CLINICAL STUDY

The Acute Effect of Aerobic Exercise on Brachial Artery Endothelial Function in Renal Transplant Recipients

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This study compared the effect of a 30-minute walk on brachial artery endothelial vasodilatation in kidney transplant (KT) recipients and healthy controls (HCs). Endothelial-dependent vasodilatation was measured by ultrasound before and after exercise. The HCs experienced a significant increase in vasodilatation after exercise 1 minute postocclusion when compared with the KT recipients (22%±13% vs 3%±4%; P<.05). Also, the HCs had a significantly higher vasodilatation from pretreadmill walk to post-treadmill walk (1 minute postocclusion) when compared with KT recipients (from 3%±6% to 22%±13% vs 1%±3% to 3%±4%; P<.05). This acute vasodilatory response observed in the HCs may be related to the immediate release of nitric oxide and the combined response to shear stress and exercise. The KT recipients had several coronary artery disease risk factors that may have adversely affected endothelial function. (Prev Cardiol. 2006;9:211–214) ©2006 Le Jacq

Renal transplant recipients are at increased risk of cardiovascular (CV) disease because of an increased prevalence of hypertension, hyperlipidemia, and diabetes. Further, CV disease is the principal cause of death in renal transplant patients.[1–3] Endothelial dysfunction is an early marker of the atherosclerotic process,[4] is associated with CV risk factors, and has been observed in this population.[5]

A single bout of exercise increases arterial dilatation in animals. Cheng et al[6] demonstrated that exercise acutely enhances receptor-mediated vasodilatation in rats by upregulating either endothelium receptor number or affinity. Jen et al[7] reported similar increases in arterial diameter in rats and pigs immediately after exercise and attributed these findings to increases in acetylcholine and NO release.

Data on the acute effects of exercise on endothelial vasoreactivity in humans are sparse. Kingwell and colleagues,[8] using pulse–wave velocity measurements, reported enhanced arterial compliance 30 minutes after a bout of 30 minutes of exercise in healthy young men. Gattullo and colleagues[9] hypothesized that exercise mitigates the vasoconstrictor effects of cardiac risk factors such as hyperlipidemia by stimulating NO synthesis and release in response to acute increases in shear stress and pulse pressure. Finally, Gaenzer et al[10] demonstrated reduced endothelium–dependent brachial artery vasodilatation in smokers when compared with healthy nonsmokers after a single bout of exercise. Regular exercise is routinely recommended for renal transplant patients to reduce their CV disease risk.[11] The present study examined whether exercise acutely improved endothelial-mediated vasodilatation among renal transplant patients.

MATERIALS AND METHODS

Subjects

Eleven renal transplant recipients (8 women and 3 men), and 11 controls (8 women and 3 men) matched by age (30–65 years old), race (8 Caucasian, 2 African American, and 1 Hispanic in each group) and sex, provided informed consent as approved by the Institutional Review Boards of Springfield College and Hartford Hospital and

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were included in the study. The transplant recipients were recruited from the transplant program at Hartford Hospital in Hartford, CT. The controls were recruited from the greater Hartford area. Transplant recipients had received their transplant at least 1 year before the study (mean, 2.9±1.5 years; range, 1–5.6 years) and had no history of CV events.

Subjects were required to be physically inactive and not to have exercised more than 30 minutes, 3 times weekly, in the past 12 weeks. Control subjects with more than 1 CV risk factor or previous history of a CV event and who were taking any CV medications, antioxidant agents, or immunosuppressants were excluded. Transplant recipients with a fistula in the right arm were excluded since the brachial ultrasound was performed on the right arm. Other exclusionary criteria for both groups included any contraindications to exercise,[12] smoking, hypertension, positive human immunodeficiency virus serology, and immunologic conditions that affect endothelial function, such as lupus, rheumatoid arthritis, thyroid disease, and diabetes mellitus.

Procedures

Subjects were asked to refrain from consuming stimulants such as caffeine and any supplements that could have an effect on endothelial function for 24 hours before the testing session. Subjects reported to the Endothelial Function Laboratory at Hartford Hospital after 8 hours of an overnight fast. Phlebotomy was performed using a forearm vein (14 mL). Serum concentrations of fasting cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and C-reactive protein[13] were determined by the Hartford Hospital clinical laboratory. Height was measured using a wall-mounted tape measure. Body weight was determined using a balance beam scale. Body mass index was then calculated for each subject (kg/m^2). Age-predicted maximal heart rate was calculated for each subject. Heart rate was monitored during exercise with a heart rate monitor (Polar Electro Inc, Lake Success, NY). Subjects were instructed on how to use the Rating of Perceived Exertion scale.[14] They were then asked to walk on the treadmill at a Rating of Perceived Exertion of 13, which corresponds to a "somewhat hard effort," for 30 minutes. Heart rate, speed, and inclination of the treadmill were recorded every 5 minutes. We used the heart rate recordings to verify that all subjects were walking at a pace between 70% and 85% of their age-predicted maximal heart rate.

Measurement of Endothelial Function

Endothelial function was determined using high-resolution ultrasound of the brachial artery and ischemic forearm occlusion before and immediately after the 30 minutes of treadmill exercise. For this procedure, subjects rested for 10 minutes in the supine position. A baseline blood pressure was taken in the left arm. The right brachial artery was imaged for a baseline measurement at the antecubital fossa using an Acuson Aspen ultrasonography machine (Acuson Corp, Mountain View, CA). A Hokanson Rapid Cuff Inflator (D.E. Hokanson Inc, Bellevue, WA) was placed over the right forearm, below the elbow, and inflated 60–80 mm Hg above the resting systolic pressure for 5 minutes. The occluding pressure was released and the artery imaged 1, 3, and 15 minutes later. Arterial cross-sectional diameter was measured from the near endothelial–luminal surface to the distal luminal surface. Endothelial function was quantified as the percent change in brachial artery diameter (vasodilatation) by dividing the change in diameter by the baseline value. B-mode scans of the right brachial artery were obtained by one experienced technician and analyzed by a different technician who was unaware of each subject's group assignment and whether the scan was before or after exercise.

Statistical Analyses

Descriptive statistics were calculated for anthropometrics and dependent variables. Statistical analyses using independent group *t* tests were performed to determine group differences at pretest for endothelial function, age, height, weight, BMI, percent body fat, fasting cholesterol, HDL, LDL, triglycerides, and C-reactive protein.

A 2 × 2 × 3 (group × occasion × time) mixed factorial analysis of variance was conducted to analyze the dependent variable, percent change in brachial artery diameter. The analysis included 1 independent variable and 2 repeated-measures factors. The independent variable group had 2 levels: posttransplant and controls. The first repeated-measures factor, occasion, also had 2 levels: pre- and post-treadmill walk. The second repeated-measures factor, time, included 3 levels: percent change diameter after 1, 3, and 15 minutes postocclusion. Tukey post hoc comparisons were conducted following significant interactions. A level of $P<.05$ was considered statistically significant.

RESULTS

The groups did not differ significantly in baseline endothelial function, age, and height. Although weight and body mass index were higher in renal transplant recipients, the differences were not significant (Table I). Furthermore, renal transplant recipients had significantly higher triglyceride levels (86.6 vs 79.1 mg/dL; $P<.05$); however, HDL-C, LDL-C, and C-reactive protein values were not significantly different between the groups (Table II). Descriptive statistics for percent change of endothelial-mediated vasodilatation at 1, 3, and 15 minutes before and after exercise are shown in Table III. The healthy group experienced a significant

increase in vasodilatation after the exercise bout 1-minute postocclusion when compared with the transplant group (22%±13% vs 3%±4%; $P<.05$). Also, the healthy group had a significantly higher vasodilatation from pre- to post-treadmill walk (1 minute postocclusion) when compared with the transplant group (from 3%±6% to 22%±13% vs 1%±3% to 3%±4%; $P<.05$). Baseline and pre-exercise percent change of endothelial-mediated vasodilatation were not statistically different within and between groups. Endothelial-mediated vasodilatation at 3 and 15 minutes postocclusion before and after exercise was not statistically different within groups.

DISCUSSION

In this double-blinded, controlled study, even though not statistically significant, physiologically, pre-exercise endothelial-mediated vasodilatation was lower in renal transplant recipients compared with healthy controls. Furthermore, whereas a single bout of exercise caused an increased endothelial-mediated vasodilatory response in the healthy control subjects, similar exercise had little effect on endothelial-mediated vasodilatory response in the transplant patients.

Our study makes an important contribution to research conducted on the effects of a single bout of aerobic exercise on endothelial-mediated vasodilatation in humans. Gaenzer et al[10] demonstrated flow-mediated dilation induced by a single bout of cycling in nonsmoking healthy subjects. Endothelial shear stress is caused by the exercise-induced increase in blood flow.[15–20] This shear stress is sensed by the endothelium, resulting in vasodilatation of the vessel. Several investigators have suggested that the primary underlying mechanism for the exercise-induced vasodilatation is the release of NO and other contributory mechanisms that include inhibition of peripheral adrenergic vasoconstriction and the release of prostacyclin.[10,17–20]

In contrast to an increased endothelial-mediated vasodilatory response in the healthy subjects, we observed no change in the renal transplant patients in the present study. Renal transplant patients in the present study had more CV risk factors than the control subjects. The CV risk factors included positive family history of premature CV disease, underlying renal disease, and a history of taking immunosuppressive medicines with side effects that include weight gain, hyperlipidemia, hypertension, and diabetes mellitus. These differences in CV risk factors could account for the differences in endothelial-mediated vasodilatation. CV risk factors increase oxidative stress and superoxide anions, which inactivate NO. Gaenzer et al[10] demonstrated that cigarette smoking, which is a risk factor for CV disease, contributed to the impaired flow-mediated dilation after one bout of exercise. Other potential mechanisms that may explain the abnormal endothelial responses in patients with CV risk factors include an increase in proinflammatory, prothrombotic, and growth-promotion factors that ultimately reduce NO availability in the vascular smooth muscle, resulting in reduced vasodilatation, and even enhanced vasoconstriction.[14–18] The impairment in endothelial-mediated vasodilatation after exercise in the renal transplant patients implies evidence for endothelial dysfunction, which is an early marker of the atherosclerotic process.

There were several limitations encountered in this study that should be addressed in future research. These included the inability to control for lipid-lowering and antihypertensive medications in the transplant patients and the small sample size.

Table I. Age and Anthropometric Measurements in the Control and Transplant Groups, Mean ± SD

Parameter	Control (n=11)	Transplant (n=11)	P*
Age, y	47.6±6.7	47.4±7.0	.95
Height, cm	165.0±0.1	1.7±0.1	.75
Weight, kg	68.2±11.5	81.7±18.8	.06
Body mass index, kg/m^2	24.9±3.5	29.4±6.3	.05

*Based on nonpaired *t* tests

Table II. Serum Lipids and C-Reactive Protein Levels and Blood Pressure in the Control and Transplant Groups, Mean ± SD

Parameter	Control (n=11)	Transplant (n=11)	P
Fasting cholesterol, mg/dL	173±26	179±15	.5
High-density lipoprotein, mg/dL	65±18	65±21	.97
Low-density lipoprotein, mg/dL	108±17	100±19	.3
Triglycerides, mg/dL	79±17	151±87	.01
C-reactive protein, mg/dL	0.2±0.2	0.3±0.3	.26
Systolic blood pressure, mm Hg	117±5	121±5	.67

Table III. Percent Change in Endothelial Diameter of Control and Transplant Groups Before and After Treadmill Walk

	Change in Diameter, Mean % ± SD	
Postocclusion Time, min	Before Treadmill	After Treadmill
Control (n=11)		
1	3.4±5.9	22.3±13.2
3	2.4±6.1	20.5±13.1
15	–1.3±7.0	15.3±13.4
Transplant (n=11)		
1	0.9±3.1	3.3±4.4
3	–1.0±6.9	2.3±5.0
15	–0.5±6.0	2.5±6.5

CONCLUSIONS

The present study demonstrated an increased endothelial-mediated vasodilatory response in healthy individuals after a single bout of exercise at a moderate intensity. The increased endothelial-mediated vasodilatory response may represent an immediate mechanism by which vascular compliance increases with an isolated bout of exercise. The present study also demonstrated that renal transplant patients did not show an enhanced endothelial-mediated vasodilatory response to an isolated exercise session. Further research is required to identify the mediators of this effect and to determine whether the abnormal endothelial-mediated vasodilatory response in the transplant patients can be normalized by aggressive risk factor management or exercise.

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