Intravascular Ultrasound Evidence of Angiographically Silent Progression in Coronary Atherosclerosis Predicts Long-Term Morbidity and Mortality After Cardiac Transplantation

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OBJECTIVES

The aim of this study was to determine whether angiographically silent early coronary intimal thickening could predict long-term morbidity and mortality.

BACKGROUND

Although intravascular ultrasound (IVUS) is widely used to detect early transplant coronary disease, its prognostic significance has not been well defined.

METHODS

The study cohort consisted of 143 patients who underwent early multivessel (2.1 ± 0.7 arteries/patient) IVUS examination 1.0 ± 0.5 month and 12.0 ± 1.0 month after transplantation. The change in intimal thickness was evaluated using paired analysis of 1,069 matched sites. Rapidly progressive vasculopathy was defined as the change in intimal thickness ≥0.5 mm. Patients were followed for a primary end point of all-cause mortality and a secondary composite end point of mortality and nonfatal myocardial infarction (MI).

Angiographic disease, defined as any ≥50% diameter stenosis, was assessed in 126 patients.

RESULTS

Intravascular ultrasound at one year demonstrated rapid progression in 54 (37%) of 143 patients and new lesions in 67 (47%) of 143 of patients. At a mean clinical follow-up of 5.9 years, more patients with rapidly progressive vasculopathy died, as compared with those without (26% vs. 11%, p = 0.03). Death and MI also occurred more frequently among those with rapid progression than in those without it (51% vs. 16%, p < 0.0001). There was no significant difference in outcome in patients with and without donor-transmitted lesions. Angiographic disease was found in 11 (22%) of 50 patients with and in 2 (2.1%) of 76 patients without (p = 0.003) rapidly progressive vasculopathy. The IVUS-defined rapid progression correlated highly with future development of angiographic disease (p = 0.0005).

CONCLUSIONS

Rapidly progressive vasculopathy by IVUS, defined as an increase of ≥0.5 mm in intimal thickness within the first year after transplantation, is a powerful predictor of all-cause mortality, MI, and angiographic abnormalities. Accordingly, such patients may be candidates for more aggressive anti-atherosclerotic and/or immunosuppressive therapy. (J Am Coll Cardiol 2005;45:1538–42) © 2005 by the American College of Cardiology Foundation

Long-term success after heart transplantation is primarily limited by the development of coronary vasculopathy, the major cause of death beyond the first post-transplant year (1,2). Early transplant coronary artery disease (CAD) is clinically silent, and ischemia is usually not evident until the disease is far advanced (3–7). Often, the first symptoms are sudden death, serious arrhythmias, or heart failure. Traditionally, annual surveillance coronary angiography has been employed to detect allograft vasculopathy in the early stages, but this approach is limited because early atherosclerosis tends to be undetectable by angiography (8).

Intravascular ultrasound (IVUS) has been proposed as a more sensitive method than angiography to detect and quantify early transplant coronary disease (8–11). A few cross-sectional studies have correlated ultrasound findings with subsequent clinical events, but did not have serial imaging data (12–16). Therefore, we performed systematic IVUS imaging at two time points—shortly after transplantation and one year later—with the goal of determining whether angiographically silent early coronary intimal thickening could predict long-term morbidity and mortality.

METHODS

Patient population. The study population consisted of 363 patients who underwent orthotopic heart transplantation between December 1992 and January 1998. Of these, 143 had baseline and one-year paired IVUS studies. Patients who survived one year after transplantation were included in the study. Ineligibility for cardiac catheterization, refusal of the patient to participate in the study, and presence of angiographic stenoses too severe to permit safe IVUS imaging were the most common reasons for exclusion. The study protocol was approved by the institutional review board, and patients signed an informed consent form.
IVUS. The method of imaging has been reported in detail \((17,18)\). After diagnostic coronary angiography, patients were given intravenous heparin and intracoronary nitroglycerin. A 30-MHz, 3.5-F monorail ultrasound catheter (Boston Scientific, Watertown, Massachusetts) connected to a dedicated scanner (Hewlett-Packard, Andover, Massachusetts) was advanced over an angioplasty guidewire. The most distal transducer location was documented by angiography, followed by a slow, steady, manual pullback from distal to proximal, with continuous recording on videotape while ultrasound landmarks were identified using voice annotation. An attempt was made to image all three coronary arteries.

**IVUS analysis.** Technicians in the IVUS core laboratory, who were blinded to clinical data, reviewed the baseline and follow-up image acquisition sequences to accurately match the coronary segments using the landmarks. They digitized full-motion ultrasound sequences (30 frames/s) into a 640 x 480 pixel matrix with 24 bits per pixel.

For each Coronary Artery Surgery Study (CASS) segment, the site of maximal intimal thickness was identified from the one-year study \((19)\). These same sites were then identified on the baseline IVUS study to yield a pair of measurements. The maximal change in intimal thickness within each segment (one year minus baseline) was calculated for each patient.

**Definitions.** A “donor lesion” was defined as a site with a maximum intimal thickness \(\geq 0.5\) mm at the baseline examination. A de novo lesion was defined as maximum intimal thickness \(\geq 0.5\) mm on follow-up examination at a site where intimal thickness was \(<0.5\) mm on the baseline study. Rapidly progressive transplant vasculopathy was defined as the presence of at least one site with an increase of \(\geq 0.5\) mm in maximum intimal thickness from baseline to one-year measurement (Fig. 1). Clinically significant angiographic disease was defined as any new lesion \(\geq 50\%\) in severity by quantitative coronary angiography.

**Clinical events.** The study's clinical end points were prospectively defined. The primary end point was all-cause mortality. The secondary end point was a composite of death and nonfatal myocardial infarction (MI). Myocardial infarction was defined by new abnormal Q waves or a new segmental wall motion abnormality at catheterization or echocardiography. Double counting of death and MI was avoided. Rejection was defined as cellular rejection grade \(\geq 3A\) based on International Society for Heart and Lung Transplantation criteria by an experienced cardiac pathologist.

**Statistical analysis.** Descriptive statistics were presented as the mean value \(\pm\) SD for continuous variables and as frequencies and percentages for categorical variables. In the multivariable Cox proportional hazard model, the following variables were collected prospectively or obtained by chart review: donor disease, de novo lesions, donor age, recipient age, hypertension, diabetes mellitus, history of smoking, recipient cytomegalovirus (CMV), lipid profile at one year, ischemic time, rejection during the first year, and the use of hydroxymethyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitors. Kaplan–Meier survival and event-free survival curves were constructed for patients with and without rapidly progressive transplant vasculopathy. A p value of \(\leq 0.05\) was considered significant. All analyses were performed using SAS statistical software, version 8.0 (SAS Institute Inc., Cary, North Carolina).

**Abbreviations and Acronyms**

- CAD = coronary artery disease
- CMV = cytomegalovirus
- IVUS = intravascular ultrasound
- MI = myocardial infarction

**IVUS Findings Predicts Post-Transplant Outcome**

**Figure 1.** There is a \(>0.5\) mm difference between the intimal thickness observed at baseline. One-year intravascular ultrasound images which demonstrate rapidly progressive transplant vasculopathy.

**Angiographic follow-up.** Most recent and one-year post-transplant angiograms were analyzed using computerized electronic calipers (Philips Inturis Suite, version 2.2, Philips Medical Systems, N.A., Bothell, Washington) or manual electronic calipers (Mitutoyo Corp., Kawasaki, Japan). Seventeen cine films were not available.

**RESULTS**

**Patient population.** The donor and recipient characteristics of the study cohort are summarized in Table 1. Rapid progression occurred more commonly in recipients with diabetes mellitus and higher triglyceride levels, as well as in those who were cytomegalovirus (CMV) positive. On multivariable logistic regression analysis, recipient CMV status and diabetes mellitus were the only independent predictors of rapidly progressive vasculopathy.

**IVUS findings.** In 143 patients, baseline and follow-up IVUS examinations were performed at 1.0 \(\pm\) 0.5 and 12.0 \(\pm\) 1.0 months after transplantation. Paired analysis of 1,069 matched sites was performed in 297 arteries (mean 2.1 arteries/patient). Atherosclerotic (donor) lesions were identified in 78 donor hearts (55%) at baseline examination. In the first year after transplantation, 67 patients (47%) developed de novo lesions. Rapidly progressive transplant vasculopathy occurred in 54 patients (37%) (Fig. 2).
Clinical outcome. Clinical follow-up was available in all patients for an average duration of 5.9 years (range 1.1 to 8.9 years) after transplantation. During the follow-up period, there were 25 deaths (17%). Fourteen (26%) of 54 patients with and 11 of 89 (12%) without rapidly progressive disease died (p = 0.027) (Fig. 3). Of the 30 (21%) MIs, 21 (40%) were in patients with and 9 (10%) were in those without rapidly progressive vasculopathy (p = 0.0001). Death or nonfatal MI occurred in 44 patients (31%); 28 (51%) in patients with and 16 (18%) in those without rapidly progressive vasculopathy (p = 0.0001). Overall survival and MI-free survival at a mean of 5.9 years of follow-up was significantly shorter in patients with rapidly progressive vasculopathy (Fig. 3). When patients were classified based on one-year ultrasound finding of de novo lesions, those with new lesions had a significantly shorter event-free survival, although overall survival was similar (Fig. 4).

Development of angiographic disease. Significant angiographic disease was observed in three patients (2.1%) at 1 year and 13 patients (10.3%) at a mean follow-up of 5.1 years (range 2.1 to 8.9 years). Of these 13 patients, 11 had IVUS-defined rapidly progressive vasculopathy, and 2 did not (p = 0.003). Although a higher percentage of patients with de novo lesions by IVUS at one year eventually developed angiographic disease, this difference was not statistically significant. Rapidly progressive vasculopathy at one-year ultrasound was strongly correlated with future development of angiographic disease (chi-square test for correlation, p = 0.0005). The sensitivity and specificity of rapidly progressive vasculopathy for predicting future angiographic disease were 84% and 64%, respectively.

Table 1. Differences in the Patients With and Without Rapidly Progressive Transplant Vasculopathy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 143)</th>
<th>Present (n = 54)</th>
<th>Absent (n = 89)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age (yrs)</td>
<td>33 ± 13</td>
<td>35 ± 13</td>
<td>31 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Recipient age (yrs)</td>
<td>52 ± 11</td>
<td>54 ± 9</td>
<td>50 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Recipient gender (male, %)</td>
<td>81</td>
<td>80</td>
<td>83</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>16</td>
<td>17</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>73</td>
<td>76</td>
<td>71</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>14</td>
<td>23</td>
<td>9</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dl)</td>
<td>1.4 ± 0.5</td>
<td>1.4 ± 0.6</td>
<td>1.4 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Recipient CMV (% positive)</td>
<td>61</td>
<td>69</td>
<td>48</td>
<td>0.03</td>
</tr>
<tr>
<td>History of ischemic cardiomyopathy (%)</td>
<td>54</td>
<td>57</td>
<td>52</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic time (min)</td>
<td>141 ± 47</td>
<td>139 ± 52</td>
<td>143 ± 44</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²) ± 1 yr</td>
<td>32.0 ± 8.5</td>
<td>34 ± 10.0</td>
<td>30.7 ± 7.2</td>
<td>NS</td>
</tr>
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<td>Total cholesterol (mg/dl)</td>
<td>230 ± 59</td>
<td>233 ± 58</td>
<td>228 ± 60</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>146 ± 50</td>
<td>144 ± 44</td>
<td>147 ± 53</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>46 ± 14</td>
<td>43 ± 14</td>
<td>47 ± 13</td>
<td>NS</td>
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<tr>
<td>Triglycerides (mg/dl)</td>
<td>200 ± 110</td>
<td>239 ± 129</td>
<td>175 ± 87</td>
<td>0.002</td>
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<td>Statins use at 1 yr (%)</td>
<td>34</td>
<td>43</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Episodes of ≥3A rejection at 1 yr (%)</td>
<td>55</td>
<td>59</td>
<td>52</td>
<td>NS</td>
</tr>
</tbody>
</table>

*p Between patients with and without rapidly progressive vasculopathy.

BMI = body mass index; CMV = cytomegalovirus; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Figure 2. Distribution of patients according intravascular ultrasound findings.

Figure 3. Distribution of events in patients with and without rapid progression of transplant vasculopathy. MI = myocardial infarction.
DISCUSSION

This study provides strong evidence supporting our hypotheses that the development of transplant vasculopathy in the first year after transplantation predicts all-cause mortality, nonfatal MI, and the subsequent development of angio-graphic coronary obstructions. These data demonstrate the ability of IVUS to identify a high-risk population in the first year after transplantation and underscore the importance of serial ultrasound examinations.

Previously published reports suggested an association between ultrasound findings and clinical outcomes. In four cross-sectional studies, patients with severe intimal thickness (defined differently as >0.3 mm, >0.5 mm, or >1 mm) at a single IVUS examination, one to five years after transplantation, had more subsequent cardiac events (12–15). However, none of these studies employed a multi-vessel, serial ultrasound examination early after transplantation, limiting their value in establishing the relationship between the development of vasculopathy and subsequent events.

Compared with available cross-sectional studies, systematic imaging early and one year after transplantation eliminates the confounding effects of differing time intervals between transplantation and ultrasound examination and allows accurate assessment of donor-transmitted atherosclerosis and allograft vasculopathy (17). In previous studies, only the most proximal segments of a single coronary artery were analyzed. We have previously shown that such an approach can lead to underdiagnosis of transplant vasculopathy, and thus we advocate multivessel imaging (20).

The present study examines the impact of IVUS findings, independent of other confounding variables, including rejection episodes, age, gender, and other atherosclerosis risk factors. Early identification of a high-risk patient population can help to focus intensive preventive measures to curtail transplant vasculopathy. The lipid profile was significantly different in patients with and without rapid progression, raising a possibility that better control of lipids may retard the progression of vasculopathy lesions and improve outcomes (21). Our data provide a rationale for including IVUS end points in clinical trials examining the effects of various therapeutic interventions, including new immunosuppressive and anti-atherosclerotic agents in transplant recipients (22). In this study, the presence of donor-transmitted disease detected by ultrasound was not associated with a worse clinical outcome. The data on the influence of donor age on the outcomes of heart transplantation are controversial (23–25).

Interestingly, there were nine patients who did not have evidence of rapidly progressive vasculopathy who developed MI on an average of 2.3 years after the IVUS examination. Potential explanations for this finding include undetected epicardial lesions secondary to sampling error, distal small vessel disease, and possibly plaque rupture.

Study limitations. There are certain limitations of our study. Selection bias may have excluded patients who might have influenced our findings. During the time period of this study, less than half of the patients were treated with statins, an intervention now known to inhibit transplant CAD (21,27). We did not measure the total plaque burden in the coronary arteries but performed manual pullback and used the most diseased site as the representative of total plaque burden. Finally, MI, which is included in the secondary end point, may be difficult to diagnose in heart transplant patients.

Conclusions. This study demonstrates that rapid progression of intimal thickening in the first year after transplantation predicts all-cause mortality, MI, and the subsequent development of angiographically severe CAD. Accordingly, such patients may be candidates for more aggressive anti-atherosclerotic and/or immunosuppressive therapies. Therapies that reduce development of rapidly progressive allograft vasculopathy in the first year after transplantation could potentially yield significant improvements in long-term prognosis.

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REFERENCES