ELSEVIER

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

ORIGINAL CLINICAL SCIENCE

Detection of early changes in the coronary artery microstructure after heart transplantation: A prospective optical coherence tomography study

Tor Skibsted Clemmensen, MD, PhD,[a,b] Niels Ramsing Holm, MD,[a] Hans Eiskjær, MD, DMSc,[a] Lars Jakobsen, MD, PhD,[a] Katrine Berg, BM,[a] Omeed Neghabat, MD,[a] Brian Bridal Løgstrup, MD, PhD,[a] Evald Høj Christiansen, MD, PhD,[a] Jouke Dijkstra, PhD,[c] Christian Juhl Terkelsen, MD, DMSc,[a] Michael Maeng, MD, PhD,[a] and Steen Hvitfeldt Poulsen, MD, DMSc[a]

From the [a]Department of Cardiology, Aarhus University Hospital Skejby, Aarhus, Denmark; [b]Department of Cardiology, Horsens Regional Hospital, Horsens, Denmark; and the [c]Division of Image Processing, Leiden University Medical Centre, Leiden, The Netherlands

KEYWORDS:
heart transplantation;
cardiac allograft vasculopathy;
optical coherence tomography;
intravascular ultrasound;
coronary artery disease;
rejection

BACKGROUND: Optical coherence tomography (OCT) enables in-vivo cardiac allograft vasculopathy (CAV) microstructure characterization. Early coronary artery microstructure changes after heart transplantation (HTx) may provide valuable mechanistic information regarding CAV development. Our in this study was to describe and characterize changes in the coronary artery microstructure during the first year after HTx using serial OCT scans.

METHODS: Twenty-six patients were enrolled at routine baseline coronary angiography 3 months after HTx. Coronary OCT scans were performed on all 3 major vessels at baseline and were repeated 12 months after HTx. We contoured the vessel layers for absolute and relative measurements. Lipid plaques, calcified plaques, layered fibrotic plaques (LFPs) and bright spots were analyzed by delineating circumferential borders and measuring angulation of total circumference.

RESULTS: A total of 8,789 frames from 71 vessels were analyzed after 3 and 12 months (vessel length 79 ± 24 mm vs 82 ± 23 mm, respectively, $p = 0.39$). Mean intima area increased by 20% from 3 months to 12 months (1.6 [1.2 to 2.7] mm^2 vs 1.9 [1.3 to 3.2] mm^2, $p < 0.0001$). Mean lumen area decreased by 2% (9.1 [7.5 to 11.6] mm^2 vs 8.9 [6.9 to 10.9] mm^2, $p < 0.01$). LFPs showed an almost 5-fold increase at follow-up (1.0% [0% to 6.5%] vs 4.8% [0% to 24.5%], $p < 0.0001$). Bright spots were also detected more frequently at 12 months (0% [0% to 2.8%] vs 0.8% [0% to 6.8%], $p < 0.001$). We found no significant difference in extent of lipid plaque ($p = 0.78$) or calcified plaque ($p = 0.37$) during follow-up. The intima area change and LFP progression during follow-up correlated strongly ($r^2 = 0.51$, $p < 0.0001$).

CONCLUSIONS: Early CAV formation during the first year after HTx is characterized by a pronounced intima layer thickening strongly associated with LFP progression. In contrast, the extent of lipid plaque and calcifications remained stable. LFP formation may be a key mechanism in CAV.

J Heart Lung Transplant ■■■■;■:■■■–■■■

Reprint requests: Tor Skibsted Clemmensen, MD, Department of Cardiology, Aarhus University Hospital Skejby, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark. Telephone: +0045 78452251. Fax: 45 7845 2260.

E-mail address: torskibstedclemmensen@gmail.com

A frequent and feared complication after heart transplantation (HTx) is cardiac allograft vasculopathy (CAV), which is strongly associated with poor long-term outcome.[1] CAV differs from conventional atherosclerosis

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2017.10.014

by its diffuse angiographic appearance and concentric fibrotic intimal thickening.[2,3] Progression of CAV is normally monitored by conventional coronary angiography, which often underestimates the severity of the condition. In some transplant centers, adjunctive intravascular ultrasound (IVUS) imaging is used routinely to determine alterations in coronary vessel layer thickness.[4–9] Optical coherence tomography (OCT) provides 10-fold greater spatial resolution than IVUS and allows for detailed characterization of plaque components.[10–13] Serial OCT evaluation during the early phase post-HTx may provide useful and previously undetectable in-vivo insights into the nature and pathogenesis of CAV. However, until now, no serial studies of CAV in HTx patients have been performed. We aimed to describe and characterize the early changes in vessel wall and plaque components during the first year after HTx by using serial OCT evaluation.

Methods

Patients

All patients ≥18 years of age and transplanted at our center from July 2013 through January 2016 were invited to participate in our study, and were enrolled after providing informed written consent accordance with the principles of the Helsinki Declaration. The Central Denmark Region Committees on Biomedical Research Ethics approved the study. The study was registered with clinicaltrials.gov (NCT02077764). Baseline coronary angiography and OCT were performed 3 months after HTx in patients with creatinine <200 μmol/liter, and follow-up angiography and OCT were performed 12 months after HTx. We used OCT data from 18 of the 52 OCT evaluations in the present study in a previous publication.[14]

Previous cytomegalovirus (CMV) infection was assessed pre-HTx in both donors and recipients. In cases of donor–recipient mismatch, patients were treated with valganciclovir during the study period.

Image acquisition

Coronary angiography was performed using a 6F guiding catheter via radial or right femoral artery access. The coronary arteries were imaged after administration of intracoronary nitroglycerin (250 μg) into the left main coronary artery (LMCA) and right coronary artery (RCA). At least 2 projections of each coronary artery were acquired. Baseline and follow-up angiography was performed with the same projections.

OCT scans were performed using Lunawave OCT (Terumo, Japan) aiming at the longest possible pullbacks and ensuring acquisition of proximal segments covering up to 150 mm of each major branch. Pullback speed was adjusted to optimize the scan time to 3 to 4 seconds while flushing with 15 to 20 ml of contrast. In the case of inadequate image quality, the recordings were repeated after adjustment of the position of the guiding catheter. Recordings were obtained for the LMCA, the left anterior descending artery (LAD), the circumflex artery (Cx) and the RCA.

Image analysis

Angiographic CAV assessment

All major branches with visual stenosis >30% were analyzed offline by 2-dimensional quantitative coronary analysis (2D-QCA; QAngioXA 7.3, Medis Medical Imaging, The Netherlands). We calculated the maximal stenosis severity of each vessel using the reference vessel size proximal and distal to the stenotic lesion.

OCT analysis

Quantitative cross-sectional OCT analysis with an approximately 1-mm longitudinal sample frequency was performed using a customized version of the validated QCU-CMS analysis software (Leiden University Medical Centre, Leiden, The Netherlands).[14] Vessel layer assessment included measurements of lumen area, intima layer area and media layer area. These parameters were obtained from 3 vessel contours: a lumen–intima interface contour; an intima–media interface contour; and a media–adventitia interface contour.

Plaque and bright-spot analysis was performed by delineating lateral plaque borders and measuring their circumferential angulation, and then reporting the percentage of total circumference in analyzed frames. Plaques were classified as: (a) lipid (lipid pools, including thin-cap fibroatheromas); (b) calcifications; or (c) layered fibrotic plaque (LFP). Lipid plaque was defined as heterogenic, signal-poor, highly attenuating intimal regions with diffuse or poorly defined borders. Calcifications were defined as sharply delineated, heterogeneous, signal-poor regions. LFP was defined as homogeneous, signal-rich tissue, but predominantly with signal intensity lower than surrounding or deeper layers of intimal tissue and with a clearly layered structure. LFP could be identified as a separate plaque component superficial to other plaque types (lipid plaque, calcified plaque). Bright spots are known to represent inflammation by macrophages and were defined as signal-rich, attenuating regions within the intima layer with a signal intensity exceeding that of adjacent fibrotic tissue. Adaptions were based on work by Tearney et al.[15] We previously reported intra- and interobserver variation of plaque and vessel-layer analysis by OCT.[14]

The vessel layers were contoured in areas with no side branches and no atherosclerosis. Therefore, only the lumen–intima contour analysis and plaque analysis were applied in areas with lipid plaque or severe calcification.

The vessel disease phenotype was estimated by qualitative analysis and characterized as normal phenotype, thrombofibrotic phenotype, atherosclerotic phenotype only and mixed atherosclerotic and thrombofibrotic phenotype. The thrombofibrotic phenotype was defined as 2 or more areas with LFP, and the atherosclerotic phenotype was defined as 1 or more areas with lipid plaque.

Coronary flow velocity reserve

Coronary flow velocity reserve (CFVR) was assessed by echocardiography on the same day as OCT. We used a high-frequency broadband transducer (S6-D, GE Healthcare, Milwaukee, WI). All subjects abstained from consuming caffeine-containing drinks for 24 hours before testing. We located the distal part of the LAD from a modified apical view using color Doppler guidance. The coronary flow velocity was obtained by