Allograft Vasculopathy
The Achilles’ Heel of Heart Transplantation

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ABSTRACT

Cardiac allograft vasculopathy (CAV) remains the Achilles’ heel of long-term survival after heart transplantation. Almost one-third of patients develop CAV by 5 years post-transplant and 1 in 8 deaths beyond a year are due to CAV. Abnormal vascular fibroproliferation in CAV occurs as a result of coronary endothelial inflammation, injury, and dysfunction triggered by immune and nonimmune insults. Surveillance methods for CAV have significant limitations, particularly for detecting early disease. Areas of investigation include myocardial and coronary blood flow quantification, and intra-coronary imaging to detect early changes in the vessel wall and high-risk plaques. Treatment approaches continue to evolve, but prevention remains the focus. Newer mammalian target of rapamycin inhibitors can significantly delay the progression of CAV; however, their optimal use remains to be established. Further investigation is needed to understand the complex pathophysiology of CAV, improve surveillance techniques, and develop therapies to prevent and slow disease progression. (J Am Coll Cardiol 2016;68:80–91) © 2016 by the American College of Cardiology Foundation.

More than 5,000 heart transplants are performed annually worldwide, improving the survival of patients with advanced heart disease (1). Cardiac allograft vasculopathy (CAV) has been a major impediment to successful long-term outcomes in heart transplantation. Registry data show a high incidence of CAV and minimal reduction over the past 2 decades, from 32% to 29% and 46% to 40% at 5 and 8 years post-transplant, respectively (1). Over the same period, 5-year survival...
for CAV detected within 3 years of transplant has improved marginally, from 71% to 76%, but remains lower than the 82% survival for patients without CAV (1). Notably, CAV is a leading cause of long-term mortality, accounting for up to 1 in 8 deaths beyond a year post-transplant (1). Evolving definitions for CAV (Table 1) and changing trends in clinical practice, including the use of statins and mammalian target of rapamycin inhibitors (mTORi), have modified the natural history of disease (2). Furthermore, the recognition of early CAV as an adverse prognostic indicator has emphasized the importance of early detection. Unfortunately, CAV surveillance remains challenging, particularly for detecting early disease by noninvasive imaging. In light of these ongoing challenges and developments, we shall review: 1) current understanding of CAV pathophysiology; 2) screening strategies, focusing on emerging imaging techniques that target assessment of coronary physiology and the arterial wall; and 3) therapeutic approaches, particularly the role of mTORi.

PATHOGENESIS

CAV is an accelerated fibroproliferative disease affecting the vasculature of the transplanted heart. Pathologically, smooth muscle proliferation, accumulation of inflammatory cells, and lipid deposition cause circumferential intimal thickening. In contrast to the focal, eccentric, proximal epicardial lesions in atherosclerosis, CAV is diffuse and affects epicardial and intramural vessels. Intravascular imaging has shown disease occurs within the first year of transplant, and has a biphasic response, involving initial intimal thickening with expansion of the external elastic membrane and relative preservation of luminal area, followed by constrictive remodeling and luminal narrowing (3). Plaque composition changes from early fibrous and fibrofatty tissue to late atheromatous necrotic core and calcification.

ENDOTHELIAL INJURY

CAV pathophysiology involves complex interplay between immune and nonimmune factors causing vascular inflammation, which triggers a final common pathway of endothelial injury and fibroproliferative cellular responses (Central Illustration) (4). The endothelium maintains vascular homeostasis through regulation of vessel tone, inhibition of platelet activation, thrombosis, leukocyte adhesion, and vascular smooth muscle cell proliferation. In CAV, endothelial injury initiates and drives a cascade of excessive tissue repair mechanisms involving vascular cell proliferation, fibrosis, and remodeling.

IMMUNE FACTORS

Allograft endothelial cells express “foreign” human leukocyte antigens (HLA) that are recognized by recipient T-lymphocytes. Activated T-lymphocytes secrete cytokines (interleukins 2, 4, 5, and 6; interferon-gamma; tumor necrosis factor-alpha), stimulating T-lymphocyte proliferation and up-regulation of endothelial adhesion molecules (intercellular and vascular cell adhesion molecule-1, P-selectin), resulting in endothelial cell activation and recruitment of inflammatory cells (5). Macrophages recruited to the intima secrete cytokines (interleukin-1 and -6, tumor necrosis factor-alpha) and growth factors (platelet-derived growth factor, insulin-like growth factor-1, transforming growth factor-alpha and -beta) that cause smooth muscle cell migration to the intima, proliferation, and extracellular matrix deposition. In vitro studies also show a role of the humoral response with high-titer class I HLA antibodies stimulating endothelial and smooth muscle cellular proliferation through activation of the mammalian target of rapamycin (mTOR)/S6 kinase/S6RP pathway, as well as redistribution of intracellular fibroblast growth factor receptors to the plasma membrane (6,7). Circulating HLA antibodies have been associated with increased rejection and development of CAV (8).

NONIMMUNE FACTORS

Nonimmune insults predisposing to CAV include vascular risk factors (in both donors and recipients of older age, male sex, obesity, hyperglycemia, hyperlipidemia), ischemic heart disease etiology, brain death, organ preservation, and ischemia-reperfusion injury. These share in common inflammatory injury causing endothelial dysfunction. Cytomegalovirus (CMV) infection is associated with the development of CAV (9). CMV generates a proatherogenic milieu through production of inflammatory cytokines, expression of adhesion molecules, mononuclear activation, and smooth muscle cell proliferation (10). CMV also impairs endothelial nitric oxide synthase-mediated coronary vasodilatation through increased production of the nitric oxide synthase inhibitor asymmetric dimethylarginine (11). There is also evidence for CMV molecular mimicry of endothelial cell surface molecules and subsequent immune-mediated endothelial injury (12).
TABLE 1 ISHLT Recommended Nomenclature for CAV

<table>
<thead>
<tr>
<th>Classification</th>
<th>Severity</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>CAV₀</td>
<td>Nonsignificant</td>
<td>No detectable angiographic lesion</td>
</tr>
<tr>
<td>CAV₁</td>
<td>Mild</td>
<td>Angiographic LM &lt;50% or Primary vessel with maximum lesion &lt;70% or Branch stenosis &lt;70%</td>
</tr>
<tr>
<td>CAV₂</td>
<td>Moderate</td>
<td>Angiographic LM &lt;50%, Single primary vessel ≥70% or Isolated branch stenosis in 2 systems ≥70%</td>
</tr>
<tr>
<td>CAV₃</td>
<td>Severe</td>
<td>Angiographic LM ≥50% or ≥2 primary vessel ≥70% or Isolated branch stenosis in all 3 systems ≥70% or CAV, or CAV₁ with allograft dysfunction (LVEF ≤45%) or evidence of significant restrictive physiology</td>
</tr>
</tbody>
</table>

A “primary vessel” denotes the proximal and middle third of the left anterior descending artery, left circumflex, the ramus, and the dominant or codominant right coronary artery. A “secondary branch vessel” includes the distal third of the primary vessels or any segment within a large septal perforator, diagonal, and obtuse marginal branch or nondominant right coronary artery. Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E/A velocity ratio >2, isovolumetric relaxation time >60 ms, deceleration time <150 ms, or restrictive hemodynamics (right atrial pressure >12 mm Hg, pulmonary capillary wedge pressure >25 mm Hg, cardiac index <2.0 L/min/m²). Reprinted with permission from Mehra et al. (2).

CAV = cardiac allograft vasculopathy; ISHLT = International Society for Heart & Lung Transplantation; LM = left main coronary artery; LVEF = left ventricular ejection fraction.

DIAGNOSIS AND PROGNOSTICATION

Routine surveillance is essential for early CAV diagnosis, as patients are frequently asymptomatic. Classic symptoms of myocardial ischemia are usually absent due to allograft denervation. Consequently, patients often present with atypical symptoms or late after the development of graft dysfunction with heart failure, arrhythmia, or sudden death. Detection of early CAV is particularly challenging. Many noninvasive modalities have been evaluated against coronary angiography using references that represent advanced disease, such as coronary stenosis ≥50%. Additionally, angiography is a relatively insensitive method for diagnosing CAV (discussed subsequently). Invasive screening remains the accepted standard of care, with interest in newer techniques that enable detailed imaging of the vessel wall, plaque characterization, and assessment of both coronary macro- and microvasculature.

NONINVASIVE IMAGING

Several noninvasive imaging modalities are used for CAV evaluation. Although acceptable results have been demonstrated as “rule out” tests for obstructive CAV, none are ideal for detecting early disease (Table 2) (13).

STRESS ECHOCARDIOGRAPHY. Dobutamine stress echocardiography (DSE) is commonly used for CAV screening. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) compared with IVUS are 72%, 83%, 88%, and 62%, respectively (14). A normal DSE, however, has a high (92% to 100%) NPV for subsequent cardiac events, indicating prognostic value (14,15). A recent large retrospective analysis (N = 497) of 1,243 DSEs performed for CAV surveillance at a median of 8.7 years post-transplant reported a low 2% prevalence of positive DSE (79% negative, 11% nondiagnostic) and a poor (7%) sensitivity for angiographic CAV (16). Ischemia on DSE did not predict cardiovascular outcomes. Small studies suggest improved performance when DSE is combined with speckle tracking or contrast echocardiography (17,18). In a Doppler contrast echocardiography study (N = 105), coronary flow reserve (CFR) calculated from flow velocity in the distal left anterior descending artery was lower in patients who subsequently developed angiographic CAV: 2.4 ± 0.6 versus 3.2 ± 0.7 (18). A CFR <2.5 was independently associated with a higher probability of new angiographic CAV and death.

MYOCARDIAL PERFUSION IMAGING. Single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has been extensively investigated in CAV. Similar to DSE, studies have shown prognostic value, but moderate diagnostic accuracy, likely related to a limited ability to detect balanced ischemia, as may be expected with the typical diffuse disease of CAV (19,20). In the largest series (N = 110), SPECT had 63% to 84% sensitivity and 70% to 78% specificity for detecting minor to severe (≥50% stenosis) CAV (20).

Positron emission tomography (PET) MPI has superior diagnostic accuracy to SPECT for evaluation of coronary artery disease (21). The prognostic value of PET perfusion and flow quantification is also well demonstrated (22,23). Flow quantification using PET holds the most potential for early CAV diagnosis by detecting homogenous reductions in flow that may occur with diffuse disease. This is in contrast to modalities that identify disease on the basis of heterogeneity in perfusion (or contractility), which rely on differences relative to a zone presumed to be normal. Such techniques define only the territory supplied by the most severe stenosis, which underestimates disease if it is diffuse with no normal reference region. Hence, flow quantification is better able to detect microvascular or diffuse disease (22). Small studies of 19 to 27 patients have shown moderate inverse correlation between PET flow reserve and IVUS indexes of CAV (24,25). Prognostic value was also reported in a retrospective study (N = 140) for PET parameters, including reduced stress myocardial blood flow and flow reserve (26). Prospective studies are needed.
Immune and nonimmune factors cause endothelial inflammation and injury, triggering vascular fibroproliferation of the coronary vasculature and allograft dysfunction. Cardiac allograft vasculopathy (CAV) pathogenesis targets for established and investigational (bold italics) evaluation methods and treatments are shown.

*Investigational. ACEI = angiotensin-converting enzyme inhibitor; CCB = calcium-channel blockers; CT = computed tomography; HLA = human leukocyte antigen; mTORi = mammalian target of rapamycin inhibitor.
Small studies have evaluated cardiac magnetic resonance (CMR) MPI for detecting CAV. An early study showed good correlation between myocardial perfusion reserve and invasive CFR, as well as high accuracy for detecting angiographic CAV (27). In another study, myocardial perfusion reserve was an independent predictor of CAV and had high diagnostic performance for moderate CAV disease (area under the curve: 0.89) (28). Both typical and atypical infarct patterns of delayed gadolinium enhancement

### TABLE 2 Imaging Techniques for CAV

<table>
<thead>
<tr>
<th>Modality</th>
<th>Surveillance Recommendations</th>
<th>Information</th>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stress echocardiography</td>
<td>Class IIa for DSE Cardiac structure and function Regional wall motion Myocardial deformation Myocardial perfusion Coronary flow reserve</td>
<td>Availability Prognostic</td>
<td>Dependent on acoustic windows</td>
<td></td>
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<tr>
<td>SPECT</td>
<td>Class IIa</td>
<td>Myocardial perfusion Ventricle function</td>
<td>Availability Prognostic</td>
<td>Radiation exposure</td>
</tr>
<tr>
<td>PET</td>
<td>Not included</td>
<td>Myocardial perfusion Myocardial flow quantification Ventricle function</td>
<td>Quantify global/regional myocardial blood flow Quantify global/regional myocardial flow reserve Some prognostic data Less radiation versus angiography and SPECT Rapid sequential rest-stress testing with Rb-82 On-site cyclotron not required for Rb-82</td>
<td>Limited availability Radiation exposure</td>
</tr>
<tr>
<td>CMR imaging</td>
<td>Not included</td>
<td>Cardiac structure and function Myocardial perfusion Late gadolinium enhancement</td>
<td>Safety Comprehensive cardiac evaluation</td>
<td>High resting heart rates post-transplant Cardiac devices contraindicated Challenging perfusion quantification software Nephrogenic systemic fibrosis in renal failure</td>
</tr>
<tr>
<td>CTCA</td>
<td>Class IIb</td>
<td>Coronary stenosis Coronary calcification</td>
<td>Evaluation of arterial lumen and wall</td>
<td>High resting heart rates post-transplant Radiation exposure Contrast-induced nephropathy Limited ability to assess smaller vessels</td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>Class I Coronary stenosis Myocardial blush</td>
<td>Prognostic</td>
<td>Evaluation limited to epicardial vessels Insensitive for detection of early disease Insensitive for detection of diffuse disease Radiation exposure Contrast nephropathy</td>
<td></td>
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<tr>
<td>IVUS</td>
<td>Class IIa</td>
<td>Arterial wall Arterial lumen Plaque volume Plaque characterization</td>
<td>High tissue penetration Highly prognostic</td>
<td>Evaluation limited to epicardial vessels Cost Limited availability</td>
</tr>
<tr>
<td>OCT</td>
<td>Not included</td>
<td>Arterial wall Arterial lumen Plaque volume Plaque characterization</td>
<td>High spatial resolution (10 μm)</td>
<td>Evaluation limited to epicardial vessels Reduced tissue penetration (compared with IVUS) Cost Limited availability</td>
</tr>
<tr>
<td>Coronary flow</td>
<td>Not included</td>
<td>Fractional flow reserve Coronary flow reserve Index of microvascular resistance</td>
<td>Functional evaluation of epicardial vessels and microvasculature</td>
<td>Risk of enhanced sensitivity to adenosine Cost Limited availability</td>
</tr>
</tbody>
</table>

*International Society of Heart & Lung Transplantation (13).
CAV = cardiac allograft vasculopathy; CMR = cardiac magnetic resonance; CTCA = computed tomography coronary angiography; DSE = dobutamine stress echocardiogram; IVUS = intravascular ultrasound; OCT = optical coherence tomography; PET = positron emission tomography; Rb = rubidium; SPECT = single-photon emission computed tomography; Tc = technetium. 
have been observed in patients with absent or mild angiographic disease, suggesting possible early CAV (29). Important limitations for clinical application in the transplant population include high resting heart rates from denervation posing difficulties for image acquisition, pacemakers contraindicating CMR, and the risk of nephrogenic systemic fibrosis with severe renal impairment.

**COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY.** New-generation multislice multidetectors and dual-source technology have improved spatial and temporal resolution of computed tomography coronary angiography (CTCA). A meta-analysis of prospective trials in CAV (N = 615) reported 94% sensitivity, 92% specificity, 99% NPV, and 67% PPV for stenosis ≥50% on invasive angiography (30). As expected, sensitivity (81%) and NPV (50%) were lower when CTCA was compared with IVUS. Radiation dose (3 to 18 mSv) and contrast (60 to 115 ml) were not insignificant. Important limitations for CAV include poor visualization of the distal coronary arteries and high resting heart rates.

**INVASIVE IMAGING**

**CORONARY ANGIOGRAPHY.** Coronary angiography is the accepted clinical standard for CAV diagnosis on the basis of clinical availability and prognostic significance (13). Large multi-institutional analyses show an approximate 19% likelihood of progression to severe CAV within 5 years once disease is evident on angiography (31). Severe angiographic CAV (>70% stenosis left main, ≥2 primary vessels, or 3 coronary systems) is associated with a 5-year 50% likelihood of death or retransplantation (31). These findings were integrated into 2010 society recommendations for CAV nomenclature (Table 1) (2). Despite its prognostic utility, angiography is an insensitive tool for detecting CAV, due to inability to visualize beyond the arterial lumen and larger epicardial vessels. These are significant limitations, as the diffuse, concentric, and longitudinal nature of CAV disease, as well as expansive vascular remodeling, cause absence or late luminal obstruction (Figure 1A).

**INTRAVASCULAR ULTRASOUND.** IVUS is a useful adjunct to angiography, providing cross-sectional imaging of the lumen and vessel wall that improves detection of angiographic occult CAV (Figure 1B) (32,33). The prognostic value of IVUS in CAV is well demonstrated. Rickenbacher et al. showed that patients with maximal intimal thickness (MIT) >0.3 mm at 1 year post-transplant had a 3-fold increased risk of developing angiographic CAV and reduced 4-year survival (73% vs. 96%) (34). In another study, severe intimal thickening (average MIT 0.9 ± 0.3 mm) was associated with a 10-fold increased risk of major cardiovascular events (32). Rapidly progressive CAV, defined as an increase in MIT ≥0.5 mm within 1 year of transplant has also been shown to predict the development of angiographic CAV (65% vs. 33%), death/graft loss (21% vs. 6%), and cardiovascular events at 5 years (33). Recently, prognostic relevance was demonstrated for an increase in MIT ≥0.35 mm on IVUS performed later, at 1 and 5 years post-transplant (35). Plaque components can also be examined on IVUS by virtual histology. Using this technique, Raichlin et al. (36) observed an association between rejection and inflammatory plaques (presence of necrotic core and dense calcium ≥30%), and subsequent CAV progression.

**OPTICAL COHERENCE TOMOGRAPHY.** Optical coherence tomography (OCT) provides high (10 to 20 μm) resolution (10-fold greater than IVUS) intravascular imaging that is ideally suited for assessing the vessel intima and plaque morphology (Figure 2). OCT-measured intimal thickness and plaque characteristics have been validated against histology and IVUS. Preliminary OCT studies have added insight on CAV pathogenesis. Increased atherosclerotic and vulnerable plaque characteristics are observed with greater time from transplantation (37). Suggesting a potential role for neovascularization in CAV, Ichibori et al. (38) reported increased microchannels in patients more than a year post-transplant, which also correlated with intimal volume and coronary risks. In support of rejection as a CAV risk factor, Dong et al. (39) showed that high-grade cellular rejection was associated with thicker intima and macrophage infiltration. Limitations of OCT include cost, contrast requirements, and lower tissue penetration that limits assessment of deep plaque features. Prospective studies are needed to determine whether OCT-derived measurements correlate with clinical outcomes.

**INVASIVE CORONARY FLOW STUDIES.** CAV affects both epicardial and microcirculatory compartments, causing complex changes in coronary physiology. Invasive coronary sensor “pressure” and “flow” wires allow independent assessment of the epicardial arteries and microvasculature by measuring fractional flow reserve (FFR) and index of microcirculatory resistance (IMR), respectively. Coronary flow across both macrovascular and microvascular compartments is measured by CFR. Discordant normal FFR and reduced CFR have been reported after heart transplantation, representing diffuse epicardial or microvascular CAV (Figure 1C) (40). Similarly, for a given epicardial plaque burden, FFR has been observed to
increase, whereas IMR deteriorated (41). Both scenarios likely reflect the reduced physiological impact of epicardial disease in the presence of microvascular dysfunction and increased microvascular resistance as the maximal achievable coronary flow is diminished (Online Figure 1). These observations highlight the importance of evaluating both epicardial arteries and microvasculature in CAV, as both are affected and changes in one may affect assessment in the other. Furthermore, the microvasculature is affected early, and small studies have shown that microvascular dysfunction, as measured by reduced CFR, increased IMR, or abnormal vasoconstrictor response to acetylcholine, predicts the development of intimal thickening and angiographic CAV (42,43).

**FIGURE 1 Invasive Coronary Evaluation of CAV**

(A) Angiogram demonstrating diffuse left anterior descending artery (LAD) disease without focal stenosis. (B) Intravascular ultrasound demonstrating LAD intimal thickening (maximal intimal thickness = 1.3 mm). (C) Intracoronary flow studies demonstrating normal fractional flow reserve (0.91) and reduced coronary flow reserve (1.2). CAV = cardiac allograft vasculopathy.

**MANAGEMENT**

Management of CAV is focused on primary prevention, imaging surveillance, and early treatment. Figure 3 shows a proposed algorithm for CAV surveillance and management.

**MEDICATIONS**

**ASPIRIN.** Antiplatelet therapy has not been well examined in heart transplantation. Aspirin is used empirically, on the basis of presumed microthrombi formation at sites of immune injury in the coronary endothelium. Interestingly, an ex vivo platelet function study showed marked platelet aggregation in response to adenosine diphosphate and aspirin
resistance in heart transplant patients compared with native coronary disease and healthy controls (44). A lower response to platelet stimulation was demonstrated in a small subset of transplant patients receiving 500 mg aspirin.

**STATINS.** Statins are standard care post-transplant. In addition to reduction in cholesterol, statins also inhibit inflammatory and immune responses, including inhibition of natural killer cell cytotoxicity (45). In a landmark trial (N = 97), pravastatin initiated 2 weeks post-transplant improved lipid profiles, and reduced severe rejection, CAV, and mortality (46). A meta-analysis of 3 randomized trials showed statins reduced 1-year mortality from 17% to 5% (47).

**VASODILATORS.** Small studies of calcium-channel blockers and angiotensin-converting enzyme inhibitors suggest improved microvascular function and delayed development of CAV (48,49). A placebo-controlled randomized trial showed diltiazem, commenced 2 to 4 weeks after transplant, decreased reduction in angiographic coronary diameter and increased 5-year freedom from graft loss or angiographic disease (56% vs. 30%) (48). A combination of an angiotensin-converting enzyme inhibitor and a calcium-channel blocker was shown to be superior to either medication alone for reducing the development of CAV (49).

**IMMUNOSUPPRESSION.** Mycophenolic acid reduces progression of intimal thickening compared with azathioprine and is the preferred antimetabolite in over 80% of patients (1). The mTORis sirolimus and everolimus inhibit vascular smooth muscle and fibroblast proliferation. Summarized in Table 3 are randomized controlled studies of mTORis in de novo heart transplant recipients, demonstrating reduced CAV incidence and progression (50–53). Traditionally, calcineurin inhibitors (CNI) have formed the foundation of maintenance immunosuppression, significantly reducing rejection and improving survival. In contrast to the CNI-reduced strategy in many of the de novo mTORi studies, the SCHEDULE (Scandinavian HEart transplant everolimus De novo stUdy with earLy calcineurin inhibitors avoidance) trial adopted a CNI-free regimen involving cyclosporine withdrawal by 7 to 11 weeks post-transplant (52). Grade ≥2R rejection was increased with the CNI-free approach (Table 3). The effect of mTORi on CAV has also been examined in maintenance heart transplant patients. Mancini et al. (54) randomized patients with severe CAV at 4.3 ± 2.3 years post-transplant to conversion from mycophenolate/azathioprine to sirolimus (n = 22) or usual immunosuppression (n = 24). Sirolimus slowed CAV progression by a semiquantitative catheterization score, but no difference was observed on IVUS. Additional studies included patients with and without CAV. Topilsky et al. (55) demonstrated attenuation of CAV on IVUS in patients converted to sirolimus with CNI withdrawal (n = 45) at 1.2 years post-transplant compared with patients continued on usual immunosuppression (n = 58). In another study (N = 29, 3.8 ± 3.4 years...
post-transplant), CNI substitution with sirolimus slowed CAV progression on IVUS, but there was no difference in the subgroup of patients more than 2 years post-transplant (56). Similarly, the randomized NOCTET (Nordic Everolimus [Certican] Trial in Heart and Lung Transplantation) substudy (N = 111) demonstrated no effect on CAV progression in patients converted to everolimus at an average of 5.8 years post-transplant (57). Hence, late conversion to mTORi appears ineffective, likely related to differing plaque composition at various stages of CAV development. An IVUS study showed significantly less plaque volume progression and greater reduction in the fibrous plaque component in patients converted to sirolimus #2 years, but not later post-transplant (58). On the basis of these studies, many programs consider early conversion to mTORi if there is evidence of CAV. Importantly, the potential benefits of mTORi need to be balanced against significant intolerance, with the need for medication cessation in up to a third of patients. Adverse effects when mTORis are used in the early post-operative period include pericardial effusions, wound healing problems, and bacterial infections. It is unclear whether adverse effects are related to dosing and whether tolerability can be improved by delaying introduction up to 3 months post-transplant, after operative recovery and wound healing.

**REVASCULARIZATION**

Revascularization for CAV is limited by diffuse coronary disease and high mortality with surgical intervention. Percutaneous coronary intervention is often undertaken for focal disease, despite the lack of evidence for any survival advantage over medical therapy. A single-center study (N = 105) showed a high 31% stent restenosis rate associated with lower freedom from a composite endpoint of death, myocardial infarction, or retransplantation at 7 years follow-up (28% vs. 63%), driven primarily by lower survival (39% vs. 84%) (59). A systematic review (N = 312) found that drug-eluting stents reduced the long-term risk of stent restenosis compared with bare-metal stents, but without any difference in clinical endpoints, including survival (60).

**RETRANSPLANTATION**

Current consensus recommendations reserve retransplantation for selected patients with advanced CAV (61). Retransplantation is controversial because of organ shortages, lower survival, and increased CAV

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**FIGURE 3 Proposed Algorithm for CAV Surveillance and Management**

Post-transplant cardiac allograft vasculopathy (CAV) prevention
- Vascular risk factor management
- Avoidance of rejection
- Cytomegalovirus prophylaxis
- Aspirin
- Statin
- De novo mTORi

Early post-transplant CAV surveillance
- Coronary angiography ± intravascular ultrasound at 6 weeks and 12 months

Does patient have CAV?*
- Therapeutic considerations:
  - Conversion to mTORi early post-transplant
  - Percutaneous coronary intervention for obstructive focal disease
  - Retransplantation for severe ISHLT grade 3 CAV with allograft dysfunction

Continue CAV prevention
- Annual CAV surveillance
- Coronary angiography +/- intravascular ultrasound for ≤5 years post-transplant
- Non-invasive imaging for ≥6 years

Preventive measures early post-transplant include consideration of de novo mammalian target of rapamycin inhibitor (mTORi). Surveillance in the first year and annually, up to 3 to 5 years post-transplant, is by invasive angiography and, if available, intravascular ultrasound (IVUS). Beyond 5 years, noninvasive imaging (dobutamine stress echocardiography, myocardial perfusion imaging, or computed tomography coronary angiography) could guide the need for invasive testing. Treatment options include conversion to mTORi (particularly if early post-transplant); percutaneous coronary intervention for focal obstructive disease; and retransplantation in selected patients with severe CAV and associated allograft systolic dysfunction. *International Society for Heart & Lung Transplantation (ISHLT) cardiac allograft vasculopathy (CAV) grade 1 to 3 or ≥0.5 mm increase in maximal intimal thickness on serial IVUS.
compared with de novo transplantation (1). A recent registry analysis reported comparable 9-year survival among patients with CAV retransplanted (n = 65) or medically managed (n = 4,530): 55% versus 51% (62). Subgroup analysis suggested a survival benefit for retransplantation with associated allograft systolic dysfunction. This finding is supported by earlier studies showing lower 5-year survival in patients with CAV or either allograft systolic dysfunction or restrictive cardiac physiology (63).

**CONCLUSIONS**

CAV is a leading cause of death after heart transplantation. Early rapid intimal thickening predicts the development of angiographic disease and adverse cardiac outcomes, including reduced survival. Accordingly, prevention strategies must be implemented early, and surveillance techniques targeting detection of early disease are essential. It is likely that an invasive approach will best identify early CAV, combining high-resolution examination of the vessel intima by IVUS or OCT and coronary physiology approaches. Investigation in noninvasive approaches will likely aid our understanding of CAV pathophysiology and provide insight into potential noninvasive approaches. Investigation in noninvasive imaging is ongoing and will most likely have highest utility in medium- to long-term follow-up and reduce the need

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Year</th>
<th>Study Name</th>
<th>Imunosuppression</th>
<th>Number</th>
<th>Follow-Up (months)</th>
<th>Intravascular Ultrasound</th>
<th>Rejection</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Arora et al. (52)</td>
<td>2015</td>
<td>SCHEDULE Multicenter (Scandinavia)</td>
<td>CsA withdrawn week 7-11 for RAD group</td>
<td>95 of 115 (83%)</td>
<td>12</td>
<td>MIT ≥0.5 mm&lt;sup&gt;+&lt;/sup&gt; - RAD: 51% - CsA: 65% - MIT change&lt;sup&gt;+&lt;/sup&gt; - RAD: 0.03 ± 0.06 mm - CsA: 0.08 ± 0.12 mm - Atheroma volume change&lt;sup&gt;+&lt;/sup&gt; - RAD: 1.3 ± 2.3% - CsA: 4.2 ± 5.0% - Atheroma volume change&lt;sup&gt;+&lt;/sup&gt; - RAD: 1.1 ± 19.2 mm&lt;sup&gt;3&lt;/sup&gt; - CsA: 13.8 ± 28.0 mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>BPAR, p = NS - RAD: 77% - CsA: 63% ≥2R grade&lt;sup&gt;+&lt;/sup&gt; - RAD: 43% - CsA: 15%</td>
<td>Allograft function NS - Less CMV for RAD: 5% versus 31%&lt;sup&gt;+&lt;/sup&gt; - Bacterial NS - Immune markers - Decline in sTNF-1 for RAD - Others NS: CRP, VEGF, VCAM-1, vWF, IL-B</td>
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<td>Kobashigawa et al. (50)</td>
<td>2014</td>
<td>RAD A2310 substudy Multicenter (Europe, America, Australia, New Zealand, Taiwan)</td>
<td>RAD 1.5 mg + CsA (n = 88) versus MMF + CsA (n = 101)</td>
<td>189 of 553 (34%)</td>
<td>12</td>
<td>MIT change ≥0.5 mm&lt;sup&gt;+&lt;/sup&gt; - RAD: 13% - MMF: 27% - MIT change&lt;sup&gt;+&lt;/sup&gt; - RAD: 0.03 ± 0.05 mm - MMF: 0.07 ± 0.11 mm - Intimal volume&lt;sup&gt;+&lt;/sup&gt; - RAD: 2.04 ± 7.00 mm&lt;sup&gt;3&lt;/sup&gt; - MMF: 7.74 ± 12.93 mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>≥2R grade, p = NS - RAD: 22% - MMF: 25%</td>
<td>Graft loss/retransplant/death NS - Serious adverse event&lt;sup&gt;+&lt;/sup&gt; - RAD: 71% - MMF: 58% - Pericardial effusion&lt;sup&gt;+&lt;/sup&gt; - RAD: 43% - MMF: 28% - Infection&lt;sup&gt;+&lt;/sup&gt; - Less CMV for RAD: 8% versus 21% - More bacterial for RAD: 30% versus 22%</td>
</tr>
<tr>
<td>Keogh et al. (51)</td>
<td>2004</td>
<td>Multicenter (Australia, New Zealand)</td>
<td>SRL + CsA (n = 92) versus AZA + CsA (n = 44)</td>
<td>136</td>
<td>24</td>
<td>MIT&lt;sup&gt;+&lt;/sup&gt; - SRL: 0.5 ± 0.3 mm - AZA: 0.9 ± 0.3 mm - Atheroma volume&lt;sup&gt;+&lt;/sup&gt; - SRL: 18.3 ± 11.3% - AZA: 28.7 ± 15.3% - Atheroma volume&lt;sup&gt;+&lt;/sup&gt; - SRL: 5.7 ± 4.1 mm&lt;sup&gt;3&lt;/sup&gt; - AZA: 7.1 ± 4.7 mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>≥2R grade 6 months&lt;sup&gt;+&lt;/sup&gt; - SRL: 3 mg/day: 32% - SRL: 5 mg/day: 35%</td>
<td>12-month survival NS</td>
</tr>
<tr>
<td>Eisen et al. (53)</td>
<td>2003</td>
<td>RAD B253 Multicenter (Europe, America)</td>
<td>RAD 1.5 mg + CsA (n = 209) versus RAD 3 mg + CsA (n = 211)</td>
<td>634</td>
<td>12</td>
<td>MIT change ≥0.5 mm&lt;sup&gt;+&lt;/sup&gt; - RAD 1.5: 36% - RAD 3: 30% - AZA: 53% - MIT change&lt;sup&gt;+&lt;/sup&gt; - RAD 1.5: 0.04 mm - RAD 3: 0.03 mm - AZA: 0.10 mm</td>
<td>≥2R grade&lt;sup&gt;+&lt;/sup&gt; - RAD 1.5: 31% - RAD 3: 21% - AZA: 46%</td>
<td>Less CMV for RAD: 8% versus 22% - More bacterial for RAD: 33%–38% versus 25%</td>
</tr>
</tbody>
</table>

*<sup>p < 0.05</sup>
AZA = azathioprine; BPAR = biopsy-proven acute rejection; CMV = cytomegalovirus; CRP = C-reactive protein; CsA = cyclosporine; IL-8 = interleukin-8; MIT = maximal intimal thickness; MMF = mycophenolic acid; mTORi = mammalian target of rapamycin inhibitor; NS = nonsignificant; RAD = everolimus; SRL = sirolimus; sTNF-1 = soluble tumor necrosis factor-1; VCAM-1 = vascular cellular adhesion molecule-1; VEGF = vascular endothelial growth factor; vWF = von Willebrand factor.
for invasive testing. Current management is focused on prevention strategies directed at modifiable immune and nonimmune targets. The mTORis have been a significant advance in slowing progression of CAV, but their optimal use needs to be established with further randomized studies.

**REFERENCES**


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Cardiac Allograft Vasculopathy


**KEY WORDS** coronary and myocardial flow reserve, endothelial injury, heart transplant, intimal hyperplasia, intravascular ultrasound, mammalian target of rapamycin inhibitors

**APPENDIX** For a supplemental figure, please see the online version of this article.