Enhanced detection of cardiac allograft arterial disease with intracoronary ultrasonographic imaging

Intracoronary ultrasonographic imaging was performed in 60 patients 0.3 to 9 years (mean 2.9 ± 1.9) after heart transplantation. By using a 1.8 mm intravascular ultrasonographic catheter, 192 (80%) of 240 angiographically visualized major epicardial coronary arteries (right, left main, anterior descending, and circumflex) were imaged by ultrasonography. Coronary luminal irregularities were detected in 15% of arteries by angiography compared with 34% by ultrasonography (p < 0.0001). The typical abnormality detected by ultrasonography consisted of crescentic and/or concentric intimal and medial thickening. Calcification in vascular lesions was rare (<1% of arteries studied). Although the prevalence of angiographic abnormalities tended to be time dependent, ultrasonographic abnormalities were more strongly associated with donor age (normal, 22 ± 8 years, vs abnormal, 33 ± 10 years; p < 0.0001). Cardiac allograft coronary arterial disease is significantly underestimated by contrast angiography. Intravascular ultrasonography may provide a useful adjunct for identification and serial follow-up of this significant problem. (Am Heart J 1993;125:1583.)

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Table I. Prevalence of coronary artery disease by angiography and intracoronary ultrasoundographic imaging related to time after transplantation

<table>
<thead>
<tr>
<th>Time after transplantation (yr)</th>
<th>&lt;1</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>7</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (n = 60)</td>
<td>1</td>
<td>22</td>
<td>19</td>
<td>2</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>No. of abnormal studies (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>1</td>
<td>10</td>
<td>12</td>
<td>2</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

Table II. Angiographic vs ultrasonographic detection of coronary artery disease in 192 coronary artery segments

<table>
<thead>
<tr>
<th>Coronary angiography</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracoronary ultrasonography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>124 (66%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>42 (21%)</td>
<td>24 (13%)</td>
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</table>

Coronary angiography. Coronary angiograms were performed by using the Judkins technique via the right femoral artery in all cases. Angioplasty guiding catheters (SF) were used to perform coronary angiograms in multiple projections to optimize visualization of all coronary artery segments. Coronary angiograms were assessed independently by two investigators experienced in reviewing transplant angiograms and who were familiar with the spectrum of cardiac allograft vascular disease. Angiographic findings were considered to be abnormal if even minor luminal irregularities were present. Disagreements were resolved by consensus. Angiographically detected abnormalities were further characterized with respect to involvement of the four main epicardial segments (right, left main, circumflex, and anterior descending coronary arteries) and distal vessels.

Intracoronary ultrasoundographic imaging. After angiography, 2500 to 5000 units of heparin were given intravenously. In the first 27 cases nitroglycerine was not given routinely; however, in the subsequent 33 cases, 200 to 400 \( \mu \)g of nitroglycerine were administered into the right and left coronary arteries if ultrasoundographic imaging was to be performed. A 0.014 inch (0.036 cm)-diameter, 175 cm-long, soft-tipped, flexible guide wire was advanced distally into the coronary artery to be imaged. The ultrasoundographic imaging catheter was passed over the guide wire (monorail system) into the coronary artery and advanced while the real time ultrasoundographic images were observed to the point where the coronary lumen remained barely visible. The catheter was then slowly withdrawn while the video images were continuously recorded. The total duration of ultrasoundographic imaging within the coronary artery was 30 to 90 seconds. The coronary arteries were not imaged if the guiding catheter wedged in the ostium of the vessel or if the ultrasoundographic catheter could not be easily passed into

METHODS

Patient population. The study consisted of 60 cardiac transplant recipients (46 men, 14 women) returning for routine follow-up in 57 cases and undergoing angiography for clinically suspected coronary artery disease in 3. Recipient mean age at transplantation was 46 ± 11 years (range 20 to 62). Donor heart mean age at the time of transplantation was 28 ± 11 years (range 11 to 53). At this institution coronary angiography is routinely performed 1 year after transplantation, every other year thereafter, and otherwise if clinically indicated. One patient was studied 4 months after transplantation; the remainder of the patients were studied ≥1 year later (Table I).
Fig. 1. Angiographically detected normal left coronary artery (top panel) 5 years after transplantation (male donor, age 19). Normal intracoronary ultrasonographic image (lower panel) from proximal anterior descending artery. Arrow, lower panel, Region of normal intimal thickness.

the artery to be studied. Coronary angiograms were repeated on completion of the ultrasonographic imaging.

Intracoronary ultrasonographic imaging was performed by using a CVIS (Cardiovascular Imaging Systems Inc., Sunnyvale, Calif.) intravascular ultrasonographic imaging device operating at 30 mHz. The imaging catheter consisted of a housed rotating (1800 rpm) mirror driven by a flexible wire shaft within a 5F (1.8 mm–diameter) catheter generating images at a frame rate of 30 frames/sec. Real-time ultrasonographic images were recorded onto a Panasonic model AG 7300 Super VHS video recording system (Panasonic Co., Secaucus, N.J.). The ultrasonographic images were subsequently reviewed by an experienced ultrasonographer unaware of the results of the coronary angiograms. A qualitative appraisal of the presence, character, and extent of intimal thickening was made for each artery imaged.

Data analysis. Means are given ± 1 SD. Comparisons were made by using unpaired two-tailed $t$ testing or single-factor analysis of variance with multiple comparisons by using Scheffe’s technique. Contingency table analysis and $\chi^2$ testing was performed on nonparametric variables. Differences were considered statistically significant at a $p$ value $\leq 0.05$. 
RESULTS

Coronary angiography. Angiograms revealed abnormalities in 16 (27%) of 60 patients. In those patients with angiographic evidence of coronary artery disease, 36 (15%) of 240 major coronary arterial segments were abnormal: 16 right, 2 left main, 8 left anterior descending, and 10 circumflex coronary arteries. Abnormalities were seen in 1 artery in 5 cases, in 2 arteries in 4 cases, in 3 arteries in 5 cases, and in all major epicardial arteries in 2 cases. Most abnormalities consisted of minor luminal irregularities (<50% luminal narrowing) of epicardial arteries with angiographically detected normal distal vessels. In five patients however, more significant obstructive large and/or small vessel disease was observed. The latter five patients were studied at 1, 4, 5, 5, and 6 years after transplantation, respectively. The prevalence of angiographically visible coronary artery disease tended to increase with time over transplantation (17% ≤ 1 year vs 32% > 1 year) although this trend did not reach statistical significance (p = 0.20). Angiographic abnormalities were unrelated to recipient age, ischemic time, or number of rejection episodes. A trend toward an association with donor age was noted in the entire group (p = 0.07), and donor age ≥30 years at transplantation was associated with
significantly more angiographically detected abnormalities than donor age <30 years (p < 0.03).

**Intracoronary ultrasonographic imaging.** Of the 240 major epicardial coronary arteries angiographically visualized (i.e., right, left main, circumflex, and anterior descending coronary arteries), 192 (80%) were studied by intracoronary ultrasonographic imaging. On average, 3.2 arteries per patient were imaged, including the left main coronary artery in all cases. In 23 (38%) cases the right coronary artery could not be imaged by ultrasonography either because the artery was small and nondominant or because of catheter wedging in the right coronary ostium. The left anterior descending coronary artery could not be visualized in 6 (10%) cases because of inability to easily pass the guide wire. The circumflex artery was not imaged in 19 (32%) cases because of inability to easily pass the guide wire and/or imaging catheter.

Sixty-five (34% of arteries studied) abnormal arteries were detected by ultrasonographic imaging. Single or multiple areas of very focal crescentic intimal hyperplasia comprised 32 (approximately 50%) of 65 of all abnormalities detected. Extensive crescentic and/or concentric intimal thickening involving long segments of artery were observed in the remainder. Calcification within a vascular lesion was uncommon and only seen in two instances. The detection of coronary artery abnormalities by intra-

**Fig. 3.** Intracoronary ultrasonographic images of marked eccentric intimal thickening (arrows, lower panel) in right coronary artery with minimal angiographic disease (arrow, top panel) 4 years after transplantation (male donor, age 33 years).
coronary ultrasonographic imaging was strongly associated with donor heart age (22 ± 8 years of age for normal studies vs 33 ± 10 years of age for abnormal studies, \( p < 0.0001 \)). There was no association of ultrasonographically detected abnormalities with recipient age, ischemic time, or number of rejection episodes.

**Comparison of angiography and ultrasonographic imaging.** Coronary angiography significantly underestimated the extent of coronary arterial disease in transplant recipients (Table II; Figs. 1-3). In 41 (21%) of 192 arteries imaged, abnormalities unsuspected on angiography were detected by ultrasonographic imaging. In only one instance was an abnormality suspected by angiography without evidence of an ultrasonographically detected abnormality, possibly because of vascular spasm. In one patient pathologic correlation was available (Fig. 4). Four months posttransplantation, the patient underwent coronary angiography and intracoronary ultrasonographic imaging 13 days before retransplantation for refractory cellular rejection and left ventricular dysfunction. Angiography underestimated the presence and extent of coronary artery disease found in the
explanted heart; however, there was good correlation between intracoronary ultrasonographic and pathologic findings.

**Adverse events.** In 9 (33%) of 27 patients who did not routinely receive intracoronary nitroglycerine, coronary artery spasm was seen on coronary angiography after completion of intracoronary ultrasonographic imaging. Spasm of the left coronary artery system was only observed in one patient. Intracoronary infusion of 200 to 400 μg of nitroglycerine resulted in the immediate reversal of spasm. In one patient ventricular fibrillation occurred during right coronary ultrasonographic imaging. After a single direct-current counter shock, repeat coronary angiography after intracoronary nitroglycerine showed no abnormality. Coronary artery spasm was more common before the routine use of intracoronary nitroglycerine (9 of 27 cases before vs 1 of 33 cases after, \( p < 0.002 \)). No other adverse events were related to ultrasonographic imaging.

**DISCUSSION**

The spectrum of coronary arterial abnormalities in cardiac transplant recipients has been best characterized by Johnson et al.\(^{14} \) in a pathologic study of 61 cardiac allografts examined 1 day to 11.9 years after transplantation. Although the cause of death or graft loss was cardiac in only 25 (41%) cases, only seven hearts had normal coronary arteries. They described four categories of abnormality. Fibrous intimal thickening confined to large and medium epicardial arteries was seen in 29 hearts predominantly early after transplantation (≤1 year). These abnormalities were found as early as 2 weeks after transplantation, indicating the rapidity by which this process may develop. Diffuse necrotizing vasculitis was seen in four patients ranging from 7 to 13 months after transplantation. Large artery atheromatous plaques (12 patients) without other vascular abnormalities occurred predominantly >1 year after transplantation. Two hearts, however, were found to have typical coronary atherosclerosis at 1.5 and 4.5 months after transplantation; the atherosclerosis was believed to have been present in the donor heart before transplantation. The remaining nine hearts were found to have a mix of diffuse fibrous intimal thickening in large and small extramural and in some intramyocardial arteries combined with typical atherosclerotic plaques. These hearts were generally more remote from transplantation (mean 56 months). The intracoronary ultrasonographic findings in our current study are in concordance with the pathologic findings noted by Johnson et al.\(^{14} \) that is, predominantly large-vessel intimal thickening, which was
found in 45% of patients even the first year after transplantation.

The cause of vascular disease in the cardiac allograft has not been clearly defined. Although immunologically mediated vascular injury likely contributes, it is also likely that a higher-than-suspected incidence of occult coronary artery disease is transplanted with the donor. The coexistence of immunologic injury in areas of preexisting intimal abnormalities (fatty streaks or fibrous lesions) may serve to advance the arteriopathy after transplantation. It is well known that fatty streaks and immature fibrous plaques are common in the "donor-aged" population, that is, second to fourth decades, and that the prevalence of these abnormalities increases with age.

The very strong association between donor age and ultrasonographic abnormalities in our current study implies that preexisting donor coronary artery abnormalities may indeed have an important role to play in the progression of coronary artery disease after transplantation. Progression of disease at sites of minimal vascular abnormality could potentially be mediated by a number of factors that cause arterial wall injury, including profound hypothermic ischemia at the time of donor harvesting, immunologic injury to vascular endothelium, and perhaps viral infection.

Although the rate of adverse events was low in the current series of patients and the procedure was well tolerated, there is nevertheless concern about the potential for coronary artery injury; intracoronary ultrasonographic imaging cannot be recommended as a routine diagnostic procedure in heart transplant recipients. Experimental data show that denudation of coronary artery endothelium and disruption of the arterial media by balloon catheter trauma induces a proliferative myocyte response resulting in intimal fibrosis. A lesser degree of injury such as might be induced by a fine guide wire has, however, been found to heal without a reactive intimal response. Thus great care was taken to avoid traumatic introduction of either the guide wire or imaging catheter. Attempts were abandoned when any difficulty was encountered and not undertaken in small vessels. The long-term effects of intracoronary ultrasonographic imaging on intimal proliferation nevertheless remain unknown. In the context of clinical investigation, however, serial intracoronary ultrasonographic studies may be helpful in providing a more accurate assessment of the prevalence, extent, and time course for the development and progression of allograft coronary artery disease and may help to direct newer therapeutic strategies.

REFERENCES


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Percutaneous transluminal coronary angioplasty through 6F diagnostic catheters: A feasibility study

This study evaluated the feasibility of performing coronary angioplasty through 6F diagnostic catheters by mainly using over-the-wire balloon systems on 84 lesions in 70 patients. Procedural variables, including vessel opacification and angioplasty outcome, were assessed. Changes in hematocrit after angioplasty were compared for 6F versus 7F and 8F systems. Successful 6F dilatation was performed in 72 (85.7%) of 84 lesions and 58 (82.9%) of 70 patients. Seven of the 12 lesions unable to be dilated with 6F systems were successfully dilated with larger French systems. Coronary artery opacification with the 6F catheters after balloon dilatation was less than optimal with the balloon and guidewire still in the catheter. Changes in hematocrit after 6F procedures were significantly less than for 8F procedures (−2.1% vs −4.2%, respectively, \( p < 0.01 \)) but not for 7F procedures (−2.4%, \( p = \) not significant). Potential cost savings for angioplasty with 6F diagnostic catheters could be significant. Thus angioplasty with over-the-wire balloon systems in 6F non-tapered diagnostic catheters are used can be performed safely and with less procedural blood loss than with 8F systems. Significant problems encountered with the current catheter design were poor vessel opacification after balloon dilatation and difficulties with balloon retraction. (Am Heart J 1993;125:1591.)

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Most percutaneous transluminal coronary angioplasties (PTCA) are performed through 6F (2.6 mm) and 7F (2.3 mm) guiding catheters. Although recent reports describe successful coronary balloon angioplasty through 6F, 5F, and even 4F diagnostic catheters, all of these procedures were performed with fixed-wire balloon systems. The development of ultralow-profile, over-the-wire balloon dilation catheters facilitates the use of smaller French guiding and even nontapered diagnostic catheters for angioplasty with over-the-wire balloon systems. Over-the-wire balloon systems are preferred by many operators because of better torque characteristics and because of