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The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Relationship between markers of plaque vulnerability in optical coherence tomography and atherosclerotic progression in adult patients with heart transplantation

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KEYWORDS:
cardiac allograft vasculopathy;
heart transplantation;
optical coherence tomography;
intravascular ultrasound;
vulnerable plaque

BACKGROUND: Cardiac allograft vasculopathy (CAV) is an accelerated form of coronary artery disease, and optical coherence tomography (OCT) provides detailed microstructural information. The current study was designed to test the hypothesis that markers of plaque vulnerability derived from OCT could predict CAV progression after heart transplantation (HTx).

METHODS: In 34 consecutive patients (median 3.1 years from HTx), intravascular ultrasound (IVUS) and OCT were performed in the left anterior descending artery (LAD) during routine annual coronary angiography. The presence of vulnerability markers, such as lipid pools, thin-cap fibroatheroma, macrophages and microchannels, was assessed in 100 consecutive frames of OCT in 20-mm segments of proximal LAD. The total number of appearances of vulnerable markers was defined as the vulnerability score (VS). Plaque volume (PV) was measured in the same study segment using IVUS at baseline and at 1-year follow-up, and the association between the baseline VS and the subsequent change in percent PV (PV / vessel volume × 100 [%PV]) was evaluated.

RESULTS: Follow-up IVUS study was conducted after 12.5 ± 1.3 months. The mean VS was 59.9 ± 44.6. Compared with the initial %PV, the follow-up %PV increased in the study segment (25.6 ± 13.7% to 31.8 ± 17.5%, $p < 0.001$). The correlations between baseline VS and Δ%PV were significant in the study segment ($r = 0.757$, $p < 0.001$). On multivariable analysis, only the VS correlated significantly with Δ%PV.

CONCLUSIONS: Our results demonstrate that the markers of plaque vulnerability in OCT can predict the progression of CAV. Therefore, in patients with HTx, OCT may aid in determining prognosis and guiding therapy related to CAV.

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Cardiac allograft vasculopathy (CAV) is an accelerated form of coronary artery disease that shares some of the features of non-transplant atherosclerosis.[1] CAV results in diffuse, progressive luminal narrowing and remains as the

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1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2016.06.004

major cause of long-term morbidity and mortality after heart transplantation (HTx).[2] However, our ability to predict CAV progression is limited.

Optical coherence tomography (OCT) provides detailed microstructural information on plaque characteristics close to histologic levels.[3,4] Recently, using OCT, we have identified new CAV parameters that greatly extend the current concept of diffuse fibrosing vasculopathy.[5] Many features of vulnerable lesions, such as lipid pools, thin-cap fibroatheroma (TCFA), macrophages and microchannels, have been detected, and the prevalence increased with the time after HTx.

We hypothesized that markers of plaque vulnerability detected by OCT could predict plaque progression after HTx. Therefore, in this study we evaluated the association between the markers of plaque vulnerability measured by OCT and the changes in atherosclerotic plaque volume (PV) in patients with HTx. Changes in PV were assessed by intravascular ultrasound (IVUS) due to the limited penetration power of OCT.[3,4]

Methods

Study population

All HTx recipients >18 years of age were eligible for this study unless they had: (1) chronic kidney disease (Stage ≥IV, glomerular filtration rate <30 ml/min/1.73 mm^2); (2) active infection; (3) significant rejection that required steroid pulse therapy; or (4) an inability to participate. From August 31, 2011 to September 2, 2012, 152 consecutive HTx patients were referred for their annual coronary angiography. Among these patients, 39 agreed to participate in the study and underwent both OCT and initial IVUS examinations of the left anterior descending coronary artery (LAD). Of this group of 39 patients, 5 were excluded because OCT imaging quality precluded analysis ($n = 4$, 10.3%) or there was lack of follow-up IVUS 1 year later ($n = 1$, 2.6%). Thus, 34 patients who underwent follow-up IVUS were included in the final analysis. The study protocols were approved by the institutional review board of the Mayo Clinic. All patients gave written informed consent.

IVUS image acquisition and analysis

The IVUS examination was performed as previously described.[6] Offline volumetric reconstruction of IVUS data was performed by 1 independent, experienced examiner who was unaware of the clinical data and the OCT findings, using Volcano Image Analysis software, version 3.1 (Volcano Corporation, Rancho Cordova, CA). Quantitative volumetric analyses was performed in the 20-mm segment of the proximal LAD and matched with OCT. On IVUS, CAV was defined as an intimal thickening of >0.5 mm.[7] The vessel volume (mm^3) was calculated by the average vessel area (mm^2) × the 20-mm vessel length. The percent PV (%PV) was determined by: (PV / vessel volume) × 100. The difference between the follow-up %PV and the initial %PV was expressed as the Δ%PV. A total of 15 segments of IVUS were also analyzed by 2 independent examiners to evaluate interobserver variability on PV and 14 days apart to calculate intraobserver variability.

OCT image acquisition

The acquisition and analysis of OCT images were performed as described elsewhere.[5,8] For acquisition of OCT images, an intravascular imaging system (C7-XR OCT; St. Jude Medical, St. Paul, MN) was used. The imaging catheter (Dragonfly; St. Jude Medical) was advanced into the mid-to-distal segment of the LAD, and automatic pull-back of 50 mm at a speed of 20 mm/s (100 frames/s) was initiated in concordance with the blood clearance through the infusion of the radio-contrast media. All OCT images were digitally stored and analyzed offline using LightLab imaging (St. Jude Medical, St. Paul, MN).

Scoring vessel vulnerability with OCT

In this study we measured the vulnerability score (VS) according to the presence of typical markers of vulnerability in OCT, such as lipid pools, TCFA, macrophages and microchannels.[4,5] The lipid pool is defined as a signal-poor region that is poorly defined or diffusely bordered by overlying signal-rich bands corresponding to a fibrous cap (Figure 1A). The thickness of the fibrous cap was measured 3 times, and its average taken for each image. TCFA was defined as a plaque with more than 2 lipid quadrants and with the thinnest part of the fibrous cap measuring <65 μm (Figure 1B). A macrophage was defined as signal-rich, distinct or confluent punctate region that exceeded the intensity of background noise. The macrophages were only evaluated at the luminal surface of fibroatheromas or in lipid pools with a clustered feature (an isolated few bright spots were excluded) (Figure 1C). A microchannel was defined as a sharply delineated, signal-poor tubuloluminal structure with a diameter of 50 to 100 μm without a connection to the vessel lumen that could be followed on more than 3 consecutive frames of OCT (Figure 1D). The VS was calculated by the summed number of lipid pools, TCFA, macrophages and microchannels appearing in each frame in a total 100 consecutive frames of OCT (20-mm length) of the proximal LAD. The maximal score in 1 frame of OCT was 4 points if all of the 4 components existed.

We also compared the qualitative macrophage score with the quantitative macrophage score. The qualitative macrophage score was defined as the number of clustered macrophages appearing in each frame in the 100 consecutive frames of OCT (20-mm length). For the quantitative macrophage score, the arc length encompassing clustered macrophages was calculated using the mean luminal diameter and the arc angle (Figure 1E). In each frame, the arc length of the macrophages was calculated and the total sum of the arc lengths determined as the quantitative macrophage score point.

OCT image analysis was performed by 1 well-trained examiner who was blinded to the clinical data and IVUS findings. To evaluate for intra- and interobserver variability, a total of 200 image slices of OCT were analyzed by 2 independent assessors. Intraobserver agreement was calculated 21 days after the first study. To match the study lesion location between OCT and IVUS, anatomic landmarks, such as side branches and calcium, were used. All matching between OCT and IVUS images was done by an independent assessor who was blinded to the analysis of IVUS and OCT. Another independent observer confirmed that the OCT, baseline IVUS and follow-up IVUS locations were the same for all study segments.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation or as median and interquartile range (25% and 75% quartiles) as appropriate. Discrete variables are presented as the frequency