Chapter

Diagnostic Intravascular Imaging Modalities for Cardiac Allograft Vasculopathy

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Abstract

Cardiac allograft vasculopathy (CAV) is one of the major factors limiting long-term survival after heart transplantation (HTX). Typically, concentric vascular thickening and fibrosis with marked intimal proliferation are found in CAV. Most of HTX patients often remain free from symptoms of typical angina. Therefore, surveillance diagnostic exams are often performed. The gold standard of diagnosing CAV is coronary angiography (CAG). However, CAG can often be a less sensitive modality for the detection of diffuse concentric lesions. Intravascular ultrasound (IVUS) is helpful for direct imaging of vessel walls and provides useful information about coronary intimal thickening; however, it is difficult to evaluate plaque morphology in detail. Optimal coherence tomography (OCT), which delivers high resolution of 10 μm, can provide more details on plaque morphology than conventional imaging modalities. Recently, OCT imaging revealed new insight in CAV such as the development of atherosclerotic lesions and complicated coronary lesions. We review the pathogenesis, clinical features, diagnosis of CAV, with a particular focus on diagnostic intravascular imaging modalities.

Keywords: cardiac allograft vasculopathy, heart transplantation, intravascular imaging, coronary angiography, intravascular ultrasound, optical coherence tomography

1. Introduction

Orthotopic heart transplantation (HTX) has become a well-established treatment option for patients with end-stage heart failure. But HTX brings following various comorbidities, including rejection, hematologic and other malignancies, infectious diseases, renal failure, and cardiac allograft vasculopathy (CAV).

CAV remains one of the most significant causes of morbidity and mortality after HTX, with almost half of survival recipients have CAV by 10 years post-transplant [1]. Concentric coronary intima thickening is usually found in CAV, but its pathophysiology has not been well known. The early detection of CAV is paramount, but can be difficult, because most of HTX recipients are free from symptoms of typical angina, and the

clinical presentation of CAV can be insidiously, secondary to the denervation of the cardiac graft. Coronary angiography (CAG) has been performed as the gold standard in routine CAV surveillance. However, the analysis of CAV by CAG has limitations, because the early detection of diffuse CAV lesions is difficult. Intravascular imaging such as intravascular ultrasound (IVUS) and optimal coherence tomography (OCT), which has been used for the evaluation of common coronary artery diseases in recent years, has made it possible to accurately evaluate the thickness and structure of the coronary arterial wall. These modalities have contributed to not only early detection of the CAV, but also provide new insights in CAV. We review the pathogenesis, clinical features, diagnosis of CAV, with a particular focus on diagnostic imaging modalities.

2. Pathophysiology

Typical CAV affects the coronary arteries diffusely. Histopathologically, CAV is characterized by concentric thickening of the vessel wall due to intima and smooth muscle hypertrophy, affecting the large and small coronary arteries (**Figure 1**). On the other hand, the pathophysiology and molecular basis of CAV also include contributions from the mechanism of atherosclerosis. The exact etiology of CAV remains well unknown, but both immunological and nonimmunological mechanisms are thought to contribute to the development of CAV [2].

The immunological mechanism may contribute to the development of CAV. It is thought that both cellular and humoral immune responses of recipients are directed against grafts. The immune response of recipients can be triggered via direct or indirect pathways. In the direct pathway, recipient T cells are activated after recognition of the allogeneic major histocompatibility complex (MHC) on the surface of donor endothelial cells by recipient dendritic cells. The indirect pathway is triggered when recipient antigen-presenting cells, mainly dendritic cells, present MHC-derived donor antigens from cardiac grafts [3]. It leads to the production of donor-specific antibodies (DSA) and inflammatory cytokines and damage to the endothelium due to B cell and T cell activation [4]. Antibodies such as anti-human leukocyte antigen (HLA) and anti-endothelial antibody also activate the complement system, which may be involved in vascular endothelial cell injury in the graft and contribute to CAV and rejection [5].

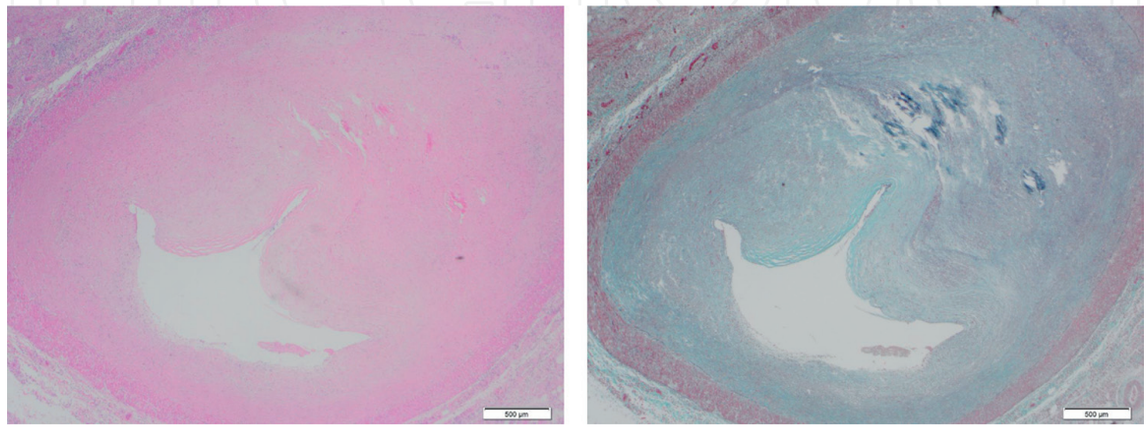

Figure 1.
Histopathological image of cardiac allograft vasculopathy. H&E (left) and Masson-trichrome (right) stain of the left anterior descending artery demonstrating fibromuscular intimal hyperplasia in a HTX recipient with cardiac allograft vasculopathy.

Damaged endothelial cells present MHC class II antigen, which activates CD4+ T cells. In addition to DSA, many non-HLA antibodies are expressed in endothelial cells and may be involved in the development of CAV [6, 7]. Many of these mediators in the immunological pathway have been demonstrated to predict the development of CAV.

The nonimmunological mechanisms include donor and peri-transplant factors, traditional risk factors for coronary atherosclerosis, and particular infections such as cytomegalovirus (CMV) infection. Donor-related factors such as older age, donor-derived coronary artery disease, higher body mass index, hypertension, diabetes mellitus, cigarette use are associated with increased risks of CAV [8–10]. Physiologic changes at the donor caused by brain death can trigger the production of proinflammatory cytokines leading to the endothelial injury [11, 12]. Systemic activation of matrix metalloproteinases in donors with intracerebral hemorrhage can contribute to the migration of smooth muscle cells from the coronary media into the intima [13]. Ischemia–reperfusion injury at the time of transplantation also plays a significant role in endothelial dysfunction and the pathophysiology of CAV [14]. Traditional cardiovascular risk factors are also associated with the development of CAV. Risk factors for coronary atherosclerosis include hypertension, dyslipidemia, glucose intolerance (diabetes), obesity, renal insufficiency [15]. It should be noted that commonly used immunosuppressive agents such as steroids, calcineurin inhibitors, and mTOR inhibitors may lead to exacerbation of these metabolic abnormalities. CMV infection may also affect the development of CAV [16].

3. Epidemiology

According to the International Society of Heart and Lung Transplantation (ISHLT) registry in 2019, the incidence of CAV is declining with each era [17]. Regardless of disease severity, CAV is detected in 7.7% of recipients by 1 year, 29.0% by 5 years, and 46.8% by 10 years after HTX. CAV is less likely to develop in female recipients than in males. CAV is the fourth leading cause of death for recipients more than 3 years after HTX. In addition, graft failure, which is another major cause of death after HTX, may reflect undiagnosed CAV. CAV remains to be associated with lower survival; however, survival in patients with CAV has improved in the most recent era.

4. Clinical features

As a result of denervation after cardiac transplantation, HTX recipients with CAV may often not notice symptoms of typical angina associated with myocardial ischemia or infarction. Therefore, most of recipients remain asymptomatic or have unspecific symptoms. However, the clinical presentation can be insidiously, and severe cardiac ischemia and/or myocardial infarction due to CAV can cause the development of heart failure, electrical instability, or sudden death [18].

5. Diagnosis

Due to the morbidity and mortality associated with CAV, diagnosis of CAV is important. CAV may present insidiously without significant symptoms in post-HTX patients. Therefore, surveillance testing is important for early detection of CAV in

CAV grade	Severity	Coronary angiographic findings	Allograft dysfunction
CAV0	Not significant	No detectable angiographic lesion	Absent
CAV1	Mild	Angiographic LM <50% or primary vessel with maximum lesion of <70% or any branch stenosis <70% (including diffuse narrowing)	Absent
CAV2	Moderate	Angiographic LM <50% or a single primary vessel ≥70% or isolated branch stenosis ≥70% in branches of 2 systems	Absent
CAV3	Severe	Angiographic LM ≥50% or two or more primary vessels ≥70% stenosis or isolated branch stenosis ≥70% in all 3 systems	Left ventricular ejection fraction ≤45% with CAV1 or CAV2 or evidence of restrictive physiology*

**Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio > 2, shortened isovolumetric relaxation time (<60 ms), shortened deceleration time (<150 ms), or restrictive hemodynamic values (Right Atrial Pressure > 12 mmHg, Pulmonary Capillary Wedge Pressure > 25 mmHg, Cardiac Index <2 l/min/m^2).*
Abbreviations: ISHLT International Society of Heart and Lung Transplantation, CAV cardiac allograft vasculopathy, LM left main.
Adapted with permission from Mehra et al. [19]

Table 1.
ISHLT nomenclature for cardiac allograft vasculopathy.

patients after HTX. Coronary angiography (CAG) is recommended by the ISHLT for diagnosing and grading CAV (**Table 1**) [19]. CAG has been the gold standard test for CAV monitoring and diagnosis. However, CAG can often be a less sensitive modality for the detection of diffuse concentric lesions because CAG can only provide information about the vessel lumen [20]. Intracoronary imaging has enabled examination of the vessel wall and detection of early intimal thickening of CAV. Intravascular ultrasound (IVUS) is helpful for direct imaging of vessel walls and provides useful information about coronary intimal thickening. Therefore, IVUS is utilized in many institutions in addition to CAG for the evaluation of CAV. Optimal coherence tomography (OCT) can deliver higher resolution and provide more details on plaque morphology than conventional imaging modalities.

Transcatheter procedures carry the risks associated with invasive examinations. These risks include bleeding, thromboembolism, contrast-induced nephropathy, vascular injury, infection, death from invasive procedures. **Table 2** summarizes the intravascular detection approaches of CAV after HTX.

5.1 Coronary angiography (CAG)

CAG has been the gold standard test and recommended by the ISHLT for definitive diagnosis and surveillance of CAV. It is commonly performed at one month after HTX and then annually or biannually. Less frequent CAG may be considered if recipients are free from CAV at 3–5 years after HTX [21]. The ISHLT recommended classification of CAV is mainly based on CAG results. By the classification, CAV can be separated into not significant (CAV0), mild (CAV1), intermediate (CAV2), and severe (CAV3) (**Table 1**) [19]. The prognostic significance of CAG was validated in HTX recipients. In a large multicenter study, 50% of recipients with severe CAV died or underwent retransplantation within 5 years after HTX [22]. Another retrospective analysis

Imaging Modality	Information	Advantages	Disadvantages
CAG	Coronary luminal stenosis	Widely available Prognostic Current gold standard for CAV screening Angiographic CAV prognostic of outcomes	Inability to assess arterial wall Low sensitivity for detecting early CAV Significant interobserver variability in grading Microvasculature not assessed Lumen patency can be preserved due to remodeling
IVUS	Luminal stenosis Arterial wall Quantification of intimal thickening Plaque characterization	High spatial resolution with good tissue penetration Prognostic More sensitive than angiography Virtual histology IVUS allows assessment of plaque components	More invasive than CAG Costly Requires technical expertise Difficult to match sites exactly for intimal measurements Catheter too large for smaller vessels
OCT	Luminal stenosis Arterial wall Quantification of intimal thickening Plaque characterization	10-fold greater resolution over IVUS Some prognostic data Detects intimal thickening earlier than IVUS Defines more detailed plaque characteristics and microstructures Low interobserver variability	More invasive than CAG Costly Requires technical expertise Additional contrast exposure Poorer tissue penetration than IVUS Unclear whether higher resolution has a beneficial outcome over IVUS
FFR	Fractional flow reserve	Evaluation of micro- and macrovascular function Some prognostic data	More invasive than CAG Costly Requires technical skills

Table 2.
Summary of intravascular imaging modalities for cardiac allograft vasculopathy.

showed no difference in outcome between HTX recipients with CAV0 and CAV1; however, CAV2 and CAV3 were associated with an increased risk of adverse events [23]. Rapidly progressive CAV and the development of CAV in the first year after HTX are associated with major adverse cardiac events [24].

One of the key limitations of CAG is the insensitivity to early detection of diffuse concentric lesions due to its inability to visualize beyond the arterial lumen. Studies comparing CAG and IVUS showed that the sensitivity and the negative predictive value (NPV) for detecting CAV were 43–44% and 27–57%, respectively [25]. A histopathological study of explanted allografts revealed that 75% had significant intimal hyperplasia with CAV, despite normal CAG results [26]. CAG is also limited for the detection of microvascular lesions. The limitations of CAG have necessitated the development of other diagnostic modalities for evaluation of vessel walls and microvascular lesions. Frequent CAG, an invasive angiography surveillance, subsequently increases the risk of treatment complications, patient discomfort, radiation, and nephrotoxicity.

5.2 Intravascular ultrasound (IVUS)

IVUS is becoming to be regarded as the new gold standard for surveillance of CAV since it can provide excellent visualization of vessel walls and lumens [20]. IVUS can

provide cross-sectional imaging of vessel walls and lumens with high penetrance and assessment of coronary plaque volume. The maximal intimal thickness (MIT) measured by IVUS provides a detailed description of plaque burden.

IVUS began to be used in the early 1990s as an imaging modality of validating CAG in HTX recipients.

A number of studies on IVUS findings revealed detailed pathophysiology of CAV progression. A study on IVUS examinations showed that the majority of recipients 1 or more years after HTX have coronary intimal thickening, although not apparent on CAG [27]. IVUS findings also showed that the most rapid progression of intimal thickening occurs in the first year after HTX, followed by a gradual progression over time [28]. Based on previous studies, it should be defined as clinically significant CAV when the width of the intima layer exceeds 0.3 mm or when the total width of the intimal and medial layer exceeds 0.5 mm [29].

There are many reports on the association between IVUS findings and the prognosis of HTX recipients. HTX recipients with severe intima thickening confirmed by IVUS were reported to have a higher incidence of cardiac events [30]. A multicenter study demonstrated that rapidly progressing CAV, defined as an increase in MIT $\geq$ 0.5 mm from baseline in the first year after HTX, is associated with not only the development of angiographic CAV but also death, graft loss, and cardiovascular events within 5 years [31]. Another study also showed that rapidly progressive CAV is a powerful predictor of all-cause mortality, myocardial infarction, and angiographic abnormalities [32]. An increase of 0.35 mm in MIT at 5 years after HTX was reported to be associated with an increased risk of significant adverse cardiovascular events [33].

IVUS technology is advancing, with higher-resolution images, 3D images, and mechanical retractions of IVUS catheters enabling more accurate assessment of coronary arteries. Recent clinical trials have performed volumetric analysis with IVUS, where the percentage of atheroma volume more accurately reflects the burden of the disease and has less variability in its measurements. According to pilot data from Cleveland Clinic, the percentage of atheroma volume was reported to increase by an average of 3.1% in the first year in HTX recipients, while in the nontransplanted population increased by 1% [19]. According to a serial 3D volumetric IVUS study, paradoxical vessel remodeling, which is defined as an increase in the intimal volume with a decrease in the overall volume of the vessel, of the proximal left anterior descending artery (LAD) segment at 1 year is a major determinant of mortality or retransplantation [34]. Interestingly, this study demonstrated that intimal thickening was more pronounced in proximal LAD while vascular remodeling was observed throughout the vessel. This is different from the increase in blood vessel size that compensates for luminal stenosis in native coronary artery disease. A recent study of serial volumetric IVUS by our group suggests that preexisting donor-transmitted atherosclerosis correlates with the worsening change in CAV several years after HTX [35].

Virtual histology IVUS (VH-IVUS) technology is based on spectral analysis of IVUS high-frequency ultrasound signals. With VH-IVUS, different plaque morphologies can be categorized into four types (for example, fibrous, fibrofatty, calcified, and necrotic core) and subsequently quantified. A study evaluating CAV with VH-IVUS showed that fibrotic plaques are the most common plaque component, while calcification and lipid plaques are less frequently observed [36]. Another study reported a significant association between inflammatory plaques and histories of previous rejection [37]. A study examining posttransplant duration and plaque morphology revealed a significant correlation between posttransplant duration and plaque components

with VH-IVUS. The study also found that necrotic core and calcium increased with time after transplantation, and both fibrous and fibrofatty components decreased at follow-up [38].

Although IVUS can provide data on changes in intimal thickness and vascular remodeling, there are still certain limitations in assessing CAV. Due to the relatively large diameter of the IVUS catheter, it can only be used in coronary arteries with sufficient lumen. Therefore, it is not possible to assess small vascular disease that may develop even in the early stages of CAV. There is evidence that the measurement of intimal thickness does not necessarily correlate with pathological findings in coronary microvascular lesions, which suggests discordant progression of CAV [39]. Drawbacks of IVUS include the cost of catheters, the expertise needed to interpret images, and the increased risk of potential complications such as coronary artery spasm and dissection, thrombosis, increased contrast doses, and vascular access due to the use of anticoagulants.

5.3 Optical coherence tomography (OCT)

Optical coherence tomography (OCT) is a novel intravascular imaging modality employing long-wavelength light, usually near-infrared light, which penetrates the coronary vessel wall. OCT was initially used noninvasively for retinal imaging. Since the development of smaller OCT catheters, their application to coronary arteries has increased. And OCT is now widely applied in the assessment of native coronary atherosclerosis. The use of OCT for CAV assessment has a relatively short history, and it is not included in CAV surveillance recommendations. However, it can provide key insights into the pathogenesis of CAV, and various studies have been conducted.

OCT can provide images of vessel walls constructed with extremely high spatial resolution of 10 μm, which is 10-fold greater than that with IVUS (**Figure 2**). Therefore, OCT can provide information such as intimal thickness, intima-media interface display, plaque characteristics, and detection of slight intimal hyperplasia. Considering the nature of CAV and excellent precision and accuracy of OCT, it can be an ideal modality for evaluation of CAV.

An early study comparing OCT and IVUS in non-HTX cadaveric coronary arteries revealed that histologically measured intima-media thickness was more highly correlated with OCT than IVUS [40]. An initial study comparing OCT and IVUS in seven posttransplant patients suggested that OCT, compared with IVUS, could be more sensitive for early detection of CAV, because intimal hyperplasia thickness ≤ 150 μm was under the resolution of IVUS and therefore could be diagnosed only with OCT [41]. Another study described that the assessment of CAV by OCT had a good correlation with IVUS measurements, but OCT could provide lower interobserver variability and better plaque characterization than IVUS [42].

High-resolution OCT images can identify plaque features and microstructures, such as fibrous plaque, fibrocalcific plaque, fibroatheroma, fibrous cap, intimal vasculature, and thrombus, providing a more detailed pathophysiological assessment of the coronary arteries (**Figure 3**) [43]. Therefore, a study using OCT clarified the difference in pathophysiology between CAV and native CAD [44]. The study showed that coronary lesions in HTX patients were more homogeneous than in non-HTX patients, involving the entire coronary vascular tree and having a higher number of microvessels. HTX patients with prior high-grade cellular rejection had similar intima areas, smaller external elastic lamia areas, smaller lumen areas, and higher prevalence of macrophages than non-HTX patients.

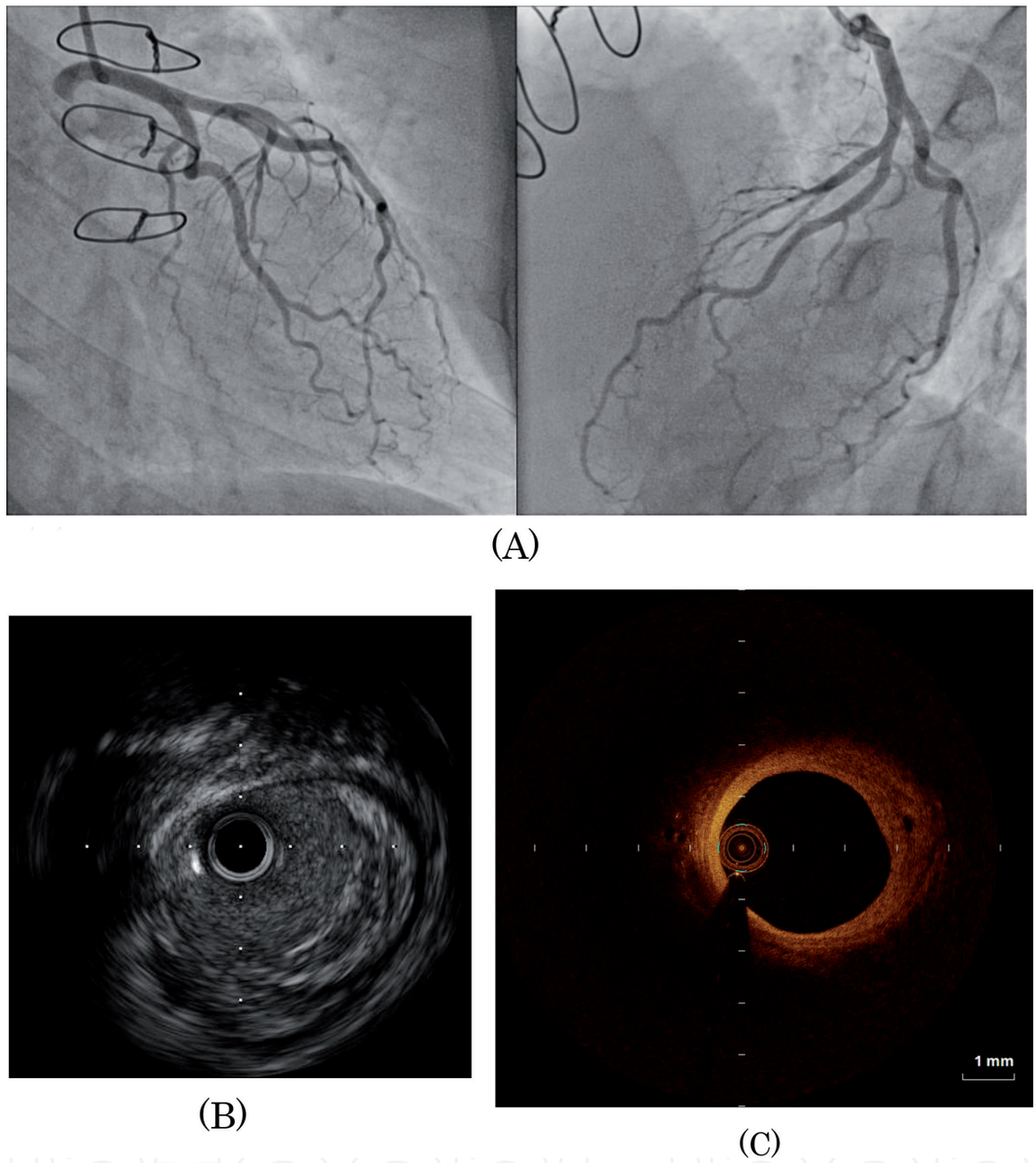

Figure 2.
Coronary angiography, intravascular ultrasound, and optical coherence tomography in cardiac allograft vasculopathy. The proximal left anterior descending (LAD) is almost angiografically normal (A), but intravascular ultrasound provides a coronary plaque image in the corresponding region (B). Optical coherence tomography provides more details on plaque morphology (C).

Analysis of plaque characteristics by OCT gives new insight into CAV that the pathogenesis is more complex than the previously reported diffuse intimal hyperplasia. The OCTCAV study suggested that in addition to post-HTX intimal hyperplasia, traditional atherosclerosis, such as lipid-rich or calcified atherosclerotic plaques, may also be a factor associated with CAV and graft failure [45]. Another study demonstrated that findings typical of atherosclerosis, such as lipid-rich pools, calcifications, and eccentric plaques, were found in CAV lesions, with a significant increase in prevalence with longer post-HTX periods [46]. In addition, the study revealed that vulnerable and complex lesions with thin-cap fibroatheromas, macrophages, microchannels, intraluminal thrombus, intimal lacerations, and layered complex plaque

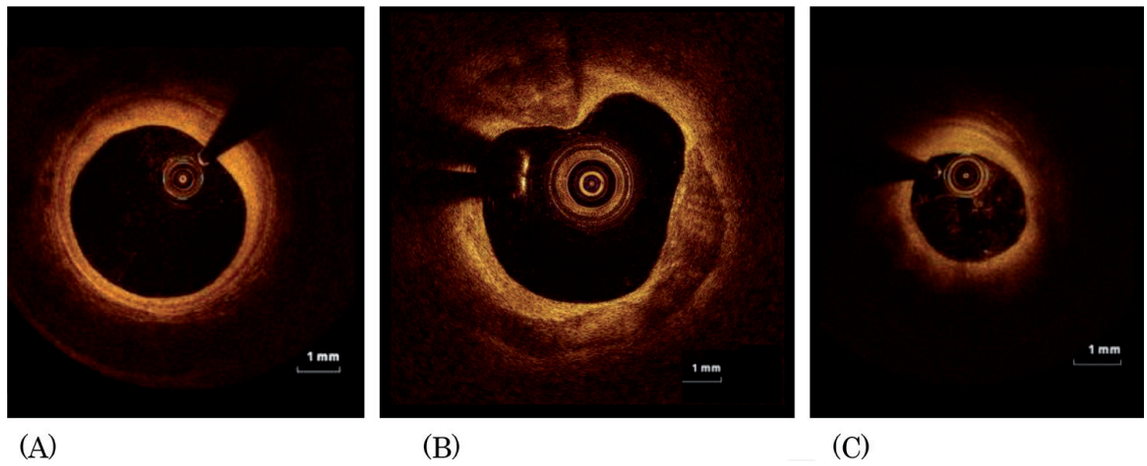

Figure 3.
Plaque morphology classified by OCT. (A) Fibrous plaque. (B) Fibrocalcific plaque. (C) Fibroatheroma.

also increased over time. At follow-up, the characteristics of plaque vulnerability evaluated by OCT correlated with changes in plaque volume 1 year later [47]. These findings regarding impacts of plaque vulnerability on the progression of CAV may suggest the importance of further aggressive treatment for previously known coronary risk factors such as dyslipidemia, diabetes, and hypertension.

Layered fibrotic plaque (LFP) is one of the microstructures that can be detected by OCT, defined as homogeneous, signal-rich tissue but predominantly with a signal intensity lower than surrounding or deeper layers of intimal tissue and with a clearly layered structure. A study characterizing the CAV phenotypes in multivessel OCT on the progression of CAV revealed that LFP was the most prevalent plaque component [48]. LFP was strongly associated with nonfatal CAV progression and suggested to be associated with the gradual progression of CAV caused by thrombus formation in vessel walls. The authors also demonstrated early changes in the coronary artery microstructure after HTX using serial OCT scans [49]. The study described that early CAV formation during the first year after HTX was characterized by a marked intimal layer thickening strongly associated with LFP progression. In contrast, the degree of lipid plaque and calcification remained stable. From these, the authors conclude that the formation of LFP plays an important role in the mechanism of CAV.

Neovascularization is also one of the microstructures of CAV, which is difficult to detect with previous imaging modalities, and OCT has provided new insights into its prevalence, distribution, and association with clinical events [50]. A study evaluating vasa vasorum (VV) by OCT in a small number of HTX recipients revealed that plaque volume of coronary artery was correlated with VV lumen volume [51]. Another study demonstrated that OCT could visualize microchannels considered to represent neovascularization, and OCT-identified microchannels increased sharply within the first year and were correlated with intimal volume and coronary risks [52]. Another study evaluating VV by OCT and the change in plaque volume by serial IVUS tests showed a significant association between the VV volume and the progression of plaque volume [53]. Another recent study also showed the significant association of OCT-detected neovessels within the intima with CAV [54]. These findings suggest that neovascularization may be a potential predictor and possible therapeutic target to attenuate CAV.

Since OCT can detect small structural changes in coronary arteries, it may be useful for elucidating the pathophysiology of CAV. The association between rejection and OCT findings has been evaluated in several studies [55–57]. A retrospective study comparing

OCT findings in pediatric and adult HTX recipients suggested age- and time-dependent differences in the prevalence of absolute and relative intimal hyperplasia [58].

A complete washout of the coronary vessels is needed, usually with a significant volume of contrast medium, to obtain high-quality OCT images. HTX recipients are often exposed to multiple risk factors for renal dysfunction, including immunosuppressive agent nephrotoxicity, hypertension, and diabetes, resulting in chronic kidney disease. Patients with moderate to severe renal failure should be concerned about the additional use of iodinated contrast. It has been reported that saline or low-molecular-weight dextran can provide similar OCT image quality as iodinated contrast, and these techniques have the potential to extend OCT to patients with renal dysfunction [59, 60].

As noted, OCT is very useful for evaluating CAV; however, it has some limitations. First, tissue penetration obtained in OCT imaging is 1.5–3 mm and lower than IVUS, which means whole vascular morphology, particularly in cases of large vessels and significant remodeling, cannot be evaluated. Second, although many studies have been conducted, it has been still unknown how the earlier detection and more accurate surveillance of CAV affect management and that will lead to significant improvement in outcomes. Procedural complications of OCT include coronary artery dissection, coronary artery spasm, and contrast-associated nephropathy.

5.4 Fractional flow reserve (FFR)

Fractional flow reserve (FFR) is not an imaging modality; however, it is a physiological assessment of coronary artery stenosis that can be performed at the same time as CAG and can accurately determine the hemodynamic severity of coronary artery disease. FFR can be quantified by measuring the intracoronary pressure using a pressure guide wire in the condition of coronary vasodilator-induced maximal myocardial hyperemia. FFR has become one of the major procedures for assessing the need for coronary intervention.

In a study comparing FFR and IVUS findings in angiographic CAV-free HTX recipients, FFR correlated with IVUS-detected plaque burden and was abnormal in a significant proportion of asymptomatic recipients [61]. A study evaluating serial changes in FFR by the same group showed that FFR correlated with anatomical changes and worsened in the first year after heart transplantation [62]. Another study showed that invasive measures of coronary physiology determined early after heart transplantation were significant predictors of late death or retransplantation [63].

Currently, FFR is generally considered to be the most accurate diagnostic method in the diagnosis of myocardial ischemia in patients with coronary artery stenosis; however, the therapeutic consequences based on hemodynamic parameters are not sufficient in CAV.

6. Conclusions

CAV remains a significant obstacle to long-term survival of HTX recipients. Current guidelines of ISHLT recommend conventional CAG as the gold standard for CAV diagnosis and grading because of its cost-effectiveness, wide availability, and low rate of complications. The intravascular imaging modalities have provided better visualization of the coronary arteries, enabling early detection of CAV and detailed pathological assessment. OCT, which provides high-resolution images, has revealed new insights into the complex pathophysiology of CAV. However, the clinical value

of detailed CAV assessments by IVUS or OCT remains often uncertain, because no randomized trials based on IVUS or OCT have been conducted. Therefore, further studies are needed to determine the clinical relevance of each parameter and the impact of early detection of CAV on the outcome of HTX recipients.

Conflict of interest

The authors declare no conflict of interest.

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