Recovery of a Normal Coronary Vascular Reserve After Rejection Therapy in Acute Human Cardiac Allograft Rejection

Alain Nitenberg, MD, Oscar Tavolaro, MD, Christophe Benvenuti, MD, Daniel Loisance, MD, Jean-Marc Foult, MD, Luc Hittinger, MD, Alain Castaigne, MD, Jean-Paul Cachera, MD, and Pierre Vernant, MD

During acute rejection, coronary vascular reserve is severely impaired in human orthotopic heart transplants. To evaluate the effects of rejection therapy on coronary vascular reserve, the ratio of peak-to-resting coronary flow velocity was assessed with a coronary Doppler catheter and a maximally vasodilating dose of intracoronary papaverine (12 mg) in nine allograft recipients without rejection (group 1) and in six recipients before and after treatment of an acute episode of rejection (group 2). All the patients had normal epicardial coronary arteries and were free of left ventricular hypertrophy. In group 2 during rejection, the coronary vascular reserve was significantly lower than in group 1, in which all the patients had a peak-to-resting coronary flow velocity ratio greater than 4 (2.3±0.5 vs. 5.4±0.8, respectively, p<0.001). In group 2 after treatment of rejection, the peak-to-resting coronary flow velocity ratio was similar to that of group 1 (4.7±0.8). Heart rate, left ventricular volumes and pressures, hemoglobin concentration, and arterial oxygen pressure were similar in the two groups. This study provides evidence that alterations of coronary vascular reserve because of acute rejection were reversible after treatment of the rejection episode. (Circulation 1990;81:1312–1318)

Human cardiac transplantation is frequently proposed as the ultimate treatment of end-stage heart failure. Together with infectious complications and early graft failure, acute rejection is a major impediment of survival. Although the early phase of acute rejection of cardiac allografts is accompanied by evidence of vascular injury,1,2 during the past decade, most of the studies dedicated to human orthotopic heart transplantation have focused on myocardial mechanical performance and accelerated atherosclerosis of the major coronary arteries. Attention has been recently directed to the coronary vascular reactivity and the coronary vasodilator reserve of the human transplanted heart. Dipyridamole-induced vasodilation3–5 and coronary vasodilator reserve assessed by Doppler velocity measurement after intracoronary papaverine6 have been reported to be normal in the absence of rejection. On the other hand, during allograft rejection, coronary flow increase after intravenous dipyridamole was severely impaired.4,5 Whether this impairment of coronary vasodilator capacity observed during heart rejection is reversible with rejection therapy might be of clinical importance.

The objective of the present study was, therefore, to assess the effects of rejection therapy on coronary vasodilator reserve in cardiac allograft recipients with acute rejection. Coronary vasodilator capacity was estimated with coronary Doppler catheter and a maximally vasodilating dose of intracoronary papaverine7,8 in allograft recipients before and after treatment of the episode of rejection. Results were compared with those of recipients without heart rejection.

Methods

Patient Selection and Posttransplant Care

Because left ventricular hypertrophy per se is a factor of reduction of coronary flow reserve,9 the study group comprised 15 selected cardiac allograft recipients without left ventricular hypertrophy at two-dimensional and M-mode echocardiography performed the day before right ventricular endomyocardial biopsy (diastolic septal or posterior wall thickness.
Orthotopic cardiac transplantation had been performed at Hôpital Henri Mondor (Service de Chirurgie Thoracique et Cardio-vasculaire, Créteil, France). Patients were investigated from the 18th month after surgery. Informed consent was obtained from all the patients for cardiac invasive evaluation including coronary arteriography, and for repetitive study after treatment of rejection crisis in patients whose endomyocardial biopsy showed signs of rejection. The protocol was approved by an institutional medical committee.

All patients were routinely evaluated for allograft rejection by right ventricular endomyocardial biopsy using femoral vein approach with a 7F curved long sheath (Cordis Corporation), and a 6F biopsy forceps (Cordis Corporation). Biopsies were performed weekly until the third month after surgery. Thereafter, biopsies were performed on alternate weeks for the next 3 months, followed by monthly biopsies for the next 6 months. At least three samples were obtained in each patient. Specimens were preserved in 10% formalin for light microscopic examination with hematoxylin-eosin stain and were read by two independent observers. Results were graded according to the Billingham criteria. Histological findings allowed identification of two groups among the 15 selected patients. Group 1 comprised nine patients whose endomyocardial biopsies did not evidence any sign of rejection. Group 2 included six patients whose endomyocardial biopsies showed mild-to-moderate rejection as defined by cellular infiltration with or without myocyte necrosis (Table 1). The catheterization procedure was achieved the day after endomyocardial biopsy. Sex, age, delay after surgery, and number and grade of previous rejection episodes of all the selected patients are presented in Table 2.

Posttransplantation immunosuppressive therapy comprised prednisolone (0.2–0.3 mg/kg/day) and cyclosporine. The dose of cyclosporine was adjusted to maintain whole blood concentration measured by radioimmunoassay (Cyclosporin SP INO230, Incstar) in the range of 250–400 ng/ml (monoclonal antibody method) or 700–1,000 ng/ml (polyclonal antibody method). Azathioprine (1.0–1.5 mg/kg/day) was administered to five of nine patients of group 1 and four of six patients of group 2. Nicardipine was prescribed to two patients of group 1 and to one patient of group 2; one patient of group 2 received nifedipine.

In Hôpital Henri Mondor, all patients with rejection, including patients with mild rejection before the sixth month after surgery and from the sixth to the 12th month after transplantation, and patients with mild rejection and previous episodes of rejection were treated with prednisolone (1 mg/kg during 6 days) until complete resolution of the rejection episode was obtained. During this period, biopsies were performed twice a week and read by two independent observers who did not know that the patients were included in the study. Thereafter, biopsies were realized on alternate weeks during 3 months. The catheterization procedure was repeated at least 1 month after complete resolution of the rejection crisis, that is, the day after a negative endomyocardial biopsy.

### Catheterization Protocol

All patients were in the fasting state for at least 12 hours before the procedure. Calcium blockers were discontinued 24 hours before the investigation. No premedication was administered, and 1% lidocaine was used for local anesthesia.

Patients underwent pulmonary artery catheterization with a thermodilution catheter (Edwards Laboratories). The Seldinger approach from a right femoral

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### Table 1. Histological Findings in Patients With Heart Rejection (Group 2)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Edema</th>
<th>Cellular infiltration</th>
<th>Myocyte necrosis</th>
<th>Interstitial fibrosis</th>
<th>Grade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>14</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

0, absent; 1, mild; 2, moderate.

*According to Billingham criteria: grade 0, absence of cellular infiltration or myocyte necrosis; grade 1, cellular infiltration without myocyte necrosis (mild rejection); grade 2, cellular infiltration with myocyte necrosis (moderate rejection); grade 3, myocardial hemorrhage (severe rejection).

### Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr) and sex</th>
<th>Postoperative mo.</th>
<th>No. of previous rejection episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (no rejection)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44 M</td>
<td>9</td>
<td>3(1,1,1)</td>
</tr>
<tr>
<td>2</td>
<td>56 M</td>
<td>5</td>
<td>1(1)</td>
</tr>
<tr>
<td>3</td>
<td>57 M</td>
<td>8</td>
<td>3(2,1,1)</td>
</tr>
<tr>
<td>4</td>
<td>46 M</td>
<td>9</td>
<td>1(1)</td>
</tr>
<tr>
<td>5</td>
<td>54 M</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>27 M</td>
<td>14</td>
<td>1(2)</td>
</tr>
<tr>
<td>7</td>
<td>37 M</td>
<td>16</td>
<td>2(2,2)</td>
</tr>
<tr>
<td>8</td>
<td>52 M</td>
<td>7</td>
<td>2(1,1)</td>
</tr>
<tr>
<td>9</td>
<td>53 M</td>
<td>10</td>
<td>4(1,2,1,1)</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>47±9</td>
<td>8.8±4.2</td>
<td>1.9±1.2</td>
</tr>
</tbody>
</table>

Group 2 (rejection) |                        |                   |                                  |
| 10      | 63 M             | 1                 | 0                                |
| 11      | 56 F             | 5                 | 1(2)                             |
| 12      | 28 M             | 1                 | 0                                |
| 13      | 56 F             | 7                 | 2(2,2)                           |
| 14      | 61 M             | 10                | 5(2,2,2,1,1)                     |
| 15      | 51 F             | 6                 | 4(2,1,2,1)                       |
| Mean±SD | 53±12            | 5.0±3.2           | 2.0±1.9                          |

p vs. group 1 NS NS NS

In brackets, grade of each previous rejection episode according to Billingham criteria.
TABLE 3. Hemodynamic and angiographic data

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2 (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=9)</td>
<td>R ⊕</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>90±6</td>
<td>86±10</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.9±0.5</td>
<td>2.9±0.5</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>131±13</td>
<td>121±18</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>10±3</td>
<td>10±4</td>
</tr>
<tr>
<td>MRAP (mm Hg)</td>
<td>4±2</td>
<td>5±4</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>107±9</td>
<td>96±15</td>
</tr>
<tr>
<td>SVR (mm Hg/l/min)</td>
<td>19.5±3.9</td>
<td>18.9±6.4</td>
</tr>
<tr>
<td>RPP (mm Hg · beats/min)</td>
<td>11,835±1,234</td>
<td>10,467±2,320</td>
</tr>
<tr>
<td>[Hb] (mmol/l)</td>
<td>7.13±0.66</td>
<td>7.18±0.64</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>12.17±1.50</td>
<td>11.46±0.82</td>
</tr>
<tr>
<td>EDV (ml/m²)</td>
<td>73±13</td>
<td>78±18</td>
</tr>
<tr>
<td>EF (%)</td>
<td>66±12</td>
<td>64±13</td>
</tr>
</tbody>
</table>

Values are mean±SD.

R ⊕, during rejection; R ⊖, after rejection therapy; HR, heart rate; CI, cardiac index; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; MAP, mean arterial pressure; SVR, systemic vascular resistances; RPP, rate-pressure product; [Hb], hemoglobin concentration; PaO₂, arterial oxygen pressure; EDV, end-diastolic volume; EF, ejection fraction.

artery was used to place a 7F pigtail angiographic catheter into the left ventricle. Basal left ventricular, aortic, right heart and pulmonary wedge pressures were recorded, and cardiac output was determined by the thermodilution method (Cardiac Output Computer model 9520A, Edwards Laboratories). Heart rate, pressures, and systemic vascular resistances were calculated by a catheterization data analysis computer system (model 5600M, Hewlett-Packard Co., Palo Alto, California) that performed on-line analysis of nine beats for averaging respiratory variations.

Left ventriculography (30 ml ioxaglate meglumine) was achieved with an electrocardiogram-gated digital subtraction technique at a rate of 25 frames/sec on a 256-pixel matrix (General Electric CGR DG 300), in a 30° right anterior oblique projection. Left ventricular end-diastolic and end-systolic volumes and ejection fraction were calculated by the area-length method. All the measures were obtained after correction of x-ray magnification by recording a frame of a calibrated grid at the assumed location of the left ventricle.

Coronary arteriograms of each coronary artery were obtained in multiple projections after maximal epicardial coronary artery vasodilation was obtained by intracoronary injection of 1.5 mg of isosorbide dinitrate. Arteriograms were obtained by digital subtraction at a rate of 6 frames/sec on a 512-pixel matrix.

To evaluate coronary vasodilator reserve, the following procedure was achieved according to Wilson et al.: After intravenous administration of 5,000 units of heparin sodium, a 3F 20-MHz coronary Doppler catheter (Millar Mikro-Tip disposable Doppler Catheter Model DC-101, Millar Instruments, Inc., Houston, Texas) connected to a single-channel 20-MHz pulsed Doppler velocimeter (model MDV-20 Single Channel Velocimeter, Millar Instruments, Inc.) was positioned into the proximal segment of the left anterior descending artery through a 8F coronary guiding catheter. The catheter position was adjusted to obtain an adequate tracing of phasic coronary blood flow velocity. Mean and phasic coronary blood flow velocity (kHz), mean aortic pressure through the guiding catheter, and electrocardiogram were continuously recorded in basal condition and after the injection of 12 mg of papaverine hydrochloride through the guiding catheter into the left coronary artery (8 mg/papaverine/ml 0.9% saline; 1.5 ml of the solution was introduced into the guiding catheter and flushed with 0.9% saline). The guiding catheter was withdrawn from the coronary ostium after injection of papaverine. Coronary flow reserve was calculated as the peak-to-resting coronary flow velocity ratio (average of two measures; the second one was performed after return to basal value of coronary flow velocity).

Statistical Analysis

Mean values±SD were calculated for each variable. Data from group 1 and group 2 patients were compared by an unpaired t test. In group 2, data before and after treatment of rejection were compared by a paired t test. Significance was determined for p values less than 0.05.

Results

Angiographic Data

Left ventricular angiography evidenced similar values of left ventricular end-diastolic and end-systolic volumes, and ejection fraction in group 1 and in group 2 patients during rejection (Table 3). In group 2 patients, results were not significantly modified after rejection therapy (Table 3). Coronary arteriography showed normal epicardial coronary arteries in all patients.
Hemodynamic Data

Values of right and left ventricular pressures, cardiac index, systemic vascular resistances, and rate-pressure product were comparable in the two groups of patients (Table 3). In group 2, all the hemodynamic parameters were similar before and after rejection therapy (Table 3). Hemoglobin concentration was higher than 10 g/100 ml blood in all patients without any statistical difference between the groups. Arterial oxygen pressure was similar in the two groups (Table 3). The extent of the decline of mean aortic pressure after intracoronary injection of papaverine was not different between group 1 and group 2, and in group 2 before and after treatment of rejection crisis (8±3% in group 1, 9±3% in group 2 during rejection, and 10±4% after rejection therapy).

Coronary Vasodilator Reserve

The coronary vasodilator reserve was significantly lower in patients with rejection as compared with patients without rejection (Figure 1). All patients without rejection had a peak-to-resting coronary blood flow velocity ratio greater than 4.0, which was higher than the lower limit of normality of 3.5 determined by Wilson et al. There was no correlation between the flow velocity ratio and the number of previous episodes of rejection. Conversely, patients with rejection had a peak-to-resting coronary blood flow velocity ratio smaller than 3.0. After rejection therapy, the ratio was dramatically increased, and all the group 2 patients had a coronary reserve similar to that of group 1 patients (Figures 1 and 2). Hence, coronary vasodilator reserve in transplant recipients with rejection returned to within the normal range after treatment of rejection crisis.

Discussion

Vascular injury of the microcirculation has been documented as a common feature during organ allograft rejection. In nonrejecting dog hearts, the response of the coronary circulation to vasodilator drugs is normal but decreases during rejection. Those alterations develop earlier than the decrease in basal coronary flow. Obviously, most animal transplants were performed with little or no immunosuppression, and rejection was more fulminating than that occurring in immunosuppressed patients. In humans, recent studies have evidenced that in patients without heart rejection, coronary vascular reserve was within the normal range when evaluated either by coronary Doppler catheter and maximally vasodilating doses of papaverine or by coronary sinus thermodilution and dipyridamole-induced vasodilation. Conversely, we have recently demonstrated that coronary reserve was greatly impaired when mild-to-moderate histological signs of rejection are present. This confirms and extends previous findings about coronary microvascular histological and functional involvement during cardiac rejection. Although there are no clinical data documenting the occurrence of ischemic events or ischemia when the myocardial metabolic demand increases during acute rejection crisis, whether these alterations of coronary vasodilator capacity are reversible with rejection therapy is a question of importance from both a pathophysiological and clinical standpoint.

The major finding of the present study was that the impairment of coronary vasodilator reserve in orthotopically transplanted patients with mild-to-moderate histological signs of rejection was reversible with rejection therapy. Additionally, although the number of group 2 patients was small, it seems that the level of coronary flow reserve during rejection did not depend on the grade of rejection and did not allow prediction of the peak-to-resting flow velocity ratio after therapy. Among the group 2 patients, patients 10 and 12 with mild rejection had a ratio lower than 1.8, and patient 15 with moderate rejection had a ratio of 2.9. After treatment, their ratios were 4.2, 5.2, and 4.0, respectively.

Several hypothetical events can explain a reversible alteration of coronary reserve in these patients. First, a transient metabolically or immunologically related change in responsiveness of vascular wall to papaverine could be involved. Although doses of papaverine that have been demonstrated to induce maximal coronary vasodilation were used, such a mechanism cannot be totally excluded. Other methods producing maximal coronary vasodilation, however, have been used to demonstrate that coronary vasodilator capacity is impaired during rejection (i.e., postocclusive hyperemia and dipyridamole or adenosine in animals, and dipyridamole in humans). Second, interstitial edema and swelling of myocardial fibers might have resulted in a com-
pression of small intramyocardial vessels that could limit vasodilation after papaverine. Third, the microvascular bed might have been obstructed by clotting, which could disappear by spontaneous thrombolysis, or obliterative intimal proliferation, which could regress. Fourth, intimal and perivascular lymphocyte and monocyte infiltration could release vasoactive mediators such as leukotrienes C4 and D4 that could have induced smooth muscle contraction, which explains the reduction of coronary vascular reserve during heart rejection. Although our data do not allow determination of the mechanism responsible for a blunted coronary arteriolar response during rejection, they certainly emphasize that these vascular abnormalities of the coronary distal bed were reversible with appropriate therapy.

The use of coronary flow reserve as a tool for evaluation of coronary distal bed functional status in patients with allograft heart transplant should be discussed. In this study, coronary vasodilator reserve was measured according to the technique previously described by Wilson et al after maximal epicardial coronary dilation produced by isosorbide dinitrate, by using the peak-to-resting coronary flow velocity ratio after intracoronary injection of a maximally vasodilating dose of papaverine. Because coronary vasodilator reserve is expressed as the ratio of peak-to-resting coronary blood flow velocity, factors that could have increased basal flow or impaired maximal flow, or increased basal flow and impaired maximal flow, during rejection, and that did not depend on alterations of the coronary microvasculature vasodilator capacity must be discussed. First, hemoglobin concentration and arterial oxygen pressure were not different between groups 1 and 2 either during rejection or after treatment. Second, because coronary reserve depends on the level of basal myocardial oxygen requirement, patients with cardiac allograft hypertrophy were excluded from the study. Additionally, the determinants of basal myocardial oxygen consumption, that is, left ventricular end-diastolic volume and pressure, mean aortic pressure, systemic vascular resistances, heart rate, and rate-pressure product, were similar in the two groups. These parameters did not vary significantly after treatment of rejection of group 2. Third, in group 2 during rejection, left ventricular end-diastolic pressure, mean aortic pressure, and mean aortic pressure decreases after intracoronary papaverine were similar to pressure decreases in group 1 and cannot explain the differences in coronary vascular reserve. That hemodynamics were not different in patients with and without rejection is a common finding until late in the course of rejection. Fourth, medications that could have interfered with papaverine vasodilation were discontinued 24 hours before the investigation. None of the patients received β-blockers or converting enzyme inhibitors. Calcium

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**Figure 2.** Simultaneous recordings of phasic and mean coronary flow velocity of left anterior descending coronary artery in same patient during episode of heart rejection and after rejection therapy. After intracoronary administration of 12 mg of papaverine, peak-to-resting coronary blood flow velocity ratio increased from 2.9 during rejection to 6.0 after treatment.
blockers used in all the groups were short-acting drugs, and although the small number of patients receiving these agents in each group did not allow statistical analysis, it is unlikely that our results could have been affected by calcium blockers. Cyclosporine, which could alter flow in allograft transplants,22,23 cannot explain differences between the two groups of patients receiving similar immunosuppressive treatment. Fifth, accelerated coronary atherosclerosis in patients treated by cyclosporine and prednisolone34,35 could be a potent mechanism of reduction of coronary reserve. This mechanism can be disregarded for all the group 2 patients who had normal epicardial coronary arteries on coronary arteriograms. Additionally, all the group 2 patients were investigated within the first year after surgery (Table 2), and previous studies demonstrated that at 1 year, the prevalence of coronary artery disease at 19% and stenoses at 50% was uncommon.34,35 Most importantly, the normalization of coronary reserve after treatment of rejection does not support fixed lesions of the coronary vasculature and suggests that even if distal atherosclerosis was present, it was not severe enough to reduce coronary reserve.

This study provides evidence that in patients with mild-to-moderate histological signs of rejection, alterations of coronary vascular reserve were reversible when immunosuppressive therapy is provided. This is in accordance with the fact that when rejection therapy is promptly administered, minor left ventricular functional and histological abnormalities because of mild-to-moderate rejection could be reversed.21,26 Such a response of coronary circulation to vasodilator drugs during acute rejection might be clinically important in the management of rejection crisis and might be interesting for future research dedicated to noninvasive monitoring of patients with heart transplantation. Thus, myocardial kinetics of Tc-MIBI,37 measurement of myocardial blood flow by positron-emission tomography38 or by ultrafast computed tomography39 could eventually serve as a means of rejection diagnosis such that coronary flow reserve is impaired even in patients with mild rejection. Consequences of more severe rejection or of repetitive rejection episodes on the coronary microvasculature are unknown. Scar fibrosis could result in extravascular compression of coronary microvessels, reduction of the number of functional vessels, or both, and could induce a gradual decline of coronary vascular reserve, which is still to be evaluated by further studies.

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References


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