Cardiac Allograft Vasculopathy

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Cardiac allograft vasculopathy (CAV) is the most important cause of morbidity and mortality following cardiac transplantation. CAV is largely mediated by immunologic damage and infiltration of the endothelium, resulting in proliferation of vascular smooth muscle cells and subsequent luminal narrowing. There are various risk factors for the development and progression of CAV. Coronary angiography is the gold standard for the diagnosis of CAV; intravascular ultrasound also plays an important role. The management of CAV includes immunosuppression, drugs that modify conventional coronary artery disease risk factors, and percutaneous coronary intervention (PCI) or surgical revascularization for severe obstructive lesions. Although revascularization with PCI has a high immediate success rate, rates of in-stent restenosis are higher as compared with PCI of native coronary arteries, although the advent of drug-eluting stents has somewhat improved in-stent restenosis rates. Thus, the only definitive treatment of CAV is repeat transplantation. Randomized trials are needed to determine the optimal immunosuppressive and conventional risk factor–modifying agents and revascularization strategies for patients who develop CAV.
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Cardiac transplantation is a well-established (and currently the definitive) therapy for patients with severe refractory congestive heart failure.[1] However, many complications and comorbidities are associated with cardiac transplantation and the immunosuppressive regimens required to preserve graft function. These include allograft rejection, infections, malignancy, renal failure, and cardiac allograft vasculopathy (CAV).[2] Of these complications, CAV remains the most clinically important late complication following cardiac transplantation, with CAV present in up to half of patients at long-term follow-up angiography.[2-5] The risk for CAV grows exponentially after 5 years, and in

some studies the prevalence was found to increase 10% every 2 years after cardiac transplantation.[6,7] Additionally, as much as 10% of early graft failure may be due to severe CAV.[7] The pathogenesis, risk factors, diagnosis, and treatment of CAV are discussed in this review.

Pathogenesis of CAV

The pathogenesis of CAV is mediated mainly by humoral and cellular immunity, although several nonimmunologic factors contribute to the progression. Histologic examination of arteries in CAV shows a subendothelial lymphocytic infiltrate composed mostly of T cells, which are associated with a strong cytotoxic immune response.[8] In addition, the inflammatory response to alloantigens as well as non–major histocompatibility complex (MHC) antigens such as cardiac myosin appears to contribute to CAV progression, and circulating antibodies to these antigens are increased after cardiac transplantation.[9] Patients who have anti-MHC antibodies (both Class I and II) have also been found to have an increased risk of developing CAV at 5 years after cardiac transplantation.[10] Additionally, densely calcified and necrotic (inflammatory) plaques that could stimulate an immunologic response are associated with an increased risk of CAV progression.[11]

The subendothelial T-cell infiltrate and alloantibodies seen in CAV patients likely mediate changes in vascular permeability secondary to endothelial damage. Subsequently, vascular smooth muscle cells proliferate and migrate from the media to the intima, producing cytokines and extracellular matrix.[12] Both epicardial arteries and intracardiac arterioles are progressively affected by this intimal hyperplasia, narrowing the vessel lumen and impairing vascular function. Vascular smooth muscle hyperplasia is thought to be triggered as a repair response to immune-mediated apoptosis, eventually resulting in CAV.[13]

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The intimal thickening and loss of endothelial function in patients with CAV is worsened by injury to the endothelium, which occurs during implantation of the allograft.[14] Free radicals such as superoxide are produced upon implantation and result in reperfusion injury, and the resulting inflammatory cytokines that are released are associated with the development of CAV.[15,16]

In addition to T lymphocytes, several other immune cells play a role in the pathogenesis of CAV. Natural killer cells are involved in the recruitment of T cells that are nonreactive to donor MHC,[17] and macrophage foam cells are commonly found in the inflammatory infiltrate of CAV. Quilty lesions, which are nodular mononuclear endocardial infiltrates of unknown etiology, are associated with younger age and an increased risk of developing CAV 5 years after transplantation in patients who did not form anti-HLA Class II antibodies.[18] Thus, Quilty lesions may be a risk factor for the development of CAV unrelated to anti-HLA antibodies, which are themselves associated with CAV.

Genetic factors also contribute to the development of CAV. Homozygosity for a polymorphism resulting in increased tumor necrosis factor (TNF)-α expression is associated with CAV development and increased mortality, possibly due to TNF-α upregulating expression of MHC and adhesion molecules and activating endothelium.[19,20] Heat shock protein 27 expression appears to be protective for CAV, as it is expressed in significantly higher amounts in patients without CAV than those with CAV.[21] Mutations resulting in lower levels of transforming growth factor (TGF)-β1 in the recipient are protective for CAV, as TGF-β1 has actions of recruiting endothelial cells, vascular smooth muscle, leukocytes, and fibroblasts, which are all found in CAV lesions.[22]

The additive effects of all of these factors, including angiogenesis, complement activation, intimal hyperplasia, and endothelial proliferation, contribute to a reduction in the surface area of the vascular elastic membrane, termed *restrictive remodeling*.[23] Angiogenesis occurs even within the expanded intima of CAV vessels as donor endothelium recanalizes and is induced by endothelial activation markers, suggesting that inhibiting damage to endothelium can decrease angiogenic recruitment to allograft vessels via decreased expression of these markers.[24] However, some of these responses may actually be adaptive against tissue inflammation. Upregulation and expression of heme oxygenase-1 is an example of this, as it is synthesized in response to inflammation by macrophages, yet it is associated with a suppression of the inflammatory response that may inhibit tissue injury.[25]

Factors Influencing Progression of CAV

Various factors associated with both the allograft donor and recipient have been shown to increase the risk of developing CAV (Table 1). The incidence of CAV is higher when the donor allograft has coronary artery disease (CAD).[26] Increasing age, male

Table 1
Factors Influencing Progression of Cardiac Allograft Vasculopathy

Donor variables
Coronary artery disease
Donor or recipient variables
Increasing age
Male sex
Hypertension
Recipient variables
ISHLT rejection grade >3
Frequent rejection episodes in the first year of transplantation
Cytomegalovirus (+) status pretransplantation
Glucose intolerance
Hyperlipidemia
Smoking
Treatment with steroids
Increased body mass index

ISHLT, International Society of Heart and Lung Transplantation.

sex, and hypertension are risk factors if they occur in either donor or recipient; risk factors associated with the recipient include International Society of Heart and Lung Transplantation (ISHLT) rejection grade ≥ 3 (severe acute rejection), frequent rejection episodes in the first year post-transplantation, positive cytomegalovirus status pretransplantation, glucose intolerance, hyperlipidemia, smoking, treatment with steroids, and increased body mass index.[7,22,27-37]

In cardiac transplant recipients who had multiple episodes of rejection posttransplant, the incidence of CAV was 40%, compared with 23% in patients with no episodes of rejection.

The immunologic basis of CAV development is further supported by the link between frequent rejection episodes and CAV. In cardiac transplant recipients who had multiple episodes of rejection posttransplant, the incidence of CAV was 40%, compared with 23% in patients with no episodes of rejection.[38] Noncompliance with immunosuppressants after 1 year posttransplantation also increases the risk of CAV, providing further evidence for the immunologic mechanism of CAV.[39] When endomyocardial biopsy was used to evaluate rejection score 6 months posttransplantation, the ISHLT rejection score was associated with a hazard ratio of 1.97 (95% confidence interval, 0.99-3.90) for developing CAV, and in patients with a rejection score > 0.3 there was a more rapid CAV onset.[40] Additionally, the higher rejection scores were associated with increased necrotic plaque as determined by intravascular ultrasound (IVUS).

Diagnosis of CAV

Cardiac transplant recipients may not experience the classic symptom of angina because of allograft denervation (Table 2). Therefore, clinical history may be unreliable in the diagnosis of CAV. Although the majority of the patients are asymptomatic, cases of reinnervation have been reported in 10% to 30% of patients, and may result in atypical symptoms including symptoms of abdominal, chest, and arm pain.[41,42] These may be suggestive of the presence of CAV and a high level of clinical suspicion is warranted. Typical angina, however, is rare.[42] In cases of significant proximal lesion with significant myocardial territory in jeopardy, patients may report reduced functional capacity. The first symptoms may be those of graft failure, including orthopnea or exertional dyspnea.[42]

Table 2
Diagnosis of Cardiac Allograft Vasculopathy

Symptoms
Noninvasive imaging
Stress radionuclide myocardial perfusion imaging
Stress echocardiography
Cardiac computed tomography
Invasive imaging
Coronary angiography
Intravascular ultrasound
Fractional flow reserve
Coronary flow reserve

Myocardial infarction (MI) may also occur secondary to CAV. In one study, two of seven deaths occurring 1 year after transplantation were due to CAV and silent MI.[43] Another study identified 29 separate acute MIs in 155 autopsies and explanted hearts following repeat transplantation.[44] Acute MI in patients with CAV involved chest or arm pain in only 12% of cases. Patients experienced symptoms including dyspnea, fatigue or weakness, syncope, emotional changes, and diaphoresis during acute MI, emphasizing the need to consider MI despite atypical symptoms.

Noninvasive assessments of ventricular function, including echocardiography (particularly if decrements in function are noted), can be used as nonspecific tests indirectly measuring the effect of CAV on graft function. Noninvasive imaging can also be used to detect the presence of ischemia in cardiac transplant recipients. Exercise studies, such as stress electrocardiography, have a sensitivity of < 50% for the detection of CAV, though specificity is approximately 80%.[45] Although the sensitivity of

echocardiography alone for detecting CAV is fairly low, the use of dobutamine stress echocardiography increases sensitivity to 72%.[46] Stress radionuclide myocardial perfusion imaging and stress echocardiography can detect ischemia in these patients with high specificity and sensitivity.[47,48] Cardiac computed tomography (CT) can evaluate wall thickening as well as intimal hyperplasia and may therefore be a useful mode of CAV evaluation, grading, and monitoring.[49] CT angiography has compared favorably with coronary angiography in detecting significant stenoses in cardiac transplant recipients.[50,51] However, the risk of contrast-induced nephropathy in cardiac transplant recipients, many of whom have chronic renal insufficiency, may preclude the widespread application of CT angiography, which requires the use of greater amounts of contrast compared with invasive coronary angiography.[52]

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Coronary angiography is the current gold standard for both the diagnosis and surveillance of CAV. The rate of CAV in patients 5 years post-transplantation as determined by angiography is 42%, with 8% of patients having moderate CAV, and 7% having severe CAV.[4] Angiography is less sensitive for the detection of CAV than for nontransplant CAD, because the disease in CAV is usually diffuse, as opposed to the more typical focal plaques observed in native CAD.[53] Our center and others perform annual surveillance angiography for the first 5 years after transplantation. Barring any significant abnormalities, subsequent coronary angiography can be performed biannually. If CAV is detected, more frequent surveillance angiography should be considered.

Based on the severity of CAV as determined by angiographic evidence of stenosis and ejection fraction, the ISHLT has recently proposed classification guidelines, with disease designated as nonsignificant, mild, moderate, or severe[54] (Table 3). Each designation is determined based on the degree of CAV involvement of the left main coronary artery and subsequent branches, as well as left ventricular ejection fraction. These

Table 3
Recommended Nomenclature for Cardiac Allograft Vasculopathy

ISHLT Classification	Lesion Severity	Comments
CAV0	Not significant	No detectable angiographic lesion
CAV1	Mild	Angiographic LM < 50%, or primary vessel with maximum lesion of < 70%, or any branch stenosis < 70% (including diffuse narrowing) without allograft dysfunction
CAV2	Moderate	Angiographic LM ≥ 50%; a single primary vessel ≥ 70%, or isolated branch stenosis ≥ 70% in branches of two systems, without allograft dysfunction
CAV3	Severe	Angiographic LM ≥ 50%, or two or more primary vessels ≥ 70% stenosis, or isolated branch stenosis ≥ 70% in all three systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤ 45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific)

A *primary vessel* denotes the proximal and middle 33% of the left anterior descending artery, the left circumflex, the ramus and the dominant or co-dominant right coronary artery with the posterior descending and posterolateral branches.

A *secondary branch vessel* includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals, and obtuse marginal branches or any portion of a nondominant right coronary artery.

Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio > 2 (> 1.5 in children), shortened isovolumetric relaxation time (< 60 ms), shortened deceleration time (< 150 ms), or restrictive hemodynamic values (right atrial pressure > 12 mm Hg, pulmonary capillary wedge pressure > 25 mm Hg, cardiac index < 2 L/min/m^2).

CAV, cardiac allograft vasculopathy; ISHLT, International Society of Heart and Lung Transplantation; LM, left main; LVEF, left ventricular ejection fraction.

guidelines provide a standardized approach to determining the severity of CAV.

Although IVUS is the most sensitive modality for detecting CAV, CT angiography is an alternative, with a sensitivity of 70% for CAV detection.

Because CAV is often a diffuse process that may be difficult to recognize through angiography, which only characterizes the vessel lumen, IVUS can be a very useful adjunct to assess CAV. Particularly in noncalcific disease, IVUS is able to assess the vessel lumen as well as all three layers of the vessel wall, and can be used to diagnose CAV in the presence of an intima thicker than 0.5 mm, as defined by the American College of Cardiology Clinical Expert Consensus document for IVUS studies.[55] Much of what has been learned regarding the distribution and morphology of CAV has come from the use of IVUS. Although CAV is often diffuse, it can also present similarly to lesions of native CAD, occurring at bifurcations. Inflammatory plaques, composed of ≥ 30% necrotic core with dense calcification as identified by IVUS, are associated with a higher rejection score when compared with noninflammatory plaques (< 30% necrotic core and calcification).[11] IVUS is also useful for stratifying risk for cardiac transplant recipients, as an increase in ≥ 0.5 mm in intimal thickness as determined by IVUS within 1 year after transplantation is a marker for developing CAV in the 5-year posttransplantation period, as well as for major adverse cardiac events.[55-58] Increased utilization of IVUS may be limited by the increased cost and inability to safely evaluate small-caliber vessels with the relatively larger IVUS catheter.[53] Although IVUS is the most sensitive modality for detecting CAV, CT angiography is an alternative, with a sensitivity of 70% for CAV detection.[50] Some institutions perform IVUS at 4 weeks and 1 year after cardiac transplantation to detect early-stage CAV. The detection of early stage CAV is increased with multivessel imaging. The prevalence of CAV lesions was found to be 27%, 41%, and 58% at 1 year, increasing to 39%, 55%, and 74% at 3 years for patients with 1-, 2- and 3-vessel imaging, respectively.[59]

Despite the prognostic value of early detection of CAV with IVUS, its routine use has been controversial and not widely adopted. Studies have not shown a clear benefit in clinical outcomes when intimal thickening is attenuated via pharmacologic intervention. Furthermore, others have demonstrated that intimal proliferation assessed via IVUS does not correlate well with small-artery disease by histologic or immunohistochemical analysis.[54,60,61]

Fractional flow reserve (FFR) measurement appears to have utility in ascertaining functional significance of CAV lesions.[62] There is an inverse correlation between IVUS plaque measurements and FFR. Additionally, even in patients without angiographic evidence of CAV, FFR values were abnormal, further emphasizing the diffuse nature of CAV. A minority of patients have a normal FFR with an abnormal coronary flow reserve, indicating involvement primarily of the microcirculation.

Treatment of CAV

Conventional CAD Risk Factor Modification

Although patients with CAV are typically counseled to incorporate lifestyle changes and other risk factor modification strategies typically used for patients with atherosclerotic heart disease, there are limited data regarding the long-term efficacy of such approaches in the CAV population. 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors lower cholesterol levels, have immunomodulatory effects (likely secondary to attenuation of inflammatory infiltrates), reduce the incidence and progression of plaques, and improve clinical outcomes posttransplant.[63-65] Additionally, lower serum lipid levels are associated with CAV plaque regression.[28] Angiotensin-converting enzyme (ACE) inhibitors may lead to CAV regression by inhibiting the mediators that promote angiogenesis, such as vascular endothelial growth factor and platelet-activating factor[28,66] (Table 4). The addition of calcium channel blockers (mainly diltiazem) to ACE inhibitors has been associated with a significant decrease in IVUS indicators of CAV when compared with ACE inhibitors alone.[67] In a murine model, angiotensin receptor blockers have comparable effects, resulting in fewer circulating mononuclear smooth muscle progenitor cells, which have been shown to contribute to CAV.[68,69] Furthermore, elevated angiotensin II receptor expression has been correlated with increased risk of the development of CAV, likely due to its effects of

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Table 4
Treatment of Cardiac Allograft Vasculopathy

- Pharmacotherapy
  - Agents that modify conventional coronary artery disease risk factors
    - ACE inhibitors
    - HMG-CoA reductase inhibitors
    - Calcium channel antagonists
  - Immunosuppressive therapies
    - Calcineurin inhibitors
      - Cyclosporine
      - Tacrolimus
    - Glucocorticoids
    - Mycophenolate mofetil
    - Azathioprine
    - mTOR inhibitors
      - Sirolimus
      - Everolimus
- Percutaneous revascularization
- Surgical revascularization
- Repeat cardiac transplantation

ACE, angiotensin-converting enzyme; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; mTOR, mammalian target of rapamycin.

promoting fibrosis, inflammation, and extracellular matrix remodeling.[70]

Immunosuppressive Therapies

In the posttransplantation period, calcineurin inhibitors (CNIs) such as cyclosporine or tacrolimus, in addition to glucocorticoids and either mycophenolate mofetil or azathioprine, are the traditional immunosuppressive agents used after cardiac transplantation. Cyclosporine is effective in preventing CAV because there is a correlation between increased cyclosporine dose and duration with decreased mononuclear cell infiltration.[71,72] Conversely, cyclosporine also has detrimental effects on endothelial function, inhibiting nitric oxide and prostacyclin synthesis, increasing thromboxane A2 synthesis, and upregulating endothelin-1 and endothelin-1 receptor expression.[73-78] The nephrotoxicity of cyclosporine is a major limiting factor in its use in cardiac transplantation.

Mycophenolate mofetil (MMF) is an inhibitor of de novo guanine nucleotide synthesis, a process that lymphocytes are dependent upon, resulting in decreased antibody production and smooth muscle cell proliferation.[79] In a randomized trial comparing MMF with azathioprine, MMF was associated with a significantly reduced risk for intimal thickness ≥3, reduced loss of luminal area, and improved mortality within the first year after transplantation.[80,81] Furthermore, MMF has the additional benefits of conferring protection against malignancy and having no known nephrotoxicity.[82]

Inhibitors of the mammalian target of rapamycin (mTOR), such as sirolimus (rapamycin) and everolimus, are playing an increasingly important role in the management of CAV, as they provide an alternative to CNIs with a much lower risk of nephrotoxicity. Sirolimus inhibits cytokine-induced lymphocyte and vascular smooth muscle proliferation, fibrosis, and vascular remodeling.[83-85] It has also been shown to reduce narrowing in the coronary lumen compared with azathioprine, and has stronger inhibitory effects on smooth muscle proliferation than cyclosporine.[86,87] In pediatric patients with CAV who were treated with sirolimus following CNI-induced renal dysfunction, renal function improved, although side effects were common in all patients treated with sirolimus; hyperlipidemia, abdominal pain, and oral ulcers each occurred in >25% of patients.[88] In one study, when CNIs were replaced with sirolimus as primary immunosuppression, CAV progression significantly decreased compared with the group that remained on CNIs.[89] Replacing the CNI with sirolimus also improved renal function. When compared with cyclosporine, sirolimus was associated with better endothelial function in allografts as measured by change in coronary artery diameter in response to nitroglycerin.[90] This may be explained by various actions of sirolimus including lower sensitivity to vasospasm compared with cyclosporine, increased prostacyclin production, unimpaired vasorelaxation, preserved endothelial nitric oxide synthase expression, and significantly less oxidative damage than cyclosporine.[90,91] Despite the many advantages of sirolimus, its use immediately following transplantation may be impractical, as it has been associated with an increase in postsurgical wound complications when used in this setting.[92]

Percutaneous Revascularization

Although CAV is often characterized by diffuse luminal narrowing and concentric intimal thickening, percutaneous revascularization may be a viable treatment option for CAV in the case of relatively focal obstructive lesions.[93] Balloon angioplasty is associated with high restenosis rates.[93-95] Although stents decrease the rates of early

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restenosis, late restenosis rates are similar to those seen with plain balloon angioplasty.[94,96] The use of stents, higher doses of antiproliferative immunosuppressant therapy, early reduction of steroid dose, and the use of MMF and HMG-CoA reductase inhibitors have been shown to decrease restenosis.[95,96] Despite these therapeutic advances, rates of in-stent restenosis are higher in CAV than in native CAD, in part due to the aggressive lymphoproliferative component of CAV.[27,97] The pathophysiology of in-stent restenosis is similar to that of CAV rather than native atherosclerosis, characterized by endothelial damage and reactive vascular smooth muscle proliferation and migration, possibly explaining the increased rate of in-stent restenosis in CAV patients.[97] Additionally, the presence of a discrete coronary artery lesion after transplantation often precedes the development of diffuse CAV, and stents have only a local effect within the coronary vasculature. Restenosis rates are also influenced by baseline inflammation, as there is a positive correlation between preprocedural levels of both von Willebrand factor and monocyte chemotactic protein-1 and percent stenosis at 6-month follow-up.[98] The presence of IgG antibody to MHC Class I was also found to be a strong predictor of restenosis.[99]

Drug-eluting stents are associated with a modestly decreased rate of in-stent restenosis and target vessel revascularization compared with bare metal stents when used to treat more focal obstructive stenoses in CAV patients.[100,101] Percutaneous revascularization with sirolimus- and paclitaxel-eluting stents appears to provide similar outcomes in patients with CAV in observational studies.[102] Percutaneous coronary intervention is also a safe and effective treatment of patients with unprotected left main coronary artery CAV lesions.[103]

Surgical Revascularization

The data on surgical revascularization for the treatment of CAV are limited. Surgical revascularization is an option in patients with focal lesions, but is largely ineffective in most patients due to the diffuse involvement of CAV and only recommended in patients with proximal lesions.[104] Arterial bypass grafts are preferred to venous grafts.[105] The 5-year survival in retrospective studies of patients with CAV who underwent coronary artery bypass graft varied between 20% and 83%, although the sample size of each study was very small.[105-109]

Repeat Transplantation

Repeat cardiac transplantation is the only definitive treatment of severe CAV. In pediatric patients, mortality following repeat transplantation is higher compared with the initial transplantation, particularly when repeat transplantation is performed within the first 180 days following the initial transplantation.[110] Adults who underwent repeat transplantation have been shown to have a mortality rate that is comparable to that of the initial transplantation.[111]

Conclusions

CAV is a major cause of morbidity and mortality in cardiac transplant recipients, responsible for over 25% of deaths, and is the most common indication for repeat transplantation. Coronary angiography and IVUS are the conclusive modalities for diagnosis and evaluation of CAV. Due to the diffuse and progressive nature of CAV, the mainstay of treatment remains pharmacologic, but may also include adjunct percutaneous or surgical revascularization when severe stenosis exists. Progression of CAV should elicit reassessment of the patient's immunosuppressive regimen, adding or titrating drugs including CNIs, sirolimus, or glucocorticoids, after taking into consideration the patient's comorbidities. In cases where diffuse disease with severe loss of luminal area, is unresponsive to pharmacotherapy, and is not amenable to percutaneous or surgical revascularization, repeat cardiac transplantation should be evaluated as it is the only definitive therapy. Randomized trials are required to determine the optimal immunosuppressive and conventional risk factor–modifying agents and revascularization strategies for patients who develop CAV. ■

In cases where diffuse disease with severe loss of luminal area, is unresponsive to pharmacotherapy, and is not amenable to percutaneous or surgical revascularization, repeat cardiac transplantation should be evaluated as it is the only definitive therapy.

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Main Points

- Cardiac allograft vasculopathy (CAV) is primarily immunologically mediated and characterized by diffuse intimal thickening and smooth muscle proliferation.
- CAV is present in up to half of patients at 5 years post-transplant and is the most significant factor in morbidity and mortality in cardiac transplant patients.
- Coronary angiography is the current gold standard for diagnosing and following CAV, whereas intravenous ultrasound has the highest sensitivity for detecting CAV.
- Of the conventional CAD risk factor–modifying agents, angiotensin-converting enzyme-inhibitors, calcium channel antagonists, and statin drugs have the greatest effect on CAV attenuation and prevention, whereas mTOR inhibitors such as sirolimus appear to be superior to other immunosuppressive agents.
- Although repeat transplantation is the only definitive treatment of severe CAV, percutaneous revascularization using drug-eluting stents is an effective intervention for focal CAV stenoses.

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