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REFERENCES

1. Van Berlo JH, Voogt WG, Kooi AJ, et al. Meta-analysis of clinical characteristics of 299 carriers of *LMNA* gene mutations. J Mol Med 2005;83:79–83.
2. Van Tintelen JP, Tio RA, Kerstjens-Frederikse WS, et al. Severe myocardial fibrosis caused by a deletion of the 5′ end of lamin A/C gene. J Am Coll Cardiol 2007;49:2430–9.
3. Jerosch-Herold M, Sheridan DC, Kushner JD, et al. Cardiac magnetic resonance imaging of myocardial contrast uptake and blood flow in patients affected with idiopathic or familial dilated cardiomyopathy. Am J Physiol Heart Circ Physiol 2008;295:H1234–42.
4. Raman SV, Sparks EA, Baker PM, et al. Mid-myocardial fibrosis by cardiac magnetic resonance in patients with lamin A/C cardiomyopathy. J Cardiovasc Magn Reson 2007;9:907–13.

▶APPENDIX

For supplemental material, please see the online version of this article.

Lipid-Rich Versus Fibrous Intimal Hyperplasia in Transplant Vasculopathy*

In the June 2012 issue of *iJACC*, Hou et al. (1) reported that the optical coherence tomography (OCT), compared with intravascular ultrasound (IVUS), was more sensitive for early detection of cardiac allograft vasculopathy (CAV). Mean intimal hyperplasia (IH) was 180 μm. IH thickness <150 μm accounted for 31% of assessable segments, which is underresolution of IVUS. Lipid-rich plaques (LCPs) with thin fibrous caps were found by OCT in 43% of transplant recipients.

The incidence of CAV is as high as 50% at 5 years after transplantation, and survival is substantially curtailed after the diagnosis of CAV is established. Despite the significant progress in the control of cellular rejection, the evolution of graft vasculopathy has continued unabated. Aggressive control of established risk factors and some of the newer antiproliferative agents remain the cornerstone of CAV management. Use of statins has demonstrated an outcome benefit by cholesterol reduction and also by the cholesterol-independent immune-modulating effect on the natural killer cells; the immunomodulatory efficacy of statins is exaggerated in the presence of a calcineurin inhibitor (2).

We need to use sensitive tools for the diagnosis and screening of CAV to develop novel treatment strategies. Due to the denervation of transplanted hearts, symptoms of vasculopathy are usually not obvious. Therefore, coronary angiography is repeated annually in most transplantation centers. However, information obtained from angiography is often limited because CAV is diffuse. IVUS is able to accurately image the 3 vessel wall layers, and the IH evaluation by IVUS correlates with the occurrence of adverse events post-transplantation. IH of >500 μm in the first year after transplantation predicts increased mortality, myocardial infarction, and late development of severe CAV and heart failure (3). Further differentiation of fibrous from lipid-rich neointima offers a significant prognostic and therapeutic advantage. Although gray-scale IVUS is unable to determine the etiology of CAV, intravascular OCT generates cross-sectional vessel images with 10-fold higher resolution than IVUS and with a more precise characterization of IH. Assessment of lipid-rich lesions is also possible by near-infrared spectroscopy (NIRS), in which the NIRS measurements are presented as a chemogram with the probability of a lipid core containing plaques on a color scale from red to yellow (0 for red, 1 for

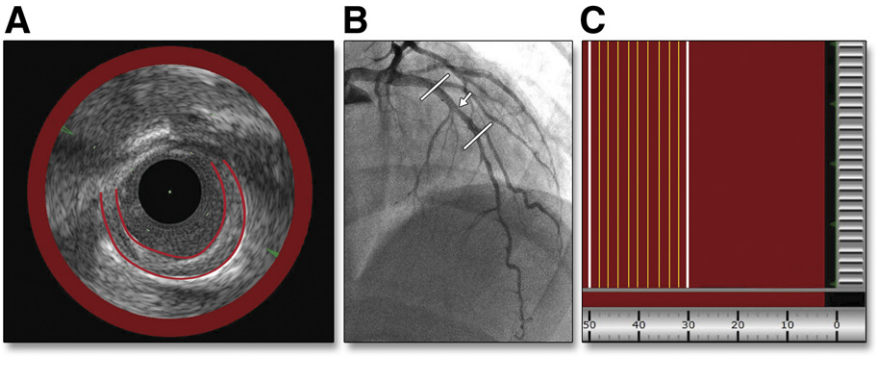

Figure 1. Diffuse Cardiac Allograft Vasculopathy

Intravascular ultrasound (IVUS) **(A)**, angiography **(B)**, and near-infrared spectroscopy (NIRS) **(C)** scans of the medial left anterior descending artery (LAD) in an 18-year-old male patient 11 years after heart transplantation for dilated cardiomyopathy. The **white arrow (B)** indicates the location of the presented IVUS cross-sectional image. **White lines (B and C)** represent a region of the angiogram corresponding to the NIRS scan. **Yellow lines (C)** represent 2-mm blocks. The patient received immunosuppressive therapy with lipid-lowering agents (tacrolimus, prednisone, mycophenolate, aspirin, and simvastatin). Coronary angiography showed diffuse disease especially prominent in the mid LAD. Pruning of the secondary and tertiary coronary vasculature is evident. IVUS minimal lumen area = 4.5 cm^2, and NIRS chemogram lipid core burden index = 0.

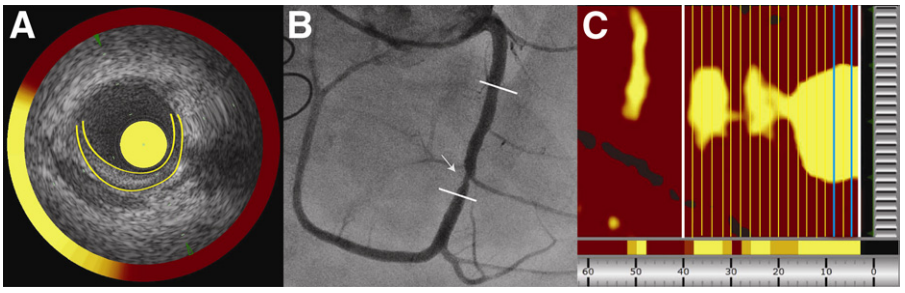

Figure 2. Lipid-Rich Cardiac Allograft Vasculopathy

IVUS **(A)**, angiography **(B)**, and NIRS **(C)** scans of the medial right coronary artery (RCA) in a 24-year-old male patient. The **white arrow (B)** indicates the location of the presented IVUS cross-sectional image. **White lines (B and C)** represent a region of the angiogram corresponding to the NIRS scan. **Yellow lines (C)** represent 2-mm blocks. The patient underwent heart transplantation 19 years earlier after aortic root wrapping surgery for an aortic root aneurysm that resulted in severe left ventricular dysfunction. His medical regimen (tacrolimus, sirolimus, nifedipine, losartan, and aspirin) did not include any lipid-lowering therapy. Coronary angiography revealed a focal 80% lesion in the mid RCA, IVUS minimal lumen area = 3.5 cm^2, and a lipid core burden index in a 4-mm segment = 524 (**blue lines**). Abbreviations as in Figure 1.

yellow). Chemogram analysis enables one to divide the scan into 2-mm blocks and quantify the amount of lipid on a scale of 0 to 1,000, termed the lipid core burden index (LCBI).

Similar to Hou et al., we captured 2 distinct patterns of CAV by NIRS during the routine hemodynamic and angiographic assessment in long-term survivors after heart transplantation. Simultaneous gray-scale IVUS and NIRS scans in the 2 allograft recipients 11 and 19 years after the transplantation demonstrated fibrotic (Fig. 1) and lipid-rich plaques (Fig. 2), respectively. Interestingly, the NIRS chemogram showed lipid-rich regions, even for the angiographically normal-appearing vessel in the latter patient who did not receive statin therapy.

The 2 different NIRS scans of CAV in transplant recipients may correspond to the difference in elapsed survival time from transplantation and use of medical therapy. Autopsy studies have confirmed that in the first 5 years after transplantation, CAV plaques are mostly composed of fibrotic tissue, whereas lipid accumulation is seen later. Gray-scale IVUS studies have provided some insight into the etiology of CAV in survivors 1 to 9 years post-transplantation (4). They have revealed diffuse and circumferential lesions in mid and distal coronary segments, suggestive of the fibrotic tissue. Focal and noncircumferential lesions observed in the proximal segment of the vessel early after transplantation indicated pre-existing atherosclerotic lesions. Radiofrequency (RF) analysis by IVUS (virtual histology) suggested that lipid-rich regions in neointima increased and fibrosis decreased with time over 1 to 20 years after the heart transplantation (5). However, the accuracy of RF-IVUS in lipid-rich plaque determination has been questioned, and characterization of the IH by other imaging modalities should be confirmatory. Interestingly, the accelerated lipid-rich atherosclerotic process in CAV seems to be slower compared with vein coronary graft plaques and in-stent restenosis development. This insidious process is often a result of younger vasculature of the allografts, which is likely to be devoid of pre-existing disease. The immunosuppressive therapy could also contribute to the delay in the process; statin supplementation further enhances the immunosuppressive efficacy of calcineurin inhibitors.

New intravascular imaging modalities may improve CAV screening in allograft recipients. They would contribute to the understanding of the disease process and help to better define management strategies. Allograft vasculopathy is not unique to heart transplantation and may occur similarly in all transplanted organs, and the knowledge gained from coronary screening may have wider implications.

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REFERENCES

1. Hou J, Lv H, Jia H, et al. OCT assessment of allograft vasculopathy in heart transplant recipients. J Am Coll Cardiol Img 2012;5:662–3.
2. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995;333:621–7.
3. Tuzcu EM, Kapadia SR, Sachar R, et al. Intravascular ultrasound evidence of angiographically silent progression in coronary atherosclerosis predicts long-term morbidity and mortality after cardiac transplantation. J Am Coll Cardiol 2005;45:1538–42.
4. Tuzcu EM, De Franco AC, Goormastic M, et al. Dichotomous pattern of coronary atherosclerosis 1 to 9 years after transplantation: insights from systematic intravascular ultrasound imaging. J Am Coll Cardiol 1996;27:839–46.
5. Hernandez JM, de Prada JA, Burgos V, et al. Virtual histology intravascular ultrasound assessment of cardiac allograft vasculopathy from 1 to 20 years after heart transplantation. J Heart Lung Transpl 2009;28:156–62.

Prognostic Value of Coronary CT Angiography

We read with interest the paper from Andreini et al. (1) that provided more evidence on the prognostic value of cardiac computed tomography angiography (CTA) in patients referred for evaluation of possible coronary