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Received March 11, 1992; revision accepted July 1, 1992.

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Supported by the Division of Sponsored Research, University of Florida, grant DSR-D-24.

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TABLE 1. Patient Characteristics and Mean Diameter of the Proximal Left Anterior Descending Coronary Artery Determined by Intravascular Ultrasound

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Rejection on study biopsy</th>
<th>CMV infection after transplantation</th>
<th>Prior rejection requiring intravenous steroids</th>
<th>LAD mean diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
<td>Adenosine</td>
</tr>
<tr>
<td>1</td>
<td>45</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3.90</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>4.22</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>4.65</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3.39</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>3.74</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>5.98</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>4.15</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3.74</td>
</tr>
<tr>
<td>9</td>
<td>48</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4.38</td>
</tr>
<tr>
<td>Mean</td>
<td>52.7</td>
<td></td>
<td></td>
<td></td>
<td>4.24</td>
</tr>
<tr>
<td>SD</td>
<td>8.1</td>
<td></td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; LAD, left anterior descending coronary artery; +, positive; 0, negative.

The mean LAD diameters in the nitroglycerin, initial, and ACh conditions expressed as a percentage of the adenosine diameter were 97.7±7.5%, 88.8±7.0%, and 83.8±8.8%, respectively. Repeated-measures ANOVA followed by Duncan’s multiple comparison procedure demonstrates that the nitroglycerin, initial, and ACh states are all significantly different (p<0.0001).

The Doppler flow measurements with adenosine and ACh are shown in Table 2, and Figure 1 shows a typical Doppler flow study after ACh administration. All four patients showed increases in flow with both ACh and adenosine. By Duncan’s multiple comparison procedure, the mean adenosine and ACh flows are significantly higher than initial flow, and the coronary flow in response to adenosine is significantly higher than that in response to ACh (p<0.05). Maximal responses occurred approximately 25–35 seconds after bolus adenosine, 20–30 seconds after ACh, and 15–25 seconds after nitroglycerin. The maximal vasoconstrictor response to ACh occurred during increased flow, with no evidence of flow-mediated dilation.

Discussion

These data show significant epicardial coronary artery vasoconstriction in response to ACh, consistent with endothelial dysfunction, in a series of nine patients studied prospectively 1 year after heart transplantation.

TABLE 2. Left Anterior Descending Coronary Artery Flow in Response to Adenosine and Acetylcholine and Coronary Flow Reserve with Adenosine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial</th>
<th>LAD flow (ml/min)</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adenosine</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>350</td>
<td>172</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>487</td>
<td>315</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>243</td>
<td>166</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>180</td>
<td>163</td>
</tr>
<tr>
<td>Mean</td>
<td>63*</td>
<td>315*</td>
<td>204*</td>
</tr>
<tr>
<td>SD</td>
<td>26.6</td>
<td>134.4</td>
<td>74.1</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; CFR, coronary flow reserve.

*p<0.05.
Subselective coronary blood flow increased significantly in response to ACh despite constriction of the epicardial vessel, suggesting that microvascular vasodilation remained intact. CFR as assessed with adenosine was normal. None of these patients had evidence of anatomic cardiac allograft vasculopathy by intravascular ultrasound or selective coronary angiography.

The coronary vasodilator response to non–endothelium-dependent agents remains intact after cardiac transplantation, as shown in both quantitative coronary angiographic and intravascular ultrasound studies. Variable responses to endothelium-dependent agents, including both ACh and substance P, have been reported. These observations have been complicated by 1) the need for contrast injection and quantitative coronary angiography, 2) variations in time from transplantation to time of study, 3) variable information concerning the patient’s past and present rejection status and CMV status, 4) uncertainty concerning the appropriate baseline for quantitative observations, and 5) variations in dose and dose–response curve.

With intravascular ultrasound imaging, the vasodilator effect of contrast and the technical difficulties of quantitative coronary angiography are eliminated. The ability to continuously monitor the arterial response to vasoactive agents with intravascular ultrasound allows assessment of the maximal response to agents with brief pharmacological duration of action and eliminates the need for infusion. Intravascular ultrasound measurements have been shown to be reproducible and accurate in vitro and in vivo. The problem of an intense chronic vasoconstrictor state after cardiac transplantation and the possibility that this could alter apparent vasomotor responses led us to use the maximum coronary diameter observed after intracoronary adenosine as a standard and to express the diameters measured in other conditions as a percentage of the maximally vasodilated state. This approach provides a stable, reproducible anatomic basis for comparison, as advocated by other investigators.

In five patients with complete data sets, we found no significant difference between adenosine and nitroglycerin responses, which probably represent the true maximal coronary diameter. In contrast, when initial, nitroglycerin, and ACh diameters are expressed as a percentage of the adenosine diameter, the initial diameter (mean 88.8%) is significantly less than nitroglycerin (97.7%), and the diameter observed after ACh challenge (83.8%) is significantly smaller than either nitroglycerin or initial, consistent with an active vasoconstrictor response.

Although limited by small numbers, the comparison of ACh responses in patients who had either CMV infection or rejection versus those who had neither still approached statistical significance, suggesting that there may be exaggerated ACh-induced vasoconstriction consistent with more severely dysfunctional endothelium in those who experienced CMV infection or rejection. This observation requires further investigation in a larger series.

The data from intravascular ultrasound imaging and Doppler flow studies allow direct calculation of volume flow and CFR in the coronary branch vessel under consideration. Our data show a CFR of 5.06 in these heart transplant patients in response to adenosine, which is consistent with the CFR in normal individuals with dipyridamole and papaverine. In striking contrast to the active vasoconstriction produced in the epicardial conduit vessels provoked by ACh, mean coronary flow increased from 63.1 to 204 ml/min after ACh, consistent with vasodilation of the microvascular resistance vessels. These findings suggest that the endothelial injury that occurs early after heart transplantation may be targeted toward larger vessels and may spare the microvasculature.

In summary, these data demonstrate consistent significant epicardial coronary vasoconstriction and an increase in coronary blood flow in response to ACh at 1 year after cardiac transplantation in a group of patients who have normal CFR in response to adenosine and no
anatomic evidence of cardiac allograft vasculopathy. The data are consistent with the hypothesis that coronary artery endothelial dysfunction occurs frequently in heart transplant recipients. Endothelial dysfunction may be more severe in those who have experienced CMV infection or required parenteral steroid therapy for rejection episodes. The preservation of CFR suggests that the microvasculature may be spared in this process. The direct cause or causes of endothelial injury, including mechanical or thermal trauma, drug effects, infection, or immunologically mediated injury, remain uncertain.

Acknowledgment
The authors wish to acknowledge the assistance of Ronald G. Marks, PhD, Professor of Biostatistics, University of Florida, with data analysis.

References
Endothelial dysfunction early after heart transplantation. Assessment with intravascular ultrasound and Doppler.
R M Mills, Jr, J M Billett and W W Nichols

Circulation. 1992;86:1171-1174
doi: 10.1161/01.CIR.86.4.1171

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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the World Wide Web at:
http://circ.ahajournals.org/content/86/4/1171

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