercise.[25] Furthermore, the extent of inhibition of nitric oxide-mediated vasodilation correlated with the degree of decline in exercise blood flow. These observations suggest a mechanistic basis for a correlation between endothelial function and exercise capacity. The current study is the largest investigation to date of the relationship between exercise capacity and endothelial function in women and indicates that this association is present in women in the clinical setting, even in the absence of ischemic heart disease.

Limitations

Information regarding daily exercise level was not available for all subjects, and since exercise training influences endothelial function, it is possible that varying degrees of physical training among our patients may have affected endothelial function. In addition, it is possible that other variables that are not accounted for could have influenced exercise capacity or endothelial function in this patient population. While initial intervention studies suggest a causative relationship between endothelial function and exercise tolerance in men, more extensive studies will be needed to determine whether interventions that improve endothelial function can also enhance exercise

capacity in women. The results of such intervention studies will further elucidate whether endothelial function plays a causative role in determining exercise capacity in women.

Conclusion

Peripheral vascular flow-mediated vasodilation correlates with exercise capacity in women, even in the absence of ischemic heart disease.

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