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Heart Failure Etiology Affects Peripheral Vascular Endothelial Function After Cardiac Transplantation

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OBJECTIVES The goal of this study was to examine the effect of heart failure etiology on peripheral vascular endothelial function in cardiac transplant recipients.

BACKGROUND Peripheral vascular endothelial dysfunction occurs in patients with heart failure of either ischemic or nonischemic etiology. The effect of heart failure etiology on peripheral endothelial function after cardiac transplantation is unknown.

METHODS Using brachial artery ultrasound, endothelium-dependent, flow-mediated dilation (FMD) was assessed in patients with heart failure with either nonischemic cardiomyopathy (n = 10) or ischemic cardiomyopathy (n = 7), cardiac transplant recipients with prior nonischemic cardiomyopathy (n = 10) or prior ischemic cardiomyopathy (n = 10) and normal controls (n = 10).

RESULTS Patients with heart failure with either ischemic cardiomyopathy or nonischemic cardiomyopathy had impaired FMD (3.6 ± 1.0% and 5.1 ± 1.2%, respectively, p = NS) compared with normal subjects (13.9 ± 1.3%, $p < 0.01$ compared with either heart failure group). In transplant recipients with antecedent nonischemic cardiomyopathy, FMD was markedly higher than that of heart failure patients with nonischemic cardiomyopathy (13.0 ± 2.4%, $p < 0.001$) and similar to that of normal subjects (p = NS). However, FMD remained impaired in transplant recipients with prior ischemic cardiomyopathy (5.5 ± 1.5%, p = 0.001 compared with normal, p = 0.002 vs. transplant recipients with previous nonischemic cardiomyopathy).

CONCLUSIONS Peripheral vascular endothelial function is normal in cardiac transplant recipients with antecedent nonischemic cardiomyopathy, but remains impaired in those with prior ischemic cardiomyopathy. In contrast, endothelial function is uniformly abnormal for patients with heart failure, regardless of etiology. These findings indicate that cardiac transplantation corrects peripheral endothelial function for patients without ischemic heart disease, but not in those with prior atherosclerotic coronary disease. (J Am Coll Cardiol 2001;37:195–200) © 2001 by the American College of Cardiology

Heart failure is increasing in incidence and prevalence in the U.S. and is associated with substantial morbidity (1). Impaired functional status due to decreased exercise tolerance contributes significantly to this morbidity. Paradoxically, the impairment in exercise tolerance correlates poorly with either central hemodynamic indexes or the degree of left ventricular dysfunction (2,3). Recent evidence indicates that peripheral factors play an important role in limiting exercise tolerance in patients with heart failure (4–8). Since the vascular endothelium plays a critical role in regulating vasomotor tone, vascular endothelial dysfunction in patients with heart failure may result in a diminished vasodilatory response to exercise and thereby contribute to impaired exercise tolerance (3,8–11).

Abnormal vascular endothelial function has been described in both the coronary and peripheral circulations, and it occurs in patients with heart failure with either ischemic or nonischemic cardiomyopathies (9,12–16). Since heightened peripheral vasomotor tone contributes to deranged hemodynamics in heart failure, the ability to reverse endothelial dysfunction has important therapeutic implications. A variety of interventions have been reported to improve vascular endothelial function in heart failure, including angiotensin-converting enzyme (ACE) inhibitor therapy, physical conditioning, vitamin C, and L-arginine (17–21). One definitive therapeutic intervention for patients with severe heart failure is cardiac transplantation. However, exercise tolerance often remains impaired in cardiac transplant recipients despite normalization of ventricular systolic function. While endothelial function has been reported to improve after cardiac transplantation (21,22), the influence of heart failure etiology on improvement of endothelial dysfunction has not previously been considered. We hypothesized that the reversibility of vascular endothelial dysfunction after cardiac transplantation is related to heart failure etiology. Differences in the reversibility of endothelial dysfunction may, in turn, contribute to variability in the improvement in functional capacity. As a first step toward addressing this hypothesis, we undertook this study to compare the effect of cardiac transplantation on peripheral

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
FMD = flow-mediated dilatation
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association

vascular endothelial function in patients with a history or either ischemic or nonischemic cardiomyopathy.

METHODS

Patients. Study subjects were recruited from the Heart Failure and Cardiac Transplantation Center at New England Medical Center. Patients were eligible for this study if they were clinically stable, were <70 years old and had either New York Heart Association (NYHA) class III heart failure and a left ventricular ejection fraction (LVEF) of ≤35% or were cardiac transplant recipients. Transplant recipients were either outpatients undergoing routine evaluation after transplant (n = 14) or stable patients admitted for routine annual evaluation after transplant (n = 6). Heart failure patients were either outpatients (n = 16) or inpatients who were clinically stable and at their baseline heart failure status (n = 1). No patients were receiving investigational drugs at the time of the study. Patients who were clinically unstable or on intravenous vasodilator or inotropic therapy were excluded. Left ventricular ejection fraction was determined by radionuclide ventriculography, echocardiography, left ventricular cineangiography or gated single-photon emission computed tomography. All heart failure patients in the ischemic heart disease group had a history of prior myocardial infarction, and the presence of coronary artery disease was confirmed by coronary angiography in six of seven patients. One patient, in whom coronary angiography was not performed, had undergone a thallium myocardial perfusion study that was consistent with ischemic heart disease. The absence of coronary artery disease in heart failure patients with nonischemic cardiomyopathy was confirmed by coronary angiography in 9 of 10 patients. The patient with nonischemic cardiomyopathy who did not undergo coronary angiography was subsequently found to have no evidence of ischemic heart disease by pathologic examination of the heart after transplantation. Transplant recipients were clinically stable and had undergone transplant at least three months before enrollment. The etiology of heart failure in transplant recipients was confirmed by coronary angiographic findings before transplantation or by pathologic examination of the explanted heart. Control subjects were recruited from a group of healthy volunteers and had no history of cardiac disease or cardiac risk factors. No subjects who smoked within the past 60 days were included. All patients enrolled in the study gave written informed consent. The study was approved by the Human Investigation Review Committee at the New England Medical Center.

Vasomotor studies. Using previously validated techniques, brachial artery imaging was performed with a 7.5 MHz linear array transducer and ultrasound machine (HDI 5000, ATL, Bothell, Washington, or SSH-140A/C, Toshiba, Japan) (23–25). Studies were performed in a quiet room with the patient lying recumbent. The transducer was placed 2 cm above the antecubital fossa, and the right brachial artery was imaged in a longitudinal view. After optimal longitudinal images were obtained, baseline brachial artery diameter was measured as the distance between the anterior and posterior intima-blood interfaces. A sphygmomanometer cuff (Hokanson, Bellevue, Washington) placed proximal to the transducer was inflated to 200 mm Hg for 5 min. One minute after cuff deflation, brachial artery diameter during reactive hyperemia was obtained. After 10 min, brachial artery measurements were repeated to establish a second baseline. Sublingual nitroglycerin 400 μg was subsequently administered, and repeat brachial artery diameter measurements were recorded after 3 and 5 min to obtain the maximal arterial diameter. All images were recorded on VHS videotape. Flow-mediated dilation (FMD) was calculated as the percent change in brachial artery diameter from baseline to reactive hyperemia: [(reactive hyperemia diameter-baseline diameter)/baseline diameter] × 100. Brachial artery dilation after nitroglycerin was calculated as the percent change in brachial artery diameter from prenitroglycerin baseline to after administration of nitroglycerin. Endothelium-dependent vasodilation was assessed by measuring FMD during reactive hyperemia. Endothelium-independent vasodilation was measured as change in arterial diameter after nitroglycerin. Two independent observers who were blinded to the patient's clinical data interpreted the studies.

Reproducibility. Analysis of reproducibility of brachial artery studies in our laboratory has demonstrated a mean difference in FMD of 1.9% for intraobserver variability and 2.8% for interobserver variability.

Statistical analysis. Comparisons of brachial artery reactivity between ischemic cardiomyopathy, nonischemic cardiomyopathy and normal control subjects were made using one-way analysis of variance, followed by Student-Newman-Keuls tests for multiple pairwise comparisons. In both the heart failure and posttransplant populations, baseline characteristics of patients with a history of ischemic cardiomyopathy and those with a history of nonischemic cardiomyopathy were compared using a Student *t*-test for continuous variables. Noncontinuous variables were compared using Fisher exact test. Data are presented as mean ± SEM, and differences were considered to be significant at a p value <0.05.

RESULTS

Baseline characteristics. Peripheral vascular endothelial function was assessed in 17 patients with NYHA class III

Table 1. Baseline Characteristics of Heart Failure Patients*

	Ischemic (n = 7)	Nonischemic (n = 10)
Age (yrs)	56 ± 3	54 ± 2
Duration of heart failure (yrs)	4.2 ± 1.3	5.3 ± 2.0
LVEF (%)	19 ± 2	17 ± 1
Hypertension (#)	1	1
Diabetes (#)	2	0
History of smoking (#)	5	5
Total cholesterol (mg/dl)	151 ± 8	166 ± 13
HDL (mg/dl)	32 ± 2	41 ± 4
LDL (mg/dl)	89 ± 5	107 ± 11
Triglycerides (mg/dl)	139 ± 42	138 ± 19
ACE-inhibitor use (#)	6	10
Mean captopril equivalent dose (mg/day)	156 ± 15	135 ± 31
ARB use (#)	1†	0
Lipid-lowering therapy (#)	5	2

*p = NS for all comparisons; †treated with losartan 50 mg daily.
ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction.

heart failure, 20 heart transplant recipients and 10 normal controls.

Patients with heart failure. Baseline characteristics of the patients with heart failure are shown in Table 1. The heart failure group included 7 patients with ischemic cardiomyopathy and 10 patients with nonischemic cardiomyopathy, with a mean LVEF of 19 ± 1% and 17 ± 1%, respectively (p = NS). The heart failure population included two postmenopausal women, both of whom had nonischemic cardiomyopathy and were not receiving hormone replacement therapy.

There were no significant differences between ischemic and nonischemic cardiomyopathy patients in baseline characteristics, including age, prevalence of diabetes and hypertension, history of prior smoking, total cholesterol levels, low-density lipoprotein cholesterol levels, mean LVEF or treatment with ACE inhibitors. As expected, there was a trend towards a higher frequency of lipid-lowering therapy for patients with ischemic heart disease (p = 0.06). In addition, there was a trend towards lower high-density lipoprotein cholesterol levels among patients with ischemic cardiomyopathy (p = 0.06).

Transplant recipients. Baseline characteristics for cardiac transplant recipients are shown in Table 2. The cardiac transplant group comprised 10 patients with a history of ischemic cardiomyopathy and 10 patients with a history of nonischemic cardiomyopathy. There were no women in the ischemic cardiomyopathy transplant group, and there were two postmenopausal women in the nonischemic group, one of whom was receiving transdermal estrogen replacement. None of the transplant recipients were current smokers. Cardiac transplant recipients were studied at an average of 33 ± 8 months after transplant. The mean pretransplant LVEF for this group was 19.8 ± 2.6% for patients with a history of ischemic cardiomyopathy and 15.7 ± 1.7% for patients with a history of nonischemic cardiomyopathy (p = NS). No patients received lymphocytolytic therapy as induction treatment. Five patients with prior ischemic cardiomyopathy and four patients with prior nonischemic cardiomyopathy had a history of rejection requiring therapy (p = NS), but none of these patients had evidence of rejection at the time of the study. Six patients (60%) with a history of ischemic cardiomyopathy and four patients (40%) with a history of nonischemic cardiomyopathy had participated in a rehabilitation program after undergoing cardiac transplant (p = NS). Five patients (50%) with a history of ischemic cardiomyopathy and five patients (50%) with prior nonischemic cardiomyopathy were receiving prednisone therapy at the time of the study (p = NS). One patient (10%) with prior ischemic cardiomyopathy and two patients (20%) with prior nonischemic cardiomyopathy were treated with mycophenolate (p = NS). Seven patients (70%) with a history of ischemic cardiomyopathy and seven patients (70%) with prior nonischemic cardiomyopathy were treated with azathioprine (p = NS). Among heart transplant recipients, there were no significant differences in baseline characteristics between ischemic cardiomyopathy and nonischemic cardiomyopathy patients.

Table 2. Baseline Characteristics of Transplant Recipients*

	Ischemic (n = 10)	Nonischemic (n = 10)
Age (yrs)	54 ± 3	50 ± 4
Time since transplant (months)	30 ± 9	38 ± 15
Duration of heart failure before transplant (yrs)	2.8 ± 0.8	3.6 ± 0.3
LVEF (%)	53 ± 3	55 ± 2
Hypertension	8	7
Systolic blood pressure (mm Hg)	136 ± 6	131 ± 3
Diastolic blood pressure (mm Hg)	85 ± 4	86 ± 3
Diabetes (#)	2	2
History of smoking (#)	7	5
Total cholesterol (mg/dl)	201 ± 17	194 ± 13
HDL (mg/dl)	43 ± 3	43 ± 3
LDL (mg/dl)	114 ± 13	97 ± 11
Cyclosporine therapy (#)	10	9
Cyclosporine level	335 ± 24	361 ± 55
Beta-blockers (#)	1	2
Calcium-channel blockers (#)	7	6
Diuretics (#)	5	3
Alpha-blockers (#)	0	1
ACE inhibitors (#)	1	1
ARB (#)	0	1
Lipid-lowering therapy (#)	7	5

*p = NS for all comparisons.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction.

Vasomotor studies. Brachial artery diameters at baseline, during reactive hyperemia, prior to nitroglycerin and after administration of nitroglycerin are shown in Table 3. Endothelium-dependent, flow-mediated vasodilation in patients with heart failure, transplant recipients and normal controls is shown in Figure 1. Patients with heart failure due to nonischemic cardiomyopathy or ischemic cardiomyopathy had markedly impaired FMD (3.6 ± 1.0% and 5.1 ± 1.2%, respectively) compared with normal controls (13.9 ± 1.3%,

Table 3. Brachial Artery Diameter at Baseline, During Reactive Hyperemia, and After Nitroglycerin

Diameter (mm)	Heart Failure Ischemic	Heart Failure Nonischemic	Transplant Ischemic	Transplant Nonischemic	Normal Control
Baseline	4.06 ± 0.15	4.29 ± 0.19	4.37 ± 0.15	4.04 ± 0.19	3.68 ± 0.18
Hyperemia	4.24 ± 0.14	4.44 ± 0.21	4.58 ± 0.17	4.51 ± 0.17	4.14 ± 0.20
Change in diameter (baseline to hyperemia)	0.17 ± 0.06*	0.15 ± 0.04*	0.24 ± 0.07*	0.51 ± 0.08	0.50 ± 0.05
Baseline 2†	4.18 ± 0.13	4.23 ± 0.20	4.45 ± 0.15	4.10 ± 0.23	3.70 ± 0.19
After nitroglycerin	4.75 ± 0.07	4.85 ± 0.22	4.96 ± 0.12	4.77 ± 0.22	4.42 ± 0.23
Change in diameter (baseline 2 to nitroglycerin)	0.54 ± 0.8	0.61 ± 0.08	0.51 ± 0.09	0.64 ± 0.09	0.66 ± 0.17

*$p < 0.05$ compared with control; †baseline 2 = prenitroglycerin baseline.

$p < 0.01$ for normal subjects vs. either nonischemic or ischemic cardiomyopathy subjects, p = NS for subjects with nonischemic cardiomyopathy vs. subjects with ischemic cardiomyopathy).

In the transplant recipient group, FMD was normal in patients with a history of nonischemic cardiomyopathy (13.0 ± 2.4%, p = NS vs. normal controls). Furthermore, FMD in transplant recipients with previous nonischemic cardiomyopathy was significantly higher than that of heart failure patients with nonischemic cardiomyopathy ($p = 0.001$). In contrast, endothelial function was severely impaired in transplant recipients with a history of ischemic cardiomyopathy (5.5 ± 1.5%, $p = 0.001$ compared with normal controls, $p = 0.002$ vs. transplant recipients with prior nonischemic cardiomyopathy).

Compared with normal controls, endothelium-independent vasodilation in response to nitroglycerin was preserved in all patient groups, regardless of heart failure etiology (Fig. 2). There were no significant differences among patient groups in endothelium-independent vasodilation ($p = 0.24$ for patients with heart failure; $p = 0.14$ for transplant recipients).

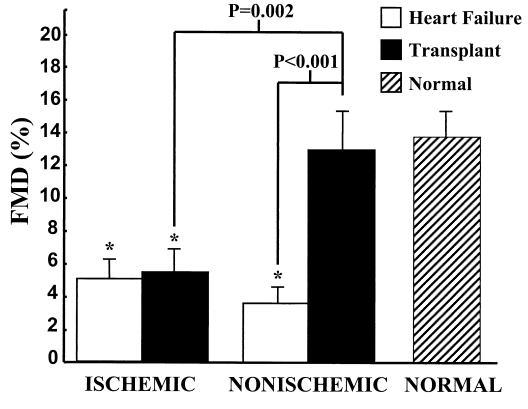

Figure 1. Endothelium-dependent vasodilation. The percent change in brachial artery diameter during reactive hyperemia in heart failure patients **(open bars)** and transplant recipients **(closed bars)** compared with normal controls **(hatched bars)** is shown. Compared with controls, flow-mediated dilation (FMD) was significantly decreased in heart failure patients with either ischemic cardiomyopathy or nonischemic cardiomyopathy. Flow-mediated dilation was also impaired in transplant recipients with a history of ischemic cardiomyopathy. In contrast, FMD in transplant recipients with a history of nonischemic cardiomyopathy was significantly higher than that of heart failure patients with nonischemic cardiomyopathy or transplant recipients with a history of ischemic heart disease. *$p < 0.05$ compared with normal control.

DISCUSSION

This study demonstrates that: 1) peripheral vascular endothelial function is similarly impaired in patients with heart failure of either ischemic or nonischemic etiology and 2) peripheral vascular endothelial function is normal after cardiac transplantation in patients with prior nonischemic cardiomyopathy, but not in those with prior ischemic cardiomyopathy. It is interesting to note that the presence of concomitant heart failure and coronary artery disease did not lead to worsened endothelial dysfunction for patients with ischemic cardiomyopathy compared with patients who had nonischemic cardiomyopathy. While previous studies have reported improvement in peripheral vascular endothelial function in patients with heart failure after cardiac transplantation, the influence of heart failure etiology on the improvement of endothelial function has not been previously assessed (21,22). The persistence of endothelial dysfunction for patients with ischemic heart disease underscores the systemic pathophysiology of the atherosclerotic process. The absence of endothelial dysfunction after transplantation in patients with nonischemic cardiomyopathy suggests that endothelial dysfunction in patients with heart

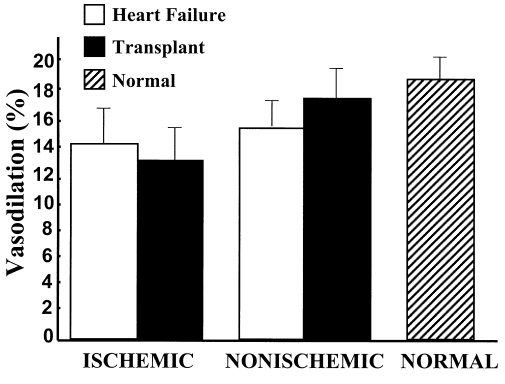

Figure 2. Endothelium-independent vasodilation. The percent change in brachial artery diameter after administration of nitroglycerin in heart failure patients **(open bars)** and transplant recipients **(closed bars)** compared with normal controls **(hatched bars)** is shown. There were no significant differences between groups.

failure of nonischemic etiology is caused by dynamic factors related to the physiologic derangements that accompany severe heart failure.

Mechanisms for endothelial dysfunction in heart failure. While the precise mechanisms that cause abnormal vasomotor function in heart failure have not been elucidated, decreased bioavailability of nitric oxide is likely to play an important role in impaired endothelium-dependent vasodilation. High tissue and circulating levels of angiotensin II for patients with heart failure may promote superoxide radical formation, resulting in increased degradation of nitric oxide (26). Improvement of endothelial function after cardiac transplantation in nonischemic cardiomyopathy patients might, therefore, be related to decreased activation of the renin-angiotensin system. However, for patients with a history of ischemic heart disease, the presence of systemic atherosclerosis may lead to persistent endothelial dysfunction in spite of improved hemodynamic and neurohormonal conditions.

Clinical implications. Peripheral vascular endothelial function may have important implications for functional capacity in patients with heart failure, as well as in transplant recipients. Exercise capacity in both heart failure patients and transplant recipients correlates poorly with LVEF and resting central hemodynamic abnormalities, and there is evidence that peripheral factors affect functional capacity in these patients (2,3,7,8). For example, Kraemer et al. (8) observed a correlation between forearm blood flow during reactive hyperemia and peak oxygen uptake during exercise in patients with heart failure. In addition, Andreassen et al. (6) recently observed that impaired endothelium-dependent vasodilation of the peripheral microcirculation was associated with diminished exercise capacity in cardiac transplant recipients. Furthermore, improvements in vasomotor function may enhance functional status. Mancini et al. (4) found a correlation between captopril-induced augmentation of peak exercise skeletal muscle blood flow and improved maximal oxygen consumption in heart failure patients. Similarly, Nakamura et al. (5) observed a correlation between improved endothelium-dependent vasodilation and peak oxygen consumption in patients with valvular disease and heart failure who underwent valve surgery. Based on these previous studies, the finding that endothelial function improves in nonischemic but not in ischemic cardiomyopathy patients after cardiac transplantation may have direct implications for functional recovery after transplantation in this patient population.

Other potential risk factors for endothelial dysfunction in transplant recipients. All transplant recipients except one received treatment with cyclosporine, and one patient received tacrolimus. Patients with prior ischemic cardiomyopathy had similar cyclosporine levels compared with those with prior nonischemic cardiomyopathy, and cyclosporine-induced hypertension was highly prevalent in both transplant groups. Of note, although hypertension is associated with impaired endothelial function (27–29), patients with nonischemic cardiomyopathy still manifested normal endothelial function after transplantation. In addition, transplant recipients in both the ischemic and nonischemic groups had similar profiles with regard to other factors known to affect endothelial function, including lipid levels, diabetes, history of smoking and use of lipid-lowering therapy.

Study limitations. The lack of longitudinal patient follow-up is a limitation of this study. However, the pretransplant characteristics of the transplant recipients with a history of nonischemic cardiomyopathy were similar to those of the corresponding heart failure group. Thus, there were no identifiable clinical differences between the nonischemic transplant recipient group and the nonischemic cardiomyopathy group that could explain the observed differences in endothelial function. In addition, the pretransplant characteristics of transplant recipients with a history of ischemic heart disease were similar to those of the patients with heart failure who had ischemic cardiomyopathy.

Conclusions. This study confirms the observation that peripheral vascular endothelial function is abnormal in patients with heart failure, regardless of etiology, and demonstrates that peripheral vascular endothelial function is normal after cardiac transplantation in patients with nonischemic cardiomyopathy, but not in those with ischemic cardiomyopathy. Thus, the reversibility of peripheral vascular endothelial dysfunction in heart failure is linked to the presence or absence of coronary atherosclerotic disease. The persistent peripheral vascular endothelial dysfunction in transplant recipients with a history of coronary atherosclerosis is presumably related to the presence of systemic atherosclerosis. In contrast, endothelial dysfunction in patients with nonischemic cardiomyopathy is likely a consequence of hemodynamic abnormalities and is reversible after cardiac transplantation. Determination of the implications of these observations as they relate to recovery of functional status in heart failure patients undergoing cardiac transplantation must await future investigation.

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