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# CAPABILITIES OF INTRAVASCULAR IMAGING TECHNIQUES IN THE DIAGNOSIS OF CARDIAC ALLOGRAFT VASCULOPATHY: LITERATURE REVIEW

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Cardiac allograft vasculopathy (CAV) is a coronary heart disease (CHD), arising after an orthotopic heart transplant (OHT), and it is one of the leading causes of death in heart recipients. The probability of death is 10%. CAV can manifest as early as 1 year after OHT. Patients do not have pain syndrome that is typical for CHD due to cardiac denervation. The first clinical manifestations may be congestive heart failure, ventricular arrhythmias or even sudden cardiac death. Coronary angiography is the routine technique for CAV detection. However, it is not sensitive enough (about 44%) for CAV detection at an early stage of the disease. Today, intravascular imaging methods (intravascular ultrasound, optical coherence tomography), which allow the evaluation of the morphology of coronary artery lesions, including CAV, have become widespread. This article is devoted to the modern capabilities of intravascular imaging methods in the diagnosis of CAV. CAV is the main cause of myocardial infarction and chronic heart failure in patients after OHT. Intravascular imaging techniques allow early detection of this condition and prevention of unfavorable outcomes in a complex category of heart recipients. Given the advantages of optical coherence tomography (OCT) and disadvantages of intravascular ultrasound (IVUS), OCT appears to be a more informative method of CAV detection.

*Keywords: cardiac allograft vasculopathy, orthotopic heart transplantation, intravascular ultrasound, optical coherence tomography.*

## INTRODUCTION

CAV is a unique form of coronary artery disease that occurs after orthotopic heart transplantation (OHT) [1]. CAV can manifest as early as 1 year after heart transplantation. The median survival of CAV patients is 14.8 years. The prevalence of CAV at 1, 5, and 10 years following cardiac transplantation is estimated to be 8%, 29%, and 47%, respectively. This pathology leads to recipient death in 10% of cases [2, 3].

Coronary angiography remains the gold standard for diagnosing CAV. The sensitivity of angiography is 44% [4]. However, several studies evaluating the histological structure of the vascular wall of the coronary arteries of transplanted heart have shown that 75% of patients had changes characteristic of CAV despite normal coronary angiography findings [5, 6]. Thus, angiography may not detect CAV at an early stage of the disease [4, 7, 8].

Today, intravascular imaging (IVI) techniques such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are widely used to evaluate the morphology of coronary artery lesions, including CAV. This article focuses on the current capabilities of IVI in diagnosing CAV.

## PATHOGENESIS OF CAV

CAV is a progressive obliterative disease due to intimal proliferation. It encompasses a constellation of vascular changes characterized by intimal fibromuscular hyperplasia (arteriosclerosis), vasculitis, and atherosclerosis. Not only arteries but also veins are affected. This condition results from a complex and incompletely understood interaction between numerous immune and non-immune factors [9, 10].

Graft endothelial cells play a central role in the development of CAV; they are the first cells recognized by the host immune system, effectively becoming antigens [11]. As a result, antibody production begins. Graft endothelial cells not only play a passive role by being recognized by the host immune system, but they can also initiate the inflammatory cascade by enhancing the major histocompatibility complex (MHC) adhesion and leading to a fibroproliferative response [1, 12].

### Immune factors

Adhesion of the polymorphic forms of MHC class I and class II discussed above leads to the development of alloimmune responses. Alloreactive host T cells mediated by T helper cells result in the production of cytokines such as interleukin 2, 4, 5 and 6, tumor necrosis factor-alpha and interferon gamma. These factors pro-

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mote smooth muscle cell migration into the intimal layer, their proliferation and deposition in the extracellular matrix. Through chemokines, there is an additional migration of T-helper cells and monocytes, which enhance the inflammatory response [10–12].

The humoral component is a crucial factor in allograft injury after OHT. Donor endothelial cells contain antibodies to human leukocyte antigen on their surface. The presence of donor-specific antibodies in the recipient causes endothelial injury through complement activation and antibody-dependent cell-mediated cytotoxicity. Also, antibodies against human leukocyte antigen can stimulate smooth muscle cell proliferation [11–13]. Numerous endogenous molecules derived from the extracellular matrix as well as cell organelles (e.g., mitochondria, cytoplasm and nucleus) can also stimulate the inflammatory process and consequently CAV development through activation of macrophages and dendritic cells [9, 10, 14].

### Non-immune factors

Vascular factors, surgical injury to the graft, and infections can cause vascular damage, increase graft immunogenicity, and lead to an alloimmune response. Donor brain death plays a key role in transplant outcome because there is a large release of catecholamines into the blood, development of endocrine disorders or organ hypoperfusion, leading to ischemic graft injury after surgery [9–11]. In the early postoperative period, reactive oxygen species are produced, which damage the microvasculature and also activate endothelial proliferation [12, 13].

Cytomegalovirus infection can mimic the endothelial surface, resulting in cross-reactivity. In addition, infection can directly activate the proliferation of graft endothelial cells and increase oxidative stress, inducing the production of adhesion molecules and promoting endothelial dysfunction by impairing the regulation and production of nitric oxide [13, 14].

## IVUS AS A METHOD FOR DIAGNOSING CAV

Currently, IVUS is becoming the new standard for CAV screening. The use of IVUS in heart recipients began in the 1990s [4, 6]. The use of IVUS has led to significant advances in early detection of the disease. Due to its high penetrating power, ultrasound visualizes the lumen and vessel wall in cross section, which contributes to better diagnosis of CAV (Fig. 1) [1]. A prospective study by Torres et al. compared the sensitivity of coronary angiography and IVUS in the diagnosis of CAV in 31 patients with a mean time after OHT of 3.7 years. IVUS detected evidence of CAV in 54.8% of patients, whereas coronary angiography in 32.3%. The study showed that IVUS is a more sensitive diagnostic tool compared to coronary angiography [1, 15].

A study by Mendiz et al. included a total of 114 post-OHT patients who underwent coronary angiography and IVUS. Mean follow-up was 87 ± 61 months. Lesions documented by coronary angiography were found in 24% of the 114 patients, while IVUS revealed CAV in 76.3% [16].

Intimal thickening is most pronounced in the first year after heart transplantation, which is likely a consequence of the increased immune response early after transplantation. In a multicenter study, Kobashigawa et al. demonstrated that an increase in maximum intima-media thickness (IMT) values ≥0.5 mm from baseline was associated with higher mortality, graft loss, and nonfatal cardiovascular events, as well as a higher likelihood of developing CAV within 5 years [4]. In turn, in a study by Potena et al., changes in IMT ≥0.35 mm 5 years after transplantation were significantly correlated with cardiovascular mortality in 131 patients. In addition, severe intimal thickening (mean IMT 0.9 ± 0.3 mm) was

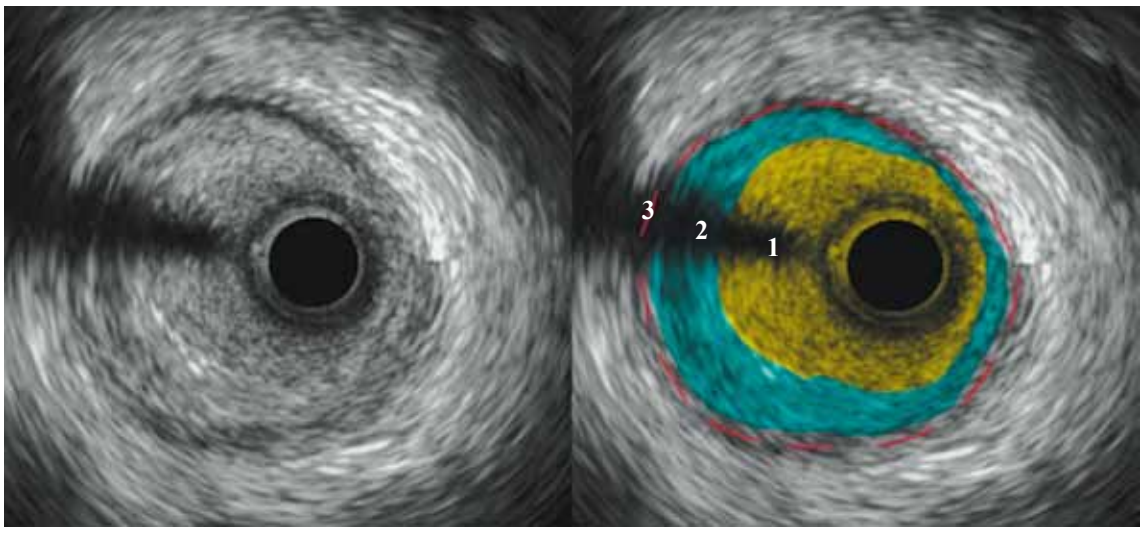


Fig. 1. IVUS in a CAV patient (1, vascular lumen; 2, intimal hyperplasia; 3, media)

associated with a tenfold increase in the risk of major adverse cardiovascular events [1, 17, 18].

IVUS can identify plaque morphology as well as detect CAV progression at an early stage [19–21]. However, despite its effectiveness, IVUS comes with limitations: normal intimal and medial thicknesses are well below the resolution of IVUS (150–200 μm). Early intimal abnormalities, when specific therapies may be potentially more efficacious, are therefore undetectable by IVUS. Also undetectable are pathologically relevant structures such as macrophages, and thin-cap fibroatheromas [6, 22, 23].

## OCT AS A DIAGNOSTIC METHOD FOR CAV

OCT is currently considered as an alternative to IVUS for screening in CAV patients [1]. OCT is a technique that uses near-infrared light, which allows for high-resolution imaging. The use of OCT for the diagnosis of CAV is a relatively recent development that has led to a better understanding of the pathogenesis of vasculopathy [14, 19, 20]. OCT can clearly distinguish a wide range of vascular wall components. OCT more accurately represents the intima-media interface, classifying tissue as fibrotic, homogeneous, fibrotic-calcified, with well-defined borders, or with diffuse borders or abundant lipids, allowing detection of intimal hyperplasia ≤150 μm [1, 24, 25]. Fig. 2 shows OCT data in a CAV patient.

To evaluate the efficacy of OCT for CAV screening, the OCTCAV study evaluated 15 patients who had undergone OHT 1 to 4 years previously. All patients underwent coronary angiography followed by OCT. No evidence of CAV was detected by angiography, but OCT revealed neointimal hyperplasia with IMT >1 mm in 8 of the 15 patients. In addition, 7 of the 15 had lipid-rich or calcified atherosclerotic plaques. The researchers concluded that OCT provides high-resolution quantitative imaging of coronary arteries, and it allows detailed assessment of the coronary artery wall and early morphologic changes that occur after heart transplantation [20, 26].

A disadvantage of OCT is its small penetration depth of 1–2 mm [20, 23]. In cases of severe intimal hyperplasia, imaging of the underlying layers is difficult with OCT. Another disadvantage is the need to obtain high-quality images of complete washout of blood cells from coronary vessels [20, 27, 28].

## OCT VS IVUS

Compared with IVUS, OCT has 10-fold higher axial resolution (10–15 μm) and provides near histological-level imaging. Structures such as macrophages, plaque fibrous cap thickness, and details of plaque ultrastructure that cannot be imaged by IVUS can clearly be seen by OCT [23, 27, 29].

One of the earliest studies comparing OCT and IVUS in native cadaveric specimens found that intima-media thickness had a higher correlation with histological examination as measured by OCT than IVUS [4]. Early studies have shown the advantages of OCT over IVUS for CAV assessment. Hou et al. assessed the proximal, middle, and distal segments of the left anterior descending artery using OCT and IVUS in 7 long-term heart transplantation survivors. Intimal hyperplasia, defined as an intima >100 μm, was seen in 66.7% of segments by OCT, but only in 14.3% of segments by IVUS. An intimal thickness <150 μm was undetectable on IVUS [4]. OCT is more sensitive in detecting pathologic changes, including vasa vasorum and thin-cap fibroatheromas that is not visible on IVUS [15, 18, 23].

## CONCLUSION

Cardiac allograft vasculopathy is the main cause of myocardial infarction and chronic heart failure in patients after OHT. Intravascular imaging allows for early diagnosis of this condition and prevention of unfavorable

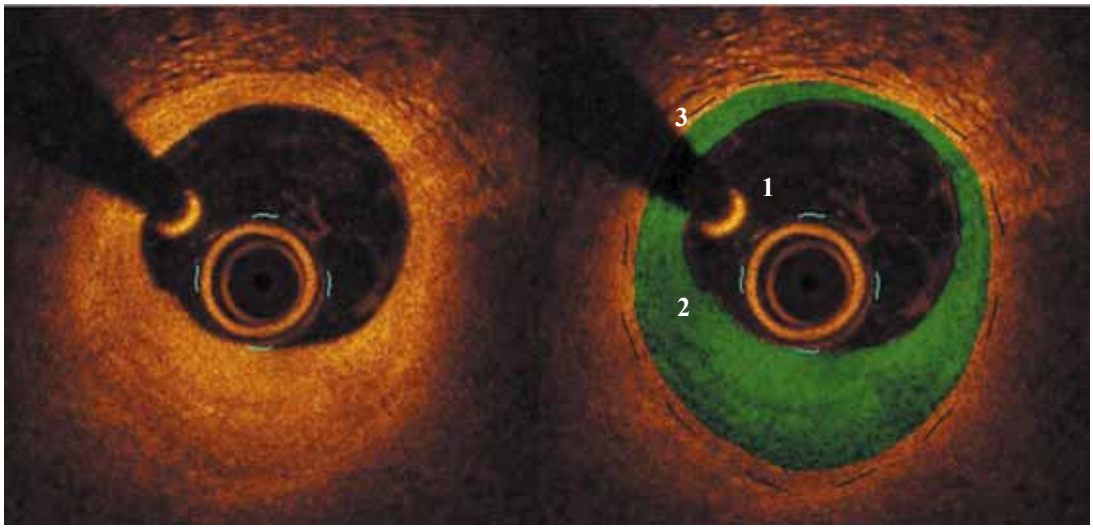


Fig. 2. OCT in a CAV patient (1, vascular lumen; 2, intimal hyperplasia; 3, media)

outcomes in a complex category of heart transplant survivors. Considering the advantages of OCT and disadvantages of IVUS, OCT seems to be a more informative method for diagnosing CAV.

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