Clinical Implications of Intracoronary Imaging in Cardiac Allograft Vasculopathy

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Despite improvements in survival and outcomes, cardiac allograft vasculopathy (CAV), a unique form of coronary artery disease, continues to remain the leading cause of late morbidity and mortality in heart transplantation (HTx) recipients and accounts for ≈30% of all-cause mortality in this group.1 CAV can develop at any stage after HTx with an incidence of ≈7% within the first year of transplantation and 30% within 5 years.2 CAV is clinically silent and asymptomatic in its initial stages, making early diagnosis particularly challenging. Annual coronary angiography is currently the imaging modality of choice for screening and surveillance of graft coronary arteries for signs of CAV.3 However, low sensitivity of coronary angiography for detecting early-stage CAV necessitates the use of more advanced intracoronary imaging to diagnose the disease in its initial stages. Recent advances in invasive coronary imaging such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have shown promising results in detecting subangiographic CAV, predicting prognosis and guiding therapy.4–6

The current article reviews the present state and future directions for the use of intracoronary imaging in the diagnosis, prognosis, and treatment of CAV.

Imaging in CAV

Several invasive and noninvasive imaging tools have been used to screen and diagnose CAV. Some of the noninvasive tests such as dobutamine stress echocardiography, myocardial perfusion imaging (exercise and pharmacological), cardiac MRI, and coronary computed tomography angiography have been studied extensively for this purpose.7–9 Although these noninvasive tests are highly specific for angiographic CAV, they lack sensitivity in detecting subangiographic CAV.7 The diffuse nature of CAV may result in inability to identify differences in radionuclide uptake in myocardial scintigraphy testing. A 2014 meta-analysis by Wever-Pinzon et al9 demonstrated that compared with coronary angiography, coronary computed tomography angiography was 97% sensitive for detecting any CAV. However, when compared with IVUS the newer 64-slice computed tomography angiography was found to be 81% sensitive and 75% specific in detecting CAV (>0.5-mm intimal thickness) with a positive predictive value of 93% and negative predictive value of 50%. In a single-center cross-sectional study, Miller et al10 demonstrated that cardiac magnetic resonance–based absolute myocardial blood flow assessment outperformed coronary angiography for detecting moderate and severe CAV. The study reported significant correlation between IVUS-derived plaque volume index and cardiac magnetic resonance–derived myocardial perfusion reserve. However, it should be noted that the study included patients with a median of 7.1 years post-HTx. Therefore, the role of cardiac MRI early after HTx is questionable. Also, quantification of myocardial blood flow by cardiac MRI currently remains a research tool and further studies are required to establish it as a standard noninvasive imaging resource. Impaired exercise tolerance and inadequate heart rate responses because of cardiac denervation in HTx recipients limit sensitivity of exercise stress testing. Also, noninvasive methods add little to the understanding of CAV pathophysiology. This makes noninvasive modalities not suitable for routine screening and diagnosis of CAV.

Coronary Angiography

Annual coronary angiography is the current recommendation for screening and surveillance of CAV.3 Angiographic evidence of CAV is common after HTx. In one of the largest studies in the field of CAV, Costanzo et al11 reported that angiographic evidence of CAV is present in ≈42% of HTx recipients by the end of 5 years. Haddad et al12 demonstrated that the prevalence of angiographic evidence of CAV increases by ≈10% with every 2-year interval after HTx. In addition, thrombolysis in myocardial infarction frame count, myocardial perfusion grading, and coronary flow reserve may provide additional information in assessing the extent of CAV. The principal advantages of coronary angiography are its wide availability, clinical acceptance, and cost-effective nature compared with other advanced intracoronary imaging modalities (Table).11

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Although coronary angiography is currently the imaging technique of choice for screening and diagnosing CAV, it lacks sensitivity when compared with IVUS, OCT, and histopathologic studies (Figure 1). The predominantly diffuse, concentric and longitudinal distribution of CAV limits diagnostic accuracy of coronary angiography in determining severity of the disease. In 54 consecutive HTx recipients, Störk et al demonstrated that the positive predictive value of coronary angiography in detecting CAV is only 44% when compared with IVUS. Johnson et al reported that lesions with <25% stenosis and which had mild to moderate intimal hyperplasia were under-rated by angiography. Similar observations were made by St Goar et al in a study comparing in vivo IVUS with coronary angiography in HTx patients. Similar to typical coronary artery disease, coronary artery walls in early-CAV respond to atheromatous plaque by undergoing positive remodeling (outward expansion) before undergoing negative or constrictive remodeling (inward shrinking). Paradoxically, this positive remodeling of coronary arteries is associated with plaque vulnerability and unstable clinical presentations. Also, rapid progression of intimal hyperplasia is thought to occur mainly in places with positive remodeling. Coronary angiography fails to detect positive remodeling of coronary arterial wall that occurs early in CAV.

Absence of significant coronary angiographic disease (<50% luminal narrowing) in HTx patients is associated with better survival rates. However, the presence of angiographic evidence of CAV predicts a 5-fold greater risk of cardiac events and poor prognosis. The International Society for Heart and Lung Transplantation-recommended nomenclature classifies CAV into CAV0 (not significant), CAV1 (mild), CAV2 (moderate), and CAV3 (severe) based on the angiographic appearance of graft coronary arteries. Although patients with CAV1 and CAV2 have been shown to be associated with poor prognosis compared with CAV0 and CAV1, angiography is not suitable to further risk stratify patients with CAV0 and CAV2. Also, in patients with CAV2 and CAV3 angiography does not allow plaque characterization and determination of plaque vulnerability. Apart from increasing our understanding of the pathophysiology of CAV, IVUS and OCT play significant roles in determining its natural history and prognosis.

### Intravascular Ultrasound

#### Grayscale IVUS

The relatively higher sensitivity of IVUS to detect early changes in the coronary arterial wall has shed light on better understanding the pathophysiology of CAV. Better tissue
penetration of ≤10 mm allows accurate assessment of plaque volume and vessel wall changes by IVUS. Percentage change in plaque volume is best assessed by serial IVUS examinations with meticulous site matching, starting early after transplantation. Intimal thickening, seen in ≈80% of patients within 1 year of HTx, is the initial finding on IVUS, and rapidly progressive CAV is defined as ≥0.5-mm increase in intimal thickness within the first year post-HTx. Matsuo et al reported that multilayer appearance on IVUS, indicative of repeated episodes of mural thrombosis, was associated with greater plaque volume change, necrotic core, and dense calcium (Figure 2). This suggests that repeated thrombosis is a likely mechanism contributing to CAV pathogenesis. Prior studies using IVUS have demonstrated that natural history of CAV is characterized by a biphasic change in external elastic lamina of the coronary arteries, an early expansion followed by late constriction.

**Virtual Histology-IVUS**

Virtual histology-IVUS (VH-IVUS) uses spectral analysis of IVUS radiofrequency data to allow in vivo characterization of different plaque morphologies (fibrous [green], fibrofatty [light green], dense calcium [white], and necrotic core [red]). Plaque characterization by VH-IVUS allows classification of lesions into inflammatory, defined as necrotic core and dense calcium ≥30% of total plaque volume, and noninflammatory, defined as necrotic core and dense calcium <30%; and advanced atherosclerotic plaques, such as fibroatheromas, into thin-cap and thick-cap fibroatheromas (Figure 3C and 3D, respectively; Table). Raichlin et al investigated coronary allograft atherosclerotic plaque tissue characterization using VH-IVUS and concluded that VH-IVUS-derived inflammatory plaque was associated with early recurrent rejection and higher subsequent progression of CAV. This study underscores inflammation as a potential common mechanism in the pathogenesis of CAV. Serial VH-IVUS examinations permit early detection of vulnerable plaques.

Unlike coronary angiography, IVUS is particularly useful in the assessment of early-stage CAV, as the initial pathological manifestations in CAV are confined to the arterial wall. It is now considered gold standard for early diagnosis of CAV. In a study comparing IVUS with coronary angiography, St Goar et al demonstrated that more than half of the HTx patients with normal angiographic results had moderate to severe intimal thickening on IVUS. In a small sample of patients Calé et al reported that IVUS was more sensitive in identifying subangiographic CAV but not significant CAV. Serial IVUS examinations, starting early after HTx, can also help distinguish early-stage CAV from donor-transmitted coronary artery disease.

Time after HTx and rate of CAV development are the primary determinants of poor prognosis in HTx recipients. Mean change in maximal intimal thickness helps identify patients at high risk for late cardiovascular events. First-year change in maximal intimal thickness detected by IVUS most probably represents a heightened immune response and is considered to be a presumptive marker for prognosis. Tuzcu et al demonstrated that rapidly progressive CAV, as measured by IVUS, is a powerful predictor of all-cause mortality, myocardial infarction, and angiographic abnormalities. Similar results were reported in a multicenter IVUS validation study in HTx patients by Kobashigawa et al. In 74 consecutive HTx patients, Mehra et al reported that 62% of the patients with cardiac events had severe intimal thickening on IVUS but normal angiograms. Plaque characterization into inflammatory and noninflammatory by VH-IVUS allows prediction of plaque progression and subsequent cardiovascular events in HTx recipients. In a study by Raichlin et al., compared with patients with VH-IVUS–derived noninflammatory plaque, those with inflammatory plaque at baseline had recurrent early graft rejections and a significant increase in plaque volume during 1-year follow-up.

**Optical Coherence Tomography**

OCT is a novel imaging technique that uses an optical analogue of ultrasound (infrared light emission) to provide cross-sectional images of the tissue with a resolution of ≤10

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Figure 2. A to D, A representative case with multilayer appearance. Eccentric plaque with multilayer appearance was identified longitudinally in the left anterior descending artery. Intraluminal thrombi (arrowheads) and a ruptured cavity (asterisk) with residual fibrous cap (arrow). Adapted from Matsuo et al with permission of the publisher. Copyright © 2013, Oxford University Press.
to 20 μm. Its higher resolution, attributed to the improved localization of the back-scattered signal origin because of the much shorter wavelength of the imaging light, enables OCT to clearly differentiate the various layers of coronary arterial vessel wall and classify tissues as fibrous, homogenous signal-rich; fibrocalcified, signal-poor with well-defined borders; or lipid-rich, signal-poor with diffuse borders.

Better plaque characterization and lower interobserver variability for luminal dimensions and intimal thickness are certainly the advantages of OCT over IVUS and coronary angiography. OCT is especially superior to other currently existing imaging techniques in identifying lipid-rich plaques and thin-cap fibroatheroma. OCT-derived thin-cap fibroatheroma, defined as fibrous cap <65-μm thick with lipid-rich plaque, is considered a vulnerable plaque characteristic and autopsy studies have implicated thin-cap fibroatheromas in the culprit lesions in patients with acute coronary syndromes (Figures 1D, 3E, and 4). In addition, OCT can accurately quantify macrophage infiltration and microchannels (vulnerable plaque characteristics; Figure 4) within an atherosclerotic plaque (Table).

OCT is superior to both coronary angiography and IVUS, as the subtle changes of the coronary intima in early-CAV are unidentified by coronary angiography and exceed the resolution of IVUS. Early-CAV tends to affect the intima primarily and an intima:media ratio >1 is indicative of intimal hyperplasia, which is identified better by OCT. In a study comparing OCT with IVUS in long-term HTx survivors, Hou et al. reported that OCT demonstrated higher sensitivity than IVUS for early detection of CAV. The higher sensitivity of OCT was attributed to its superior resolution of ≤10 μm, which is 10× higher than that of IVUS. In addition, the study also demonstrated that OCT provides detailed characteristics of intimal hyperplasia such as lipid plaques and thin-cap fibroatheroma.

OCT-defined vulnerable plaque characteristics can certainly help predict prognosis of CAV. Cassar et al. characterized CAV in vivo using OCT, and concluded that OCT identified CAV morphology better than any other imaging modality. A strong correlation was observed between OCT and IVUS measurements of maximal intimal thickness. Vulnerable plaque tissue characteristics such as thin-cap fibroatheroma, macrophages,
and microchannels were identified better by OCT (Figure 4). This technique therefore provides new insights into better understanding the prognosis of CAV.

Assessment of Therapy
The standard therapeutic approach to CAV includes optimal immunosuppression and aggressive risk factor modification. Serial assessment of graft coronary arteries using IVUS and OCT can help determine the efficacy of treatment over time and allows timely alterations in the treatment strategy to improve prognosis and survival.

Immunosuppression
Several randomized clinical trials designed to evaluate the efficacy of immunosuppressants in HTx have used first year change in maximal intimal thickness as a surrogate endpoint. Optimal immunosuppression is maintained traditionally with a calcineurin inhibitor (CNI) in combination with mycophenolate mofetil or azathioprine and corticosteroids. Since the early 1980s, cyclosporine A has been the CNI of choice in HTx subjects for maintenance of immunosuppression. Later, studies have reported tacrolimus as a superior alternative to cyclosporine in preventing acute rejection episodes and CAV. However, CNI-based maintenance immunosuppression did not completely prevent long-term development of CAV and was also reported to have been associated with renal failure, hypertension, hyperlipidemia, and new-onset diabetes mellitus after transplantation which are in turn risk factors for CAV. Efficacy of proliferation signal inhibitors, sirolimus and everolimus, as secondary immunosuppressive agents has been evaluated using IVUS in several clinical trials. A recent study by Kobashigawa et al concluded that everolimus is significantly more effective than mycophenolate mofetil in restricting progression of intimal thickening and preventing CAV at 1 year post-HTx. Andreassen et al, in a recent randomized trial, demonstrated that everolimus-based primary immunosuppression was associated with smaller increase in maximum intimal thickness compared with standard cyclosporin-based immunosuppression. Also, the study noted that at 12 months after HTx, incidence of CAV was lower in the everolimus group than in the cyclosporin group. Sirolimus as primary immunosuppressant has been shown to be associated with reduced plaque volume parameters, as measured by 3-dimensional IVUS, and improved survival in HTx recipients. Raichlin et al reported that conversion to sirolimus as primary immunosuppressant with complete CNI withdrawal was associated with attenuated progression of CAV as assessed by IVUS. These results were further strengthened by 2 later studies with larger study population. Further large-scale randomized studies with longer follow-up are required to establish proliferation signal inhibitors as definitive primary immunosuppressants in HTx recipients. Currently, in patients who do not tolerate CNIs or have life-threatening adverse effects from their use, proliferation signal inhibitors may serve as better alternatives.

The large ongoing Prevention of Cardiac Allograft Vasculopathy Using Rituximab (Rituxan) Therapy in Cardiac Transplantation (CTOT-11) is another example of an investigation where IVUS-derived change in percent atheroma volume at 1 year is being used as a primary end point in assessing the efficacy of rituximab immunosuppressant.

Risk Factor Modification
Incidence of hyperlipidemia is common after HTx and the pathogenesis is thought to be multifactorial. The 2010 ISHLT guidelines for the care of HTx recipients recommend the use of statins beginning 1 to 2 weeks after HTx regardless of serum cholesterol levels. Pravastatin and simvastatin are the 2 statins that have been studied extensively in HTx recipients. Randomized clinical trials that studied the efficacy of these 2 statins in HTx recipients have reported lower intimal thickening, as assessed by intracoronary imaging, lower incidence of graft rejection, decreased development of angiographic CAV, and better survival rates post-HTx. The favorable effects of statins in HTx have been attributed partly to their anti-inflammatory and immunomodulatory effects.

Treatment with angiotensin-converting enzyme inhibitors and calcium channel blockers has been shown to be associated with significantly less intimal hyperplasia, 1 year after HTx. Bae et al demonstrated that the use of angiotensin-converting enzyme inhibitors post-HTx is associated with plaque regression, as assessed by IVUS. As mentioned previously, the finding of multilayer appearance on IVUS is indicative of repeated episodes of mural thrombosis and is not infrequent in asymptomatic HTx recipients. Therefore, the possibility that antiplatelet agents may attenuate CAV progression, especially in the early years of transplantation, must be considered.

Potential Challenges to Intracoronary Imaging
Although both IVUS and OCT are highly sensitive and specific in detecting early-stage CAV, and in determining prognosis and treatment efficacy, their routine use in CAV assessment is significantly limited. First, compared with coronary angiography both procedures are highly expensive and are not widely available. The use of specialized catheters, training of personnel in IVUS and OCT further add up to increased healthcare costs. Second, the use of IVUS and OCT catheters is limited to large epicardial vessels and determination of CAV in smaller vessels is not possible. Claussel et al demonstrated that intimal index as assessed by IVUS did not correlate significantly with small-vessel disease by histological or immunohistochemical analysis in HTx recipients. Current practice involves the visualization of only one of the major epicardial vessels using IVUS or OCT. Also, extensive postprocedure offline volumetric reconstruction is needed for accurate assessment of plaque characteristics. Third, both IVUS and OCT are performed at the time of coronary angiography and therefore contribute to longer duration of sedation and increased procedural risks.

Future Perspective

Compared with OCT, IVUS has lower resolution but greater tissue penetration. Therefore, their combined application may allow better plaque characterization in early-stage CAV. In
typical coronary artery disease patients a combined modality approach has shown favorable results in identifying thin-cap fibroatheromas. However, this approach has not been explored in HTx recipients. Large-scale randomized trials and cost-effectiveness studies are required to determine the additional predictive value of IVUS and OCT to angiography and to establish them as standard surveillance techniques in diagnosing CAV, determining prognosis, and monitoring the effect of newer immunosuppressive therapies.

Conclusions
Both IVUS and OCT can provide additional information to angiography in detecting early-CAV-associated coronary wall changes and accordingly risk stratify patients. Despite being associated with increased healthcare costs, early detection of angiographically silent CAV using IVUS and OCT, combined with closer monitoring, risk factor modification, and optimal immunosuppression, may lead to prolonged graft survival in HTx recipients. Once angiographic CAV is evident, at later stages of HTx, both IVUS and OCT can aid in plaque characterization and in defining plaque vulnerability and prognosis. However, the benefit of routine surveillance using these techniques in angiographic CAV is currently questionable because of lack of sufficient evidence. An individualized diagnostic strategy based on baseline imaging may be of value in preventing and treating CAV.

Disclosures
None.

References
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