Coronary Interventions

Optical Coherence Tomographic Evaluation of Transplant Coronary Artery Vasculopathy With Correlation to Cellular Rejection

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Background—Cardiac allograft vasculopathy is an accelerated fibroproliferative process that affects the coronary arteries of transplanted hearts. Intracoronary imaging with optical coherence tomography enables detection of subangiographic cardiac allograft vasculopathy.

Methods and Results—At the time of routine surveillance coronary angiography, 48 consecutive heart transplant recipients underwent optical coherence tomographic imaging of 1 coronary artery. Imaging findings were compared per rejection history that was graded according to the International Society of Heart and Lung Transplantation classification as none/mild (International Society of Heart and Lung Transplantation 0, 1A/1B, or 2) or high-grade rejection (≥3A). Compared with the none/mild rejection group (37 patients) using Mann–Whitney U test, patients in the high-grade rejection group (11 patients) had a thicker intima in all coronary segments (distal: 0.22 mm [0.09–0.41] versus 0.09 mm [0.06–0.17], P=0.02; middle: 0.35 mm [0.00–0.45] versus 0.14 mm [0.08–0.24], P=0.002; and proximal: 0.34 mm [0.21–0.44] versus 0.15 mm [0.11–0.21], P=0.005) and a higher prevalence of foamy macrophages (distal: 55% versus 9%, P=0.003; middle: 55% versus 22%, P=0.004; and proximal: 44% versus 13%, P=0.05) using χ² statistics. Side branches in the high-grade rejection group had smaller lumen diameters and a higher prevalence of intimal thickening (54% versus 36%; P=0.01). Intimal microvessels were also more prevalent in the high-grade rejection group versus the none/mild rejection group (46% versus 11%; P=0.02).

Conclusions—Coronary optical coherence tomographic evaluation revealed that patients with a history of high-grade cellular rejection, compared with those with none/mild rejection, had more coronary artery intimal thickening with macrophage infiltration, involving all coronary segments and side branches.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01403142.


Key Words: heart transplantation ■ tomography, optical coherence

Coronary allograft vasculopathy (CAV) is a unique form of accelerated coronary artery disease that is a major cause of morbidity and mortality in heart transplant recipients, especially those who survive beyond the first year after transplantation. The pathophysiology of CAV involves immunologic and nonimmunologic factors that cause localized inflammation with persistent vascular injury and endothelial dysfunction. Despite improvements in immunotherapy, the incidence of angiographically detected CAV has not changed appreciably during the past 2 decades, and limited progress has been made in characterizing this disease process. Emerging evidence now suggests that alterations in medical therapy may interrupt the progression of CAV. Because of the absence of typical ischemic symptoms, early diagnosis and surveillance of CAV remain important clinical challenges. Optical coherence tomography (OCT) provides high-resolution (10–20 μm) intravascular imaging in vivo and has been used to visualize and characterize coronary atherosclerotic plaque composition. The current study used OCT to identify CAV disease patterns and to investigate the relationship to prior acute cellular rejection.

Methods

Study Population

The analysis included 48 consecutive heart transplant recipients who underwent routine surveillance coronary angiography between February 2011 to December 2012. These patients underwent...
WHAT IS KNOWN

• Pathological reports showed that cardiac allograft vasculopathy is a diffuse, accelerated fibroproliferative process that affects the coronary arteries of transplanted hearts.

• Previous intravascular ultrasound studies of cardiac allograft vasculopathy showed intimal thickening with advanced morphological changes.

WHAT THE STUDY ADDS

• Intracoronary imaging with optical coherence tomography enables detection of cardiac allograft vasculopathy more clearly both quantitatively and qualitatively.

• Coronary optical coherence tomography revealed that patients with a history of high-grade cellular rejection, compared with those with no/mild rejection, had more coronary artery intimal thickening with macrophage infiltration involving all coronary segments, as well as side branches.

orthotopic cardiac transplantation at Columbia University Medical Center (New York, NY) between January 1996 and August 2011 and were followed for acute cellular rejection by serial right ventricular endomyocardial biopsies. The study was approved by the institutional review board, and all patients gave written informed consent.

Classification of Transplant Cellular Rejection

All patients underwent serial right ventricular endomyocardial biopsies according to institutional protocol and clinical needs. The presence of acute cellular rejection was graded according to the International Society of Heart and Lung Transplantation (ISHLT) classification proposed in 1990: grade 1A, focal, mild acute rejection; grade 1B, diffuse, mild acute rejection; grade 2, focal, moderate acute rejection; grade 3A, multifocal, moderate rejection; grade 3B, diffuse, borderline severe acute rejection; and grade 4, severe acute rejection.

In consideration of the updated classification proposed in 2005, we categorized tissue as showing none/mild rejection (ISHLT 0, 1A/1B), or 2) or high-grade rejection (grade 3R, diffuse, accelerated fibroproliferation with advanced morphological changes).

Quantitative Coronary Angiographic Analysis

Angiographic analysis was done using QAngio XA version 7.2.3.4.0 (Medis Medical Imaging Systems, Leiden, The Netherlands) blinded to the OCT findings. After guiding catheter calibration, proximal, mid, and distal coronary artery segments were identified that corresponded to the areas of OCT analysis, and the minimal lumen diameter in each segment was measured. Qualitative analysis included side branch narrowing, lumen irregularity, and calcium.

OCT Imaging, Definitions, and Analysis

After diagnostic coronary angiography, patients received intravenous coronary heparin and nitroglycerin (100 μg). A 2.7F OCT imaging catheter (C7 Dragonfly, St Jude Medical, St Paul, MN) was advanced over an angioplasty guidewire into a target vessel. The target vessel was either (1) the vessel showing the most severe disease or irregularities on angiography or (2) the left anterior descending (LAD) when all 3 vessels looked the same or appeared to be normal. OCT images were obtained using the LightLab C7-XR Frequency Domain OCT system during continuous contrast injection (4 mL/s, 14–18 mL total) with a motorized pullback speed of 20 mm/s, a frame rate of 100/s, and a maximum scan length of 54 mm.

OCT images were analyzed off-line by 2 independent investigators (L.D. and A.M.) using LightLab ORW software (version C.0.4). Each OCT pullback was separated into 3 segments (proximal, middle, and distal) corresponding with the coronary angiogram. After coregistration of OCT and angiographic studies and assessment of the angiograms based on the American Heart Association classification of proximal, middle, and distal segments, the OCT image was divided into (1) 3 equal segments if all 3 (proximal, middle, and distal) angiographic segments had been visualized by OCT or (2) 2 equal segments if only 2 angiographic segments (proximal and middle or middle and distal) had been visualized by OCT. Calibration was done for each segment, and every frame was evaluated.

For interpretation of the OCT images, the internal elastic lamina (IEL) and external elastic lamina (EEL) were identified as high backscattering bands (≈20 μm). The intima is a thickening inside of the IEL, the media is a low backscattering layer between the IEL and EEL, and the adventitia is a high backscattering and heterogeneous layer outside the EEL. Plaque with attenuation has fast signal drop-off indicates lipidic plaque or macrophages; attenuation behind surface high backscattering with a narrow trailing shadow that changes frame by frame is considered to represent foamy macrophages rather than lipidic plaque.9 Thrombi are graded as (1) red blood cell–rich thrombus that has strong backscattering with a high degree of attenuation, (2) platelet-rich thrombus that has less backscattering with a lower degree of attenuation, or (3) mixed thrombus.9,10 Organized thrombus shows low backscattering with little attenuation.10 Microvessels within the intima appear as signal-poor voids that are sharply delineated and can usually be followed in multiple contiguous frames. Calcium is a signal-poor region with sharply delineated borders. Ruptured plaques show features of intimal tearing, disruption, or dissection of the cap.

A visible abnormal branch structure (VABS) was defined as the presence of intimal thickening inside of a side branch in which both the lumen and the media of the side branch connected to the main vessel (Figure 1). For every visible side branch, the lumen diameter was measured as the largest of the minimum diameters among consecutive frames to avoid overestimation because of angulation.

For quantitative analysis, we chose the frame with minimum lumen area and the maximum plaque thickness in each segment to measure EEL, IEL, and lumen area. Percent media/EEL area, intima/EEL area, and intima/IEL area were calculated:

Table 1. Rejection Grade and Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>ISHLT 1990</th>
<th>ISHLT 2004</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>None/mild rejection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=37)</td>
<td>1A</td>
<td>1B</td>
<td>2</td>
</tr>
<tr>
<td>High-grade rejection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=11)</td>
<td>3A</td>
<td>3B</td>
<td>4</td>
</tr>
</tbody>
</table>

ISHLT indicates International Society of Heart and Lung Transplantation; and N/A, not applicable.
slice. We only contoured the EEL if this helped to fill in the missing arc of EEL. In this cohort, 89% of the attenuation had the appearance of trailing attenuation with narrow shadow. Therefore, even with attenuation, in most (90%) of the slices the EEL was analyzable.

**Statistical Methods**

Statistical analysis was performed with SAS software, version 9.1 (SAS Institute Inc, Cary, NC). For patient level data, categorical variables are presented as frequencies and compared between groups with \( \chi^2 \) statistics or Fisher exact test (if there was an expected cell value <5), and continuous variables are presented as median and first to third quartiles and compared between groups using Mann–Whitney \( U \) test. The correlation between mean intimal thickness versus IEL area was analyzed using Pearson correlation. Intraobserver and interobserver variability for the qualitative analysis was measured by \( \kappa \) test of concordance. For side branch data, a model with the generalized estimating equations approach was used to compensate for any potential cluster effect of multiple side branches in the same patient and is presented as least square means with 95% confidence intervals. To identify independent predictors of lumen dimensions, clinical variables with \( P < 0.2 \) were entered into the multiple linear regression model. A \( P < 0.05 \) was considered statistically significant.

**Results**

**Clinical Characteristics**

The coronary arteries that were imaged included 44 LAD arteries, 3 left circumflex arteries, and 1 right coronary artery. OCT imaging of all 3 segments (proximal, mid, and distal) was successful in 38 cases, whereas imaging of either the distal or proximal segment was incomplete in 10 cases.

Patient age at heart transplantation was 56±14 years (median, 61 years), and 77% were men. The median duration from transplantation to OCT imaging was 5.6 years: 8.2 years in the high-grade rejection group and 4.9 years in the low-grade rejection group (\( P = 0.03 \)). Among the 37 low-grade rejection patients, there were 19 patients (51%) who were >4 years after transplantation, whereas among the 11 high-grade rejection patients, there were 10 patients (91%) who were >4 years after transplantation. In 11 high-grade rejection patients, the median time of rejection from the transplantation was 4.2 years.

About half of the transplant recipients were whites (26 of 48). The none/mild rejection group included 37 patients (ISHLT 0 in 4 cases, ISHLT 1A in 21 cases, ISHLT 1B in 7 cases, and ISHLT 2 in 5 cases), whereas the high-grade rejection group included 11 patients (ISHLT 3A in all cases; Table 1). There were no patients with ISHLT grade 3B or grade 4 rejection.

The age of donor at heart transplantation was 31±11 years (high rejection group versus none/mild rejection group: 29±8 years versus 32±12 years; \( P = 0.42 \)). Among them, 58% were men (high rejection group versus none/mild rejection group: 40% versus 63%; \( P > 0.99 \)); and 46% of donors were cytomegalovirus positive (high rejection group versus none/mild rejection group: 11% versus 57%; \( P = 0.02 \)).

Patient characteristics are summarized in Table 2. There were no significant clinical differences between the none/mild versus high-grade rejection groups except for the time from heart transplant that was longer in the high-grade rejection group. Sirolimus and clopidogrel were more often prescribed in patients with high-grade rejection, but there were no other significant differences in medical treatment between groups (Table 3).

**Angiographic Findings**

Angiographic findings are shown in Table 4. Comparing patients with high-grade rejection to those with none/mild rejection, there were no significant differences in minimal lumen diameter in the proximal or mid segments, but the

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**Table 2. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>None/Mild Rejection (n=37)</th>
<th>High-Grade Rejection (n=11)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60 (53–65)</td>
<td>64 (32–66)</td>
<td>0.81</td>
</tr>
<tr>
<td>Male sex</td>
<td>76% (28)</td>
<td>82% (9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175 (170–180)</td>
<td>175 (167–183)</td>
<td>1.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>88 (69–104)</td>
<td>86 (75–103)</td>
<td>1.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8 (23.8–32.3)</td>
<td>27.5 (26.4–30.6)</td>
<td>0.6</td>
</tr>
<tr>
<td>HTx indication for ICM</td>
<td>35% (13)</td>
<td>46% (5)</td>
<td>0.72</td>
</tr>
<tr>
<td>Duration post HTx, y</td>
<td>4.9 (1.0–9.0)</td>
<td>8.2 (7.0–11.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Humoral rejection</td>
<td>8% (3)</td>
<td>9% (1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38% (14)</td>
<td>27% (3)</td>
<td>0.72</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>38% (14)</td>
<td>36% (4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30% (11)</td>
<td>36% (4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Smoking</td>
<td>30% (11)</td>
<td>36% (4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Prior coronary artery disease</td>
<td>41% (15)</td>
<td>46% (5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Prior peripheral vessel disease</td>
<td>5% (2)</td>
<td>9% (1)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

HTx indicates heart transplantation; and ICM, ischemic cardiomyopathy.
minimal lumen diameter in the distal segment was significantly smaller in high-grade rejection patients. Qualitative parameters were not different between the 2 groups.

Quantitative OCT Findings

OCT findings are shown in Table 5 and Figures 2 through 4. There were no significant differences in EEL areas, IEL areas, or %media/EEL between the 2 groups. However, the mean intimal thickness, %intima/EEL area, and %intima/IEL area were all significantly greater in the high-grade rejection group, resulting in smaller lumen areas. Comparing proximal versus middle versus distal segments in the 2 groups separately, mean intimal thickness was not significantly different between any adjacent segment, including (1) distal versus middle, \( P=0.15 \), and middle versus proximal, \( P=0.90 \), in the high-grade rejection group and (2) distal versus middle, \( P=0.43 \), and middle versus proximal, \( P=0.10 \), in the none/mild rejection group. By regression analysis, mean intimal thickness did not correlate with IEL area in the high-grade rejection group (\( P=0.76 \)), although there was a moderate correlation between mean intimal thickness and IEL area (\( R=0.38; P=0.0004 \)) in the none/mild rejection group.

Table 3. Medical Treatment

<table>
<thead>
<tr>
<th>Medical Treatment</th>
<th>None/Mild Rejection (n=37)</th>
<th>High-Grade Rejection (n=11)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>87% (32)</td>
<td>82% (9)</td>
<td>0.65</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0% (0)</td>
<td>18% (2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Statin</td>
<td>76% (28)</td>
<td>64% (7)</td>
<td>0.46</td>
</tr>
<tr>
<td>( \beta )-Blocker</td>
<td>19% (7)</td>
<td>18% (2)</td>
<td>1</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>30% (11)</td>
<td>27% (3)</td>
<td>1</td>
</tr>
<tr>
<td>CCB</td>
<td>46% (17)</td>
<td>46% (5)</td>
<td>0.98</td>
</tr>
<tr>
<td>Steroid</td>
<td>76% (28)</td>
<td>73% (8)</td>
<td>1</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>57% (21)</td>
<td>55% (6)</td>
<td>1</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>8% (3)</td>
<td>36% (4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>68% (25)</td>
<td>46% (5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>16% (6)</td>
<td>9% (1)</td>
<td>1</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>38% (14)</td>
<td>36% (4)</td>
<td>1</td>
</tr>
</tbody>
</table>

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; and CCB, calcium channel blockers.

Table 4. Angiographic Findings

<table>
<thead>
<tr>
<th>Angiographic Findings</th>
<th>None/Mild Rejection (n=37)</th>
<th>High-Grade Rejection (n=11)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD, mm</td>
<td>2.04 (1.64–2.37)</td>
<td>1.70 (1.19–1.96)</td>
<td>0.009</td>
</tr>
<tr>
<td>Mid segment MLD, mm</td>
<td>2.37 (2.12–2.67)</td>
<td>2.29 (1.83–2.53)</td>
<td>0.25</td>
</tr>
<tr>
<td>Proximal segment MLD, mm</td>
<td>2.57 (2.24–2.94)</td>
<td>2.35 (2.09–3.29)</td>
<td>0.5</td>
</tr>
<tr>
<td>Lumen irregularity</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Branch orifice narrowing</td>
<td>3% (1)</td>
<td>0% (0)</td>
<td>1</td>
</tr>
<tr>
<td>Calcification</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

MLD indicates minimum lumen diameter; and N/A, not applicable.

In the high-grade rejection group, there were 5 patients who had 2 episodes of high-grade rejection and 6 patients who had a single episode of high-grade rejection (none had \( >2 \) episodes). Patients with 2 episodes of high-grade rejection tended toward a smaller IEL area compared with patients with a single episode of high-grade rejection (4.6 [3.2–6.4] versus 6.2 [5.7–6.6] mm\(^2\); \( P=0.13 \)).

Only 4 patients (3 in the none/mild rejection group and one in the high-grade rejection group) had a history of humoral rejection. Percent intimal/IEL area trended toward larger in the patients with a history of humoral rejection compared with those without a history of humoral rejection (26.1% [18.3%–43.9%] versus 13.6% [8.8%–24.7%]; \( P=0.09 \)).

Qualitative OCT Findings

Intraobserver and interobserver variability yielded good concordance for the diagnosis of trailing attenuation with narrow...
shadow ($\kappa=0.90$ and $\kappa=0.90$), microvessels ($\kappa=0.95$ and $\kappa=0.84$), thrombus ($\kappa=0.89$ and $\kappa=0.89$), and VABS ($\kappa=0.84$ and $\kappa=0.80$). Qualitative analysis showed that patients in the high-grade rejection group had significantly greater prevalence of plaque with attenuation than the none/mild rejection group in all 3 segments: proximal, middle, and distal. The majority of attenuation had the appearance of trailing with narrow shadow, suggesting macrophages; this finding was present in 89% of plaque with attenuation in the none/mild rejection group and in all plaque with attenuation in the high-grade rejection group.

Mural thrombus was found in 3 of 48 patients (6%), including 1 in the none/mild rejection group (involving <1 quadrant and 1.6 mm in length) and 2 in the high-grade rejection group. In the patient in the none/mild rejection group, a mixed thrombus was observed in the middle segment of the LAD artery. One of the patients from the high-grade rejection group had multiple mixed thrombi in both the middle and proximal segment (Figure 5A), involving 4 quadrants and a total length of 11 mm, whereas the other had an organized thrombus in the proximal segment of the LAD (Figure 5A'), involving 2 quadrants and a total length of 9 mm. One plaque rupture with no associated thrombus was found in a single patient in the high-grade rejection group.

Intimal microvessels were visualized in 9 patients (19%): 5 patients with high-grade rejection and 4 patients with none/mild rejection (46% versus 11%; $P=0.02$). Multiple segment involvement was observed in 4 patients and single segment involvement in 5 patients. Overall, microvessels were observed in 8 distal segments, 6 middle segments, and 8 proximal segments. In 55% (12 of 22) of the microvessels, the distribution pattern was mainly localized parallel to the lumen of the main vessel and with >3 microvessels circumferentially in one image frame (Figure 5B).

Eight patients (3 with high-grade rejection and 5 with none/mild rejection cases) had intimal calcification in ≥1 coronary artery segment (17%), and 3 patients had it in >1 segment. Overall, calcification was found in 16 segments, including 2 distal, 7 middle, and 7 proximal. In 3 patients, the calcium was found in >1 coronary artery segment, and in 5 patients, the calcium was found in only 1 segment. Calcification was crescent-shaped, thin (maximum thickness <0.3 mm), and superficial in 10 instances (63%; Figure 5C).

Other than the greater prevalence of plaque with attenuation and intimal microvessels in the high-grade rejection group, none of the other qualitative findings were different between the 2 groups.

**Side Branch OCT Analysis**

The analysis included 332 side branches from 44 LAD arteries. Side branch diameter was smaller in the high-grade rejection group compared with the none/mild rejection group (1.01 [0.80–1.21] versus 1.23 [1.10–1.36] mm; $P=0.06$). The prevalence of small side branches (<0.5 mm in lumen diameter) in the high-grade rejection group was greater compared with the none/mild rejection group (34.2% versus 23.0%; $P=0.05$). The prevalence of VABS was also significantly greater in the

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**Figure 2.** Optical coherence tomographic findings. Mean intima thickness, %intima/IEL area, and prevalence of plaque with attenuation were greater in the high-grade rejection group, which resulted in smaller minimum lumen areas in high-grade rejection group.

**Figure 3.** Representative none/mild rejection grade case. In the angiogram (A), the vessel looks normal from the distal to the proximal segments. In the corresponding optical coherence tomographic images (B), 3 layers of normal arterial structures are seen without any abnormal intimal thickness or attenuation.
high-grade rejection group than in the none/mild rejection group (54% [47/87] versus 36% [98/272]; \(P = 0.01\)).

Within the none/mild group, the 12 patients with either ISHLT grade 1B or 2 rejection had a higher prevalence of VABS compared with the 25 patients with either ISHLT grade 0 or 1A rejection (57.3% versus 23.8%; \(P = 0.0003\)). However, the 12 patients with either ISHLT grade 1B or 2 rejection had similar mean intimal thickness and a similar prevalence of plaque with attenuation compared with the 25 patients with either ISHLT 0 or 1A rejection grade.

**Predictors of OCT Findings**

Using multivariate linear regression, only high-grade rejection (versus none/mild rejection) was an independent predictor of lumen area at distal segment, lumen area at middle segment, lumen area at proximal segment, and the average diameter of side branch per patient (regression coefficient [95% confidence interval] and \(P\) value: lumen area at proximal segment, \(-3.61 [-7.28, 0.06], P = 0.06\); lumen area at middle segment, \(-2.93 [-5.41, -0.45], P = 0.03\); lumen area at distal segment, \(-2.66 [-5.03, -0.29], P = 0.03\); average diameter of side branch per patient, \(-0.33 [-0.68, 0.02], P = 0.07\). Conversely, duration after transplant or other clinical factors including age, transplant indication for ischemic heart disease, and diabetes mellitus were not predictors. When %intima/IEL area at distal or middle segment was used as the dependent variable, both high-grade rejection group (versus none/mild rejection) and duration post transplant were independent predictors. When %intima/IEL area at proximal segment was used as the dependent variable, only high-grade rejection group was an independent variable.

**Discussion**

The principal findings of the present study are that (1) OCT demonstrated greater intimal thickening and findings suggestive of a higher prevalence of foamy macrophages in all coronary segments in patients with prior high-grade cellular rejection than those with none/mild rejection, and (2) OCT demonstrated more intimal thickening within side branches and VABS as a part of the more diffuse involvement in patients with prior high-grade rejection.

The pathophysiology of CAV involves immunologic and nonimmunologic factors that cause localized inflammation with persistent vascular injury and endothelial dysfunction.\(^{12,13}\) As such, CAV may be conceived of as a form of chronic rejection,\(^{14}\) and the prevalence of CAV increases with time: 20% at 3 years, 30% at 5 years, and 45% at 8 years after transplantation.\(^{15}\) Histologically, there is subendothelial accumulation of lymphocytes (primarily T cells), myointimal proliferation of smooth muscle cells, development of lipid-laden foam cells, and perivascular fibrosis. Concentric intimal hyperplasia leads to progressive luminal compromise and typically results in a diffuse obliterative process of the intramural and epicardial coronary arteries.\(^{16}\)

The early diagnosis of CAV is essential to facilitate treatment of CAV before progression to the point of requiring revascularization. However, ischemic symptoms are frequently absent or atypical because of allograft denervation. Multiple noninvasive modalities, including dobutamine stress echocardiography, pharmacological radionuclide myocardial...
perfusion imaging, computerized tomographic angiography, and MRI, are available, but none has replaced angiography that remains the gold standard for diagnosing CAV. Routine coronary angiography is, therefore, performed on a periodic basis at many cardiac transplant centers.

On angiography, CAV usually seems diffuse and concentric, similar to the pathology findings, and differs from the lesions of typical atherosclerotic disease that tend to be more proximal, focal, and eccentric. The angiographic diagnosis of CAV provides important prognostic information. In one study, absence of angiographic disease was a significant predictor of cardiac event-free survival in heart transplant recipients.

However, coronary angiography frequently underestimates the extent and severity of the disease. The positive predictive power of coronary angiography (compared with intravascular ultrasound [IVUS]) is only 44%, and IVUS detects a 5x greater number of CAV lesions than can be found angiographically in the same patients. The process of lumen loss can also be studied using serial IVUS. In one study of 38 cases studied annually for 5 years, the investigators found that early lumen loss was primarily caused by intimal thickening and that late lumen loss was caused primarily by vessel constriction (negative remodeling). Furthermore, intimal thickening determined using IVUS showed a poor prognosis in heart transplant recipients, even in the presence of normal angiography.

Because of its higher resolution compared with IVUS, OCT may be more suitable for the assessment of vessel intima and small structures and provides greater information about plaque components. For example, in 15 patients who were studied a mean of 2.8 years after cardiac transplant, half of the patients had lipid-rich or calcified atherosclerotic plaques. Another OCT evaluation of 53 heart transplant patients showed that the prevalence of thin-cap fibroatheroma, macrophages, and microchannels increased in relation to the duration from the transplant.

In the current study, intimal microvessel formation, thrombus, calcification, and plaque rupture were found in 15% of patients and were located within middle or proximal segments except microvessels, which were located equally from the distal to the proximal segments. Previous OCT studies in atherosclerotic coronary artery disease in nontransplant patients suggested that intimal microvessels were related to plaque vulnerability such as thin-cap fibroatheroma or plaque rupture along with serum high sensitivity C-reactive protein and were a potential predictor of subsequent progression of nonsignificant coronary plaques, as well as intraluminal thrombi.

CAV is a diffuse process that involves not only distal arterial segments but also side branches. Because of limited resolution, previous IVUS or virtual histology-IVUS studies were unable to evaluate changes in side branches that can be detected by OCT. The effect of intimal proliferation on the luminal area of side branches may explain the significantly higher prevalence of small side branches (diameter <0.5 mm) in the high-grade rejection group in the current study. In addition, VABS was present even in some patients with none/mild rejection and before intimal thickening in the main vessel; this suggests that side branch involvement may appear earlier than the main vessel disease and may be used as a predictor of early rejection.

Limitations

This study included only 48 patients with only 11 patients having a history of high-grade rejection, and OCT imaging was limited to 1 coronary artery. This may have affected the statistical analysis because of the 3:1 ratio of low-to-high-grade rejection patients. The distribution of years after transplantation is skewed, especially in the high-grade rejection group who were assessed significantly later than the none/mild rejection group; this may confound the relationship between the rejection grade and the OCT findings. Many patients died from the first to the 12th year in both groups such that sampling was incomplete in both groups. None of the patients in this analysis had grade 3B or 4 (3R) rejection, so conclusions cannot be drawn about the effect of severe rejection of CAV. Correlation of OCT findings with histopathologic finding is not available. Because there was no OCT evaluation at the time of the transplant, we cannot eliminate the possibility that intimal hyperplasia already existed in the donor hearts. Despite the good reproducibility for the assessment of VABS in the current study, this diagnosis may be difficult because the side branch is located in the farfield. Finally, type I statistical error may have occurred, given the number of patients and the number of statistical tests; therefore, this analysis should be considered hypothesis generating.

Conclusions

In patients after cardiac allograft transplantation, OCT imaging demonstrated greater intimal thickening in patients with a history of high-grade rejection than those with mild or without rejection. Involvement was diffuse and included distal, middle, and proximal segments, as well as side branches. OCT may have the potential for early detection of CAV in heart transplantation patients.

Acknowledgments

We thank Khady N. Fall, MD, for her assistance in acquiring optical coherence tomographic data.

Disclosures

Dr Dong received grant support from Boston Scientific. Dr Mintz is a consultant for Volcano Corporation (research grant) and Boston Scientific (grant support). Dr Maehara received grant support (institutional) from Boston Scientific and honoraria from Boston Scientific. Dr Weisz is a consultant for InfraReDx. The other authors report no conflicts. The study has no external funding.

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Liang Dong, Akiko Maehara, Tamim M. Nazif, Ari T. Pollack, Shigeo Saito, LeRoy E. Rabbani, Mark A. Apfelbaum, Kate Dalton, Jeffrey W. Moses, Ulrich P. Jorde, Ke Xu, Gary S. Mintz, Donna M. Mancini and Giora Weisz

Circ Cardiovasc Interv. 2014;7:199-206; originally published online April 8, 2014; doi: 10.1161/CIRCINTERVENTIONS.113.000949
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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