JACC: ASIA VOL. 6, NO. 7, 2026

BRIEF REPORT

Cardiac Allograft Vasculopathy

5-Year Longitudinal Morphological Changes Assessed by Optical Coherence Tomography

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Cardiac allograft vasculopathy (CAV) remains a major cause of long-term mortality in heart transplantation (HTx) recipients.[1,2] Clinically, CAV is characterized by progressive coronary artery narrowing, most commonly affecting the left anterior descending artery (LAD), and is usually evaluated by coronary angiography (CAG).[1] Unlike native atherosclerosis, CAV develops diffusely and rapidly through immune-mediated inflammatory mechanisms rather than gradual lipid-driven progression.[1,3] Intravascular imaging, particularly intravascular ultrasound (IVUS), has contributed substantially to understanding CAV pathophysiology and prognosis by visualizing vessel wall morphology beyond CAG.[4,5] Optical coherence tomography (OCT), with higher spatial resolution than IVUS, enables more detailed assessment of coronary microstructure and superficial inflammatory changes.[6] Because CAV often progresses silently until advanced luminal narrowing develops, high-resolution intracoronary imaging is particularly valuable for detecting early structural abnormalities that may not be apparent on conventional angiography, especially in transplanted hearts in which denervation may delay symptom recognition. However, long-term serial OCT data on CAV progression remain limited. This study aimed to characterize annual morphological changes in CAV over 5 years after HTx, focusing on inflammatory OCT findings.

This retrospective single-center study included 10 HTx recipients who underwent annual OCT imaging of the LAD for 5 years after HTx. Twelve patients underwent HTx at our institution between July 2013 and May 2018, and 2 were excluded because of death within the first year after HTx or lack of OCT imaging at 1-year follow-up. According to International Society for Heart and Lung Transplantation grading,[1] 10 patients were classified at 1 year into no-CAV (grade 0, n = 5) and CAV (grades 1-3, n = 5) groups. All patients received standard triple immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil, and prednisolone. At 6 months post-HTx, mycophenolate mofetil was switched to or combined with everolimus unless contraindicated, and prednisolone was tapered within 1 year. Lipid-lowering therapy was initiated immediately after HTx, maintaining low-density lipoprotein (LDL)-cholesterol below 100 mg/dL during follow-up.[4] At year 5, LDL-cholesterol remained comparably controlled in both groups (CAV 26 ± 30 mg/dL vs no-CAV 51 ± 11 mg/dL, $P = 0.72$).

A total of 2,253 OCT cross-sections were analyzed at 1-mm intervals from the proximal to middle LAD using diagonal and septal branches as landmarks. Lesions were categorized as mild (<500 μm) or severe (≥500 μm) intimal thickening, fibrous plaque, calcification, or fibroatheroma, with the most advanced lesion prioritized when multiple findings coexisted. Inflammatory features including layered fibrotic pla-

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 4, 2025; revised manuscript received March 26, 2026, accepted April 13, 2026.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2026.04.012

que (LFP) and bright spots were also assessed. LFP was defined as a distinct layered structure with homogeneous lower signal intensity than deeper intimal tissue, meanwhile bright spots were defined as signal-rich attenuating areas exceeding adjacent fibrotic tissue intensity.[5] The prevalence of each OCT feature was calculated as the percentage of cross-sections containing that feature. For longitudinal inference on prevalence, we adopted a binomial generalized linear mixed-effect model with a logit link including year (continuous), CAV group, and their interaction as fixed effects and a patient-level random. Model adequacy of overdispersion and zero inflation was assessed using simulation-based residual diagnostics. All statistical analyses were performed using STATA/MP 17.0 (StataCorp) or R software 4.5.0 (R Foundation for Statistical Computing) with lme4 and DHARMa packages. This study was approved by the Ethics Committees of Tohoku University (No. 2024-1-801).

Baseline coronary risk factors were comparable between groups, although donor age was higher in the CAV group (median 50 vs 35 years; $P = 0.03$). Proven predictors including cytomegalovirus mismatch, acute cellular rejection, and antibody-mediated rejection were similar between groups. At 1 year after HTx, fibroatheroma was significantly more prevalent in the CAV group ($P < 0.01$), whereas the no-CAV group predominantly exhibited mild or severe intimal thickening (Figure 1). Simultaneously, LFP and bright spots were more frequently observed in the CAV group ($P < 0.01$) (Figure 1). These structural and inflammatory differences persisted throughout follow-up. In the CAV group, fibroatheroma increased progressively over 5 years (odds ratio per year: 1.16; 95% confidence interval: 1.06-1.28; $P = 0.002$; incidence rate: 1.08; 95% confidence interval: 1.01-1.15; $P = 0.03$). During follow-up, 2 patients in the CAV group underwent percutaneous coronary intervention for functionally significant proximal LAD stenosis with fractional flow reserve values of 0.8 or lower.

To our knowledge, this is the first study demonstrating serial OCT findings over 5 years after

ABBREVIATIONS AND ACRONYMS

CAG = coronary angiography

CAV = cardiac allograft vasculopathy

CI = confidence interval

HTx = heart transplantation

IVUS = intravascular ultrasound

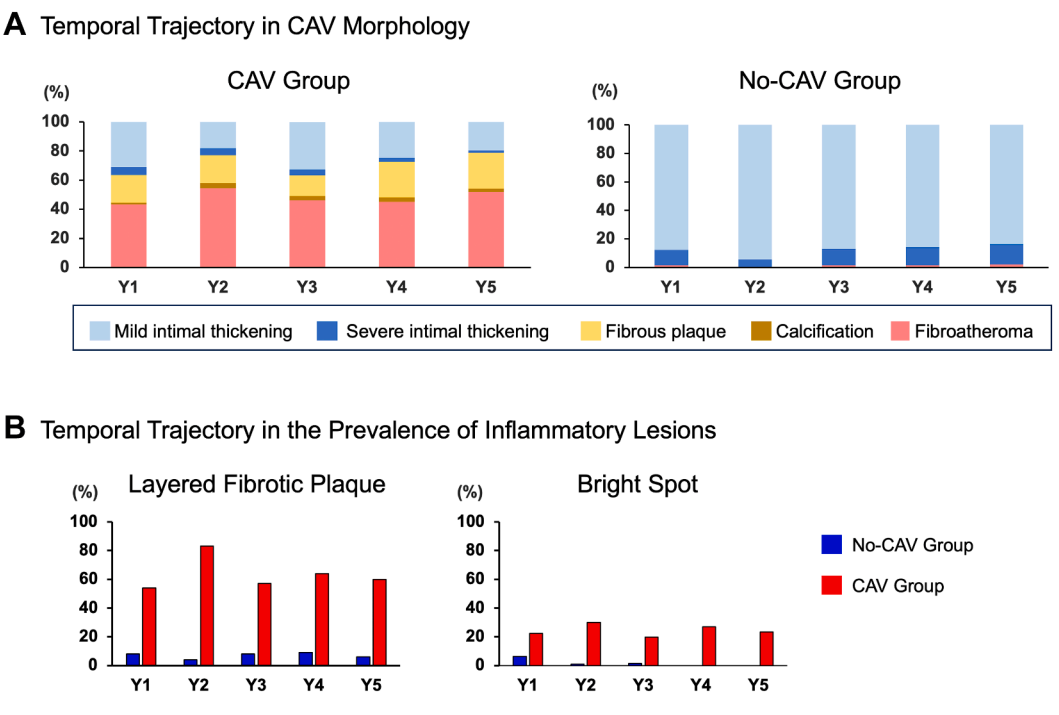
LAD = left anterior descending artery

LDL = low-density lipoprotein

LFP = layered fibrotic plaque

OCT = optical coherence tomography

FIGURE 1 5-Year Changes in Plaque Morphology



(A) The CAV group demonstrated a higher prevalence of fibrotic and fibroatheromatous plaques compared with the no-CAV group over 5 years. (B) The prevalence of LFP and bright spots was higher in the CAV group than in the no-CAV group. CAV = cardiac allograft vasculopathy.

HTx. OCT consistently identified persistent fibroatheromatous and inflammatory features in the CAV group despite appropriate immunosuppression and LDL control.[2,4] LFP and bright spots may reflect ongoing vascular injury, organized mural thrombus formation, and macrophage-related inflammation associated with lesion progression.[3,5] These findings suggest that much of CAV progression may already be established within the first year after HTx. Although intensive lipid lowering is recommended after HTx,[2,4] persistent progression despite adequate LDL control indicates that inflammatory mechanisms beyond lipid metabolism contribute substantially to CAV evolution.[7,8] The sustained separation of OCT phenotypes between groups further suggests that early intracoronary imaging may detect high-risk vascular remodeling before overt angiographic progression becomes clinically apparent. This study has several limitations. First, it was conducted as a single-center retrospective analysis involving only 10 patients and LAD-only imaging. This may be concerning in terms of both bias and the generalizability of findings. Second, the study did not include OCT follow-up within the first year after HTx, which could provide valuable information on early and subtle changes in CAV morphology and inflammatory lesions. Third, 3-vessel OCT pullbacks were not performed. This could result in an incomplete representation of CAV landscape. In conclusion, serial OCT identified persistent inflammatory and structural differences in CAV morphology, supporting its utility for longitudinal surveillance and early risk stratification after HTx.

ACKNOWLEDGMENTS The authors thank all doctors and staff of the Department of Cardiovascular Medicine, Tohoku University Hospital and Ms. Miki Akiba for their contributions to the present study.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cardiac allograft vasculopathy, fibroatheroma, heart transplantation, layered fibrotic plaque, optical coherence tomography