Coronary Vasodilator Reserve After Human Orthotopic Cardiac Transplantation

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Cardiac transplantation is frequently associated with accelerated coronary atherosclerosis and immune-mediated microvascular injury. To determine if orthotopic cardiac transplantation impairs the capacity of the coronary vasculature to vasodilate and conduct hyperemic blood flow, maximal coronary vasodilator reserve was measured in 25 cardiac allograft recipients with no evidence of rejection 6–57 months after transplantation and in 20 normal subjects. Left ventricular wall thickness was assessed echocardiographically, and epicardial coronary anatomy was evaluated by quantitative coronary angiography. Coronary vasodilator reserve (CVDR) was measured in all patients with a coronary Doppler catheter and a maximally vasodilating dose of intracoronary papaverine. CVDR measured in the transplant recipients with normal coronary arteries, left ventricular function, and wall thickness (5.0 ± 0.3 [mean ± SEM] peak/resting velocity; range, 3.8–7.3; n = 16) was not different from that of normal subjects (4.8 ± 0.2; range, 3.7–8.3). CVDR in the five cardiac allograft recipients with diffuse coronary atherosclerosis producing 30 ± 5% narrowing (range, 25–38%) of epicardial vessel diameter also was normal (5.1 ± 0.3; range, 4.3–6.2; n = 5). The CVDR was reduced, however, in two of the four cardiac allograft recipients with left ventricular hypertrophy. In the only transplant recipient in whom a regional wall motion abnormality was present, CVDR was abnormal in the vascular distribution of the hypokinetic wall segment (1.8) but was normal in the artery that supplied normally functioning myocardium (4.0). These findings demonstrate that in the absence of allograft rejection, acquired left ventricular hypertrophy, and regional wall motion abnormalities, coronary vasodilator reserve is normal after orthotopic human cardiac transplantation. Mild-to-moderate diffuse atherosclerosis, frequently noted after transplantation, is not associated with diminished maximal coronary vasodilator reserve. (Circulation 1988;78:1200–1209)

Myocardial mechanical performance is remarkably normal after uncomplicated human orthotopic cardiac transplantation.1,2 In the absence of rejection, the donor left ventricle exhibits normal resting systolic function and normal contractile reserve in response to β-adrenergic stimulation.3 Similarly, diastolic left ventricular function after cardiac transplantation, although incompletely characterized, is predominantly normal in the absence of allograft rejection and hypertrophy.4 Although myocardial mechanical function usually is preserved, there are several reasons why the coronary vasculature might be affected adversely by cardiac transplantation. First, the coronary vessels may be compromised by the development of proliferative arteriolar occlusion from acute immune-mediated microvascular injury5,6 or by accelerated atherosclerosis associated with chronic allograft rejection.5,7 Arterial narrowing is commonly observed in the first 3 years after transplantation5,9 and is the leading cause of death among patients who survive 1 year.10–12 Of importance is that these immunological vascular lesions are sometimes confined to small coronary arteries and arterioles and, therefore, may not be detected by the methods routinely used to screen for allograft rejection (coronary angiography13 and endomyocardial biopsy9). Second, left ventricular hypertrophy may be acquired after cardiac transplantation due to increased systemic impedance associated with cyclosporine therapy14 or heightened peripheral vasoconstrictor tone associated with end-
stage heart disease. Both systemic hypertension and ventricular hypertrophy have been shown to increase minimal coronary vascular resistance in nontransplanted myocardium. Third, anoxic allograft injury may result from prolonged myocardial ischemia occurring between procurement and revascularization of the donor heart. Fourth, immunosuppression therapy with cyclosporine or azathioprine commonly is associated with the development of myocardial interstitial edema and fibrosis. Any of these conditions might be expected to result in decreased coronary vasodilator reserve. Moreover, the effect of autonomic cardiac denervation on coronary vasodilator reserve has not been previously defined in humans.

Methodological problems and the limited number of patients undergoing cardiac transplantation have previously hampered experimental assessment of the denervated coronary microvascular circulation. One aspect of microvascular function, maximal coronary vasodilator reserve, can now be assessed accurately with an extensively validated 3F coronary Doppler catheter and a maximally vasodilating dose of intra-coronary papaverine. The purpose of this study was to determine if cardiac transplantation or the consequences of transplantation (cardiac denervation, atherosclerosis, or acquired left ventricular hypertrophy) alter maximal coronary vasodilator reserve.

**Patients and Methods**

**Patient Selection**

Two groups of patients were studied: 25 cardiac allograft recipients and 20 patients with angiographically normal coronary anatomy.

**Cardiac allograft recipients.** Twenty-five sequential cardiac allograft recipients undergoing a routine annual invasive cardiac evaluation (coronary angiography, right heart catheterization, and right ventricular endomyocardial biopsy) for the purpose of screening for subacute-chronic allograft rejection were studied between January 1987 and February 1988. Patients were studied an average of 25 ± 2 months after heart transplantation (range, 6–57 months). Cardiac transplantation had been performed in individuals with end-stage dilated cardiomyopathy secondary to coronary atherosclerosis (n = 9), congenital heart disease (n = 2), rheumatic valvular heart disease (n = 2), familial cardiomyopathy (n = 3), and idiopathic causes (n = 8). One patient was studied after combined heart-lung transplantation. Post-transplantation immunosuppression was achieved in each patient with cyclosporine, azathioprine, and prednisone. All patients were routinely evaluated for allograft rejection by light microscopic examination of right ventricular septal endomyocardial biopsy specimens obtained at regular intervals after transplantation. Although the absence of allograft rejection was not a criterion for inclusion in this study, none of the patients evaluated had a previous episode of rejection at any time after transplantation. Hemoglobin concentration and echocardiographic (cross-sectional and M-mode) evaluation of left ventricular wall thickness and systolic performance were obtained 1 day before catheterization in each subject. In five transplant recipients, the studies described in this report were repeated 9–12 months after an initial evaluation.

**Normal patients.** We compared measurements obtained in transplanted hearts to those obtained from 20 patients who underwent cardiac catheterization for the diagnosis of a chest pain syndrome. In these normal patients, coronary angiography and contrast or equilibrium radionuclide left ventriculography were normal (left ventricular ejection fraction > 50% with no focal wall motion abnormality). None of the normal patients had the following conditions that might have affected the vasodilator capacity of the coronary vasculature: 1) historical or electrocardiographic evidence of myocardial infarction, which was defined by either clinical history of infarction associated with total serum creatine kinase elevation, increased creatine kinase MB fraction, and classic evolutionary electrocardiographic changes (with or without the development of Q waves) or an electrocardiogram showing pathological Q waves of more than 0.04 seconds in duration and a focal wall motion abnormality demonstrated by contrast or equilibrium radionuclide ventriculography; 2) valvular heart disease; 3) historical or clinical observations consistent with variant angina pectoris or recent ergonovine maleate administration (within 6 hours); 4) left ventricular hypertrophy (echocardiographic left ventricular posterior wall or interventricular septal thickness > 11 mm); or 5) anemia (hemoglobin < 10.0 g/dl).

Informed consent was obtained from each patient. All studies were approved by the Institutional Review Board of the University of Minnesota.

**Catheterization Protocol**

Patients came to the cardiac catheterization laboratory having fasted overnight. Medications with cardiac or vasoactive properties (i.e., nitrates, calcium channel or β-adrenergic receptor blocking agents, and arterial vasodilators) were discontinued at least 12 hours before the procedure in all patients except for one cardiac allograft recipient who took atenolol 25 mg and nifedipine 10 mg p.o. 4 hours before catheterization. Thirteen of the 25 transplant patients were treated chronically with long-acting β-adrenergic receptor antagonist agents (atenolol or metoprolol). Twenty-two of the 25 cardiac allograft recipients were premedicated with diazepam (10 mg p.o. or i.v.). No patient received narcotic analgesia or atropine.

Patients studied after transplantation underwent pulmonary artery catheterization with measurement of right heart pressures and cardiac output (thermodilution method, 7F Swan-Ganz thermodilution catheter, American Edwards Laboratories), followed by biopsy of the right ventricular septum and apex (6F Biopsy Forceps, Cordis). To produce
maximal epicardial coronary artery vasodilation, intracoronary nitroglycerin was then administered (200–400 mg) to 24 of 25 patients, and coronary angiograms were obtained in multiple projections, two of which were orthogonal (e.g., 30° right anterior oblique and 60° left anterior oblique). Biplane left ventriculography was performed in one patient to more completely evaluate myocardial function. Subsequently, heparin sodium (5–10,000 units i.v.) was administered to increase the activated clotting time to at least twice the control level. A 3F 20-mHz coronary Doppler catheter (NuMed, Hopkinton, New York) was then advanced through an 8F large lumen coronary guiding catheter (CR Bard) into the proximal segment of the following coronary arteries: 11 left anterior descending, 11 left circumflex, and three right coronary arteries. The catheter position and the Doppler range-gate were adjusted to obtain a high-quality tracing of phasic coronary blood flow velocity. Mean and phasic signals of coronary blood flow velocity (kilohertz shift), arterial pressure obtained through the guiding catheter, heart rate, and electrocardiogram were recorded continuously on a multichannel Gould direct-writing recorder. This technique has been previously described. Because the arterial waveform obtained from the guiding catheter was damped by the presence of the coronary Doppler catheter, only mean arterial pressure could be accurately monitored.

After baseline measurements of resting coronary blood flow velocity were obtained, 8–14 mg papaverine hydrochloride (2 mg/ml 0.9% saline) were injected through the guiding catheter into the coronary ostium, and the resultant increase in coronary blood flow velocity was recorded. To confirm that maximal hyperemia was produced in each patient, progressively larger doses of papaverine (increases of 2–4 mg/injection) were administered until coronary blood flow velocity was maximal. Blood flow velocity was allowed to return to baseline levels between doses of papaverine. It has been previously demonstrated that, administered in this fashion, intracoronary papaverine produces maximal coronary hyperemia equal in magnitude to that effected by intravenous dipyridamole infusion. In normal subjects, a similar protocol was followed. Nitroglycerin was administered (200–400 μg i.c. or i.v.), followed by coronary angiography and contrast or equilibrium radionuclide left ventriculography. Subselective coronary artery catheterization with the Doppler catheter (11 left anterior descending, seven left circumflex, and two right coronary arteries), and measurement of coronary vasodilator reserve were then performed as previously discussed.

**Coronary Vasodilator Reserve**

Coronary vasodilator reserve was determined as the quotient of the peak blood flow velocity (maximal kilohertz shift after papaverine administration) and resting blood flow velocity. To characterize the change in coronary vascular resistance at maximal hyperemia, an index of minimal coronary vascular resistance was calculated as the quotient of (mean aortic blood pressure at peak flow velocity [millimeters mercury]/peak blood flow velocity [kilohertz shift]) and (mean aortic blood pressure at resting flow velocity/resting blood flow velocity).

**Quantitative Coronary Angiography**

Each coronary cineangiogram was visually inspected by three observers blinded to clinical history and experimental data. From this initial screening, five cardiac allograft recipients with epicardial luminal irregularities were identified. The diameter (mm) and maximal percent stenosis of the most severe narrowing in each patient was characterized quantitatively with the PIE Data-Reiber method of quantitative coronary angiography. This method has been described in detail elsewhere. Briefly, a 35-mm cinefilm frame is digitized to a 1,200 × 1,500 pixel matrix containing 256 gray levels. After the operator identifies the limits of the coronary catheter and the arterial segment to be analyzed, the vascular edges of the segment are automatically detected, the arterial contour is corrected for magnification and pincushion distortion, and the minimum arterial diameter of the entire vascular segment and maximal percent diameter stenosis are then determined by computer. Studies from our laboratory with the PIE Data-Reiber Cardiovascular Angiography Analysis System demonstrate that the interstudy variability of this method is 0.05 mm (SEE of paired interstudy differences). In this study, coronary atherosclerosis was defined by the presence of any epicardial stenosis that produced 10% or more narrowing of coronary arterial caliber.

**Echocardiography**

Left ventricular wall motion and thickness were evaluated in each patient by M-mode and two-dimensional echocardiography with Hewlett-Packard (Model 77020A) or IREX (Meridian) imaging systems. Wall thickness was assessed by measuring the interventricular septum and posterior wall dimensions according to the standards of the American Society of Echocardiography. Left ventricular hypertrophy was defined as diastolic septal or posterior wall thickness more than 11 mm. Measurements were performed independently by two observers blinded to clinical history and experimental data.

**Statistical Analysis**

Differences between group means were analyzed by analysis of variance (ANOVA, CLINFO). Correlation coefficients were calculated with the least-squares linear regression method. Except where noted, all values are expressed as mean ± SEM. Statistical significance was defined by \( p < 0.05 \).

**Results**

**Patient Characteristics**

The mean age of the cardiac allograft recipients (49 ± 2 years) and normal subjects (52 ± 2 years) was
similar. The transplant recipients were studied an average of 25 ± 2 months after transplantation (range, 6–57 months). The mean age of the donor hearts was 25 ± 1 years (range, 14–39 years). The mean duration of the allograft ischemia after procurement and before transplantation was 154 ± 9 minutes (range, 64–239 minutes). None exhibited histological evidence of cardiac allograft rejection at any time after transplantation. Hemoglobin concentration was more than 10.0 g/dl in all patients.

Echocardiographic evaluation of left ventricular systolic performance was normal in 24 of 25 patients. Hypokinesis of a segment of the posterolateral left ventricular wall was demonstrated in one transplant recipient by biplane ventriculography.

**Hemodynamic Measurements**

Table I displays the hemodynamic parameters measured in the normal subjects and transplant recipients. The mean heart rate and arterial blood pressure of the cardiac allograft recipients were greater than those of normal subjects. Mean pulmonary capillary wedge pressure was normal in 24 of the 25 cardiac allograft recipients (9 ± 1 mm Hg; range, 4–13 mm Hg) but was moderately increased in the transplant patient with left ventricular dysfunction (16 mm Hg). The resting cardiac index also was normal in 20 of the 25 transplant patients (2.6 ± 0.1 l/min/m²) but was reduced (<2.1 l/min/m²) in five allograft recipients (range, 1.7–2.0 l/min/m²).

**Maximal Coronary Vasodilator Reserve**

**Normal left ventricular wall thickness and function.** Sixteen transplant recipients had normal coronary arteries and normal left ventricular wall motion and thickness. The average coronary vasodilator reserve in these allograft recipients was not different from that in normal subjects (Table I and Figures 1 and 2). Similarly, no significant difference in the minimal coronary vascular resistance was present between the two groups (Table I).

Although mean arterial pressure and heart rate were higher in the transplant recipients, these parameters were not correlated with the maximal coronary vasodilator reserve (mean arterial pressure, \( r = -0.04 \); heart rate, \( r = -0.01 \); Figure 3). To determine further if vasodilator reserve was affected by differences in these hemodynamic parameters, the coronary vasodilator reserve of the eight transplant patients with the highest mean arterial pressure (106 ± 3 mm Hg) was compared with that of the eight transplant patients with the lowest mean arterial pressure (84 ± 4 mm Hg, \( p < 0.01 \)). The coronary vasodilator reserve (CVDR) measured in the eight cardiac transplant patients with the *highest* mean arterial pressure (4.6 ± 0.4; range, 3.8–7.1) was similar to that in the eight transplant patients with the *lowest* mean arterial pressure (5.4 ± 0.4; range, 4.2–7.3; \( p = NS \)). Similarly, the coronary vasodilator reserve measured in the eight cardiac transplant patients with the *highest* heart rate (CVDR, 4.6 ± 0.4; range, 3.8–7.3; heart rate, 93 ± 3 beats/min) was not significantly different from that in the eight allograft recipients with the *lowest* heart rate (CVDR, 5.5 ± 0.4; range 4.0–7.1; \( p = NS \) vs. CVDR of highest heart rate; HR, 73 ± 2 beats/min; \( p < 0.01 \) vs. highest heart rate). Coronary vasodilator reserve also was unrelated to the product of mean arterial pressure and heart rate (\( r = -0.41 \)). These observations suggest that differences in mean arterial pressure and heart rate between normal subjects and allograft recipients did not significantly alter coronary vasodilator reserve. The coronary vasodilator reserve of the transplant patients without left ventricular hypertrophy who had been chronically treated with long-acting \( \beta \)-adrenergic receptor antagonist agents (CVDR, 5.1 ± 0.3; heart rate, 77 ± 3 beats/min; mean arterial pressure, 97 ± 4 mm Hg; \( n = 13 \)) was not significantly different from that of patients who did not take these medications (CVDR, 4.6 ± 0.3; heart rate, 91 ± 3 beats/min; mean arterial pressure, 93 ± 4 mm Hg; \( n = 8 \)). Additionally, maximal coronary vasodilator reserve did not correlate with the duration of allograft ischemia before revascularization (\( r = 0.13 \)).

Hence, maximal coronary vasodilator reserve in the transplant recipients with normal coronary arter-

**Table I.** Coronary Vasodilator Reserve and Hemodynamic Measurements

<table>
<thead>
<tr>
<th>Group</th>
<th>( n )</th>
<th>Coronary vasodilator reserve (peak/resting velocity)</th>
<th>Minimal coronary vascular resistance</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac index (l/min/m²)</th>
<th>Pulmonary capillary wedge pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>20</td>
<td>4.8 ± 0.2</td>
<td>3.7–8.3</td>
<td>0.20 ± 0.01</td>
<td>85 ± 3</td>
<td>74 ± 3</td>
<td></td>
</tr>
<tr>
<td>Cardiac allograft recipients</td>
<td>25</td>
<td>4.9 ± 0.2</td>
<td>1.8–7.3</td>
<td>0.20 ± 0.01</td>
<td>93 ± 3</td>
<td>82 ± 2</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>Normal</td>
<td>16</td>
<td>5.0 ± 0.3</td>
<td>3.8–7.3</td>
<td>0.19 ± 0.01</td>
<td>95 ± 4</td>
<td>83 ± 3</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>5</td>
<td>5.1 ± 0.3</td>
<td>4.3–6.2</td>
<td>0.18 ± 0.01</td>
<td>93 ± 3</td>
<td>83 ± 7</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>4</td>
<td>4.2 ± 0.5‡</td>
<td>3.4–5.6</td>
<td>0.22 ± 0.03</td>
<td>89 ± 9</td>
<td>90 ± 8</td>
<td>3.0 ± 0.3</td>
</tr>
<tr>
<td>Ventricular dysfunction</td>
<td>1</td>
<td>1.8</td>
<td>...</td>
<td>0.49</td>
<td>106</td>
<td>80</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*Of the 25 allograft recipients evaluated, one individual with left ventricular hypertrophy also had coronary atherosclerosis.

† \( p < 0.05 \) vs. normal subjects.

‡ \( p = 0.29 \) vs. normal subjects.
Phasic CBFV (kHz shift)

Mean CBFV (kHz shift)

Aortic Pressure (mmHg)

Coronary Pressure (mmHg)

Heart Rate (bpm)

EKG

Mean Aortic Pressure (mmHg)

FIGURE 1. Simultaneous recordings of phasic and mean left anterior descending coronary blood flow velocity (CBFV), phasic aortic blood pressure measured through the guiding catheter, coronary arterial pressure measured through the Doppler catheter, heart rate, electrocardiogram (EKG), and mean aortic pressure obtained from a cardiac allograft recipient with normal left ventricular wall motion and thickness. After administration of a maximally vasodilating dose of papaverine (13 mg), coronary blood flow velocity rose 4.8 times resting levels.

Acquired coronary atherosclerosis. Epicardial coronary atherosclerosis was found in five cardiac allograft recipients. Quantitative angiographic analysis of the most significant coronary artery stenosis in these patients demonstrated a mean reduction in luminal diameter of 30 ± 5% (range, 26–38%). The minimal diameter of these vessels averaged 2.4 ± 0.2 mm (range, 1.8–2.9 mm). The diameter of the adjacent “normal” segment was 3.2 ± 0.3 mm (range, 2.6–4.2 mm).

Despite the occurrence of accelerated atherosclerosis, the coronary vasodilator reserve of the five cardiac allograft recipients with diffuse coronary atherosclerosis (5.1 ± 0.3, Table 1) was similar to that measured in the allograft recipients without atherosclerosis (5.0 ± 0.3) and the normal control subjects (4.8 ± 0.2). Although the time between transplantation and study was significantly longer in cardiac allograft recipients with coronary atherosclerosis (40 ± 8 months; range, 12–57 months) than it was in transplant patients with normal epicardial coronary anatomy (19 ± 2 months; range, 6–39 months), mean arterial pressure and heart rate were similar in both groups (Table 1).

Left ventricular hypertrophy. Concentric left ventricular hypertrophy was present in four cardiac allograft recipients (diastolic posterior wall and interventricular septal thickness, 12.5 ± 0.3 mm; range, 12.0–13.0 mm). In these transplant...
recipients, coronary vasodilator reserve was abnormally reduced in two subjects (3.4 and 3.4), measured at the lower limit of normal (3.7) in one patient, and was normal in the fourth subject (5.6). The heart rate and mean arterial pressure of these patients (heart rate, 90 ± 8 beats/min; mean arterial pressure, 89 ± 9 mm Hg) were similar to those of patients without hypotrophy.

Abnormal left ventricular wall motion. Postero-lateral left ventricular hypokinesis in the vascular distribution of the left circumflex coronary artery was documented by biplane left ventriculography in one cardiac allograft recipient who was studied 12 months after transplantation. The coronary vasodilator reserve was markedly reduced in this artery (1.8) but was normal in the left anterior descending coronary artery (4.0), which supplied a normally functioning anterior left ventricular wall (Figure 4). The allograft ischemic time was not prolonged in this patient (127 minutes).

Reproducibility of Coronary Vasodilator Reserve Measurements

In five allograft recipients, a second measurement of coronary vasodilator reserve was obtained 9–12 months after the initial study. Initial measurements of coronary vasodilator reserve were highly correlated with repeat measurements 11.4 ± 0.5 months later (r = 0.95; mean difference, 7 ± 1%). Between these serial measurements, small differences in heart rate and mean arterial pressure were present (mean difference in heart rate, 4 ± 2%; mean difference in mean arterial pressure, 7 ± 2%) but were not statistically significant.

Discussion

This study demonstrates that in the absence of acquired hypotrophy or abnormalities of left ventricular wall motion, coronary vasodilator reserve is normal in a large group of patients 1–5 years after uncomplicated human cardiac transplantation. This preservation of vasodilator reserve occurs despite the presence of mild-to-moderate diffuse coronary atherosclerosis. The presence of left ventricular hypotrophy acquired within 1–3 years after transplantation, however, may reduce coronary vasodilator reserve.

Potential Methodological Limitations

Several potential methodological limitations must be considered when interpreting these data. First, measurements of the coronary vasodilator reserve obtained with the Doppler catheter might be affected by changes in the caliber of the coronary vessel containing the catheter, obstruction of hyperemic blood flow by the guiding catheter, altered velocity

FIGURE 2. Plot of coronary vasodilator reserve measurements in normal subjects and cardiac allograft recipients. Coronary vasodilator reserve was normal in transplant recipients with normal left ventricular wall motion and thickness or coronary atherosclerosis but was reduced in two of four patients with left ventricular hypertrophy and in one patient with posterolateral left ventricular hypokinesis. The lower limit of normal coronary vasodilator reserve (peak/resting coronary blood flow velocity = 3.7) is depicted on the graph by the dashed line (–).
profiles, etc. These potential problems have been discussed in detail elsewhere. Of importance is that in each patient vasodilator reserve was measured after maximal epicardial coronary vasodilation was produced with nitroglycerin and the guiding catheter was withdrawn from the coronary ostium at peak hyperemia.

Second, the heart rate and the mean arterial pressure were higher in the cardiac allograft recipients than in the normal subjects. These differences in heart rate and mean arterial pressure, presumably related primarily to cardiac denervation and the hypertensive effect of cyclosporine therapy, could have reduced the measured coronary reserve by increasing resting blood flow. Alternatively, increased arterial driving pressure during maximal coronary dilation could have increased the measured reserve. The data from this study indicates, however, that neither the heart rate nor the mean arterial pressure correlated well with coronary vasodilator reserve \( r = -0.01 \) and \( -0.04 \), respectively. Moreover, the group of allograft recipients with the lowest arterial pressure \( 84 \pm 4 \text{ mm Hg, } n = 8 \) had a vasodilator reserve and arterial pressure nearly identical to the normal control group. Furthermore, although the cardiac index was mildly reduced in five cardiac allograft recipients, resting cardiac index did not correlate with coronary vasodilator reserve \( r = -0.29 \). A reduction in cardiac index of this magnitude has been reported previously in patients after uncomplicated heart transplantation. These differences in systemic hemodynamic parameters did not appreciably affect maximal coronary vasodilator reserve.

Third, coronary vasodilator reserve was expressed as the ratio of peak to resting CBFV, and, consequently, an abnormally high or low resting blood flow velocity might alter the calculated coronary flow reserve without changing maximal hyperemic blood flow. Although individuals with conditions known to produce alterations in resting or hyperemic myocardial blood flow were not included in this study \( e.g., \) severe anemia, polycythemia, and hypoxia or hemoglobin-oxygen dissociation abnormalities, resting coronary blood flow might have been increased secondary to interruption of neuroly mediated vasocconstrictor tone. While Lavallee et al have shown that denervation of the canine heart does not alter myocardial perfusion, Orlick et al measuring coronary sinus blood flow (thermodilution technique) in humans after transplantation, found resting blood flow to be elevated compared with normal subjects. Although the coronary sinus thermodilution technique has several methodological problems that make comparison of blood flow between subjects difficult, if basal coronary blood flow had been increased significantly in the cardiac allograft recipients, the measured coronary vasodilator reserve should have been reduced. We found, instead, that...
coronary vasodilator reserve in the transplant recipients was normal.

Fourth, coronary vasodilator reserve measurements might have been influenced by pharmacological alterations in resting or maximal hyperemic coronary blood flow. Although intracoronary nitroglycerin was administered to produce maximal epicardial coronary dilation before coronary vasodilator reserve measurements, the effect of intracoronary nitroglycerin on coronary blood flow is brief.34,35 Furthermore, while medications with cardiac or vasoactive properties were discontinued at least 12 hours before the study, 13 transplant patients were treated chronically with β-adrenergic receptor antagonists that have a relatively long duration of action. While some residual β-adrenergic receptor blocking effect probably was present in these patients, this factor is unlikely to have had a significant effect on our results. There was a trend for the coronary vasodilator reserve to be higher in the group with residual β-adrenergic receptor antagonist effect (ρ = 0.37 vs. absence of β-adrenergic antagonist therapy), possibly related to the reduced heart rate of the individuals previously medicated with atenolol or metoprolol. The heart rate of this group (77 ± 3 beats/min), however, approximated that of the normal “control” group (74 ± 3 beats/min). Consequently, it is unlikely that the effects of cardiac medications affected our conclusions that coronary vasodilator reserve is normal after transplantation.

Fifth, in this study, coronary atherosclerosis was defined cineangiographically by the presence of luminal irregularities that produced at least 10% narrowing of vessel diameter. This degree of coronary arterial stenosis was chosen because the SEE of the PIE Data-Reiber method for evaluation of vascular caliber is 0.05 mm in our laboratory. The diameter of the “normal” vascular segment adjacent to the stenosis was 3.2 ± 0.3 mm. Hence, the 10% variation criterion for defining the presence of coronary atherosclerosis (± 0.3 mm) represents a 99% likelihood that the irregularities present were not due to measurement artifact. Although the most severe diameter stenosis in any patient measured only 38% (approximately 62% area stenosis), the accelerated coronary atherosclerosis associated with transplantation often involves the more distal vasculature that cannot be quantified in this manner. Normal coronary vasodilator reserve in each of the five cardiac allograft recipients with mild-to-moderate large-vessel coronary atherosclerosis, however, suggests that any distal atherosclerosis associated with this degree of proximal stenosis was not severe enough to impair maximal coronary hyperemia.

Finally, there are limits to the accuracy and precision of echocardiographic assessment of left ventricular wall dimensions. Nevertheless, left ventricular wall thickness evaluated in this manner was successful in identifying a subgroup of transplant recipients with hypertrophy and abnormally reduced coronary vasodilator reserve. It is possible that lesser degrees of hypertrophy were undetected.

Previous Studies

The effect of cardiac transplantation on coronary vasodilator reserve has not been elucidated. Tavolaro et al36 found that coronary sinus blood flow rose 2.7 ± 0.1-fold in three of four cardiac allograft recipients with angiographically normal coronary arteries and left ventricular function studied 13 ± 10 months post-transplantation. Markedly reduced coronary vasodilator reserve was present in the fourth transplant recipient, whose endomyocardial biopsy revealed evidence of allograft rejection. Unfortunately, coronary hyperemia was produced by administering a submaximally vasodilating dose of intravenous dipyridamole, and coronary arterial flow was estimated with methodologically problematic thermodilution measurements of coronary sinus blood flow.

Our findings that mild-to-moderate diffuse atherosclerosis did not impair coronary vasodilator reserve is consistent with a previous report from our laboratory that demonstrated that mild-to-moderate atherosclerosis after coronary artery bypass surgery does not impair maximal coronary hyperemia.37 In that study, it was shown that lesions at the bypass graft—coronary arterial insertion did not limit peak flow if the residual minimal cross-sectional area was 2.0 mm² or more (mid—left anterior descending artery or distal right coronary artery). All transplant recipients with atherosclerosis evaluated in the present study had a minimal coronary diameter of more than 1.6 mm, which corresponds to a minimal cross-sectional area of 2.0 mm² or more.

Implications

Three physiological considerations emerge from analysis of this study. First, the ability of the denervated coronary vasculature to vasodilate and conduct hyperemic blood flow is normal after uncomplicated human orthotopic cardiac transplantation. This preservation of coronary vasodilator reserve is consistent with previously reported normal left ventricular contractile reserve3 and exercise tolerance38 in cardiac allograft recipients and is not dependent on intact autonomic cardiac innervation.

Second, cardiac allograft hypertrophy acquired within 1—3 years after transplantation may be associated with reduced coronary vasodilator reserve. The presumed etiology of the hypertrophy is systemic hypertension because post-transplantation arterial blood pressure frequently was elevated in these subjects. Both left ventricular hypertrophy and chronic systemic hypertension have been shown to reduce the vasodilator reserve of nontransplanted myocardium in animals39,40 and in humans.15—17 Reduced coronary vasodilator reserve in the cardiac allograft recipients with left ventricular hypertrophy, therefore, might be due to the microvascular effects of hypertension as well as the presence of hypertrophy. Consequently, meticulous control of
systemic blood pressure would seem to be important in these patients.

Third, chronic allograft rejection is the leading cause of mortality in cardiac allograft recipients who survive 1 year. The most important component of chronic rejection is accelerated coronary atherosclerosis, Because the coronary vasculature is chronically denervated after cardiac transplantation, the development of occlusive coronary artery disease related to allograft rejection occurs without angina pectoris and may be heralded only by myocardial infarction, congestive heart failure, or sudden death. Previous studies in cardiac allograft recipients have demonstrated that exercise thallium-201 scintigraphy does not reliably predict the presence of accelerated coronary atherosclerosis. It has been hypothesized that coronary microvascular involvement might be responsible for exercise-induced scintigraphic defects exhibiting normal reperfusion in the absence of angiographically significant epicardial disease. The present study demonstrates, however, that in the absence of acute allograft rejection the functional integrity of the coronary microvasculature, as assessed by coronary vasodilator reserve, remains normal despite the presence of mild-to-moderate epicardial coronary atherosclerosis. Whether measurement of coronary vasodilator reserve will prove to be useful in the detection of acute and chronic allograft rejection should become evident as these and other patients are followed longitudinally.

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References


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