ABSTRACT

Coronary artery disease in the transplanted heart, also known as cardiac allograft vasculopathy (CAV), is a major cause of late mortality after transplantation. A variety of immune and nonimmune factors contribute to the pathogenesis. Intravascular ultrasonography (IVUS) is the most sensitive method for detecting early CAV; first-year IVUS results can predict 5-year outcomes after transplantation. Optimal prophylaxis is not established, but several studies now indicate that the proliferation signal inhibitors (eg, sirolimus and everolimus) and the statins (eg, pravastatin) help reduce development of CAV; mycophenolate mofetil, antihypertensives, vitamins C and E, and ganciclovir may also reduce the risk of this posttransplant complication. For those patients with established CAV, revascularization with angioplasty offers effective palliative therapy. This article reviews the pathogenesis, diagnosis, and treatment options for CAV. (Adv Stud Med. 2008;8(6):189-195)

CARDIAC ALLOGRAFT VASCULOPATHY: BACKGROUND AND RECENT ADVANCES*

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CARDIAC ALLOGRAFT VASCULOPATHY is a major factor limiting long-term survival after cardiac transplantation. Detectable in more than 50% of patients at 10 years after transplantation, early CAV (diagnosed within the first year after transplantation) is a powerful predictor of 5-year mortality (relative risk = 2.06, 95% confidence interval, 1.57–2.70, P < .0001). This chronic complication is believed to be immune mediated but nonimmune factors are also of importance. Current therapies are not effective and can, at best, only slow the progression of CAV. This article will describe our current understanding of CAV pathogenesis, explain the potential value of intravascular ultrasound (IVUS) in predicting long-term outcomes and guiding therapy, and outline current options for medical and surgical treatment.

PATHOGENESIS

The unique accelerated form of coronary artery disease known as CAV starts when ischemia causes injury to the donated organ’s endothelial cells. In response, both immune and nonimmune factors act on the endothelium, initiating a cascade of further immunologic responses. Eventually, upregulation of complement, inflammatory mediators, and cytokines lead to the development of full CAV. A variety of factors—including the use of immunosuppressive medications, such as cyclosporine and corticosteroids—are now thought to contribute to endothelial cell injury and ultimately to the intimal hyperplasia that is characteristic of CAV (Figure 1).

Although CAV exhibits similarities to the classic or “native vessel” atherosclerosis (eg, leukocyte infiltration, cytokine production, extracellular matrix accumulation, lipid buildup, intimal smooth muscle migration, and endothelial dysfunction), these diseases...
are distinct from one another—perhaps mostly because of the underlying immunologic trigger in the allogenic setting that confers a more diffuse and concentric distribution, in addition to a slightly altered lesion constitution (i.e., more inflammation or intact internal elastic lamina).3,4 Whereas immunologic factors clearly play a role in CAV development, the exact contribution of acute rejection to CAV pathophysiology and graft dysfunction remains under investigation. Smoldering cellular rejection, defined as a high first-year average biopsy score, has been well established as a significant risk factor for CAV5,6 More recently, researchers have also documented that severe hemodynamic-compromising rejection, which is mostly humorally mediated, also appears to be a prime risk factor in CAV and death.7

**DIAGNOSIS**

Despite its poor inherent sensitivity, the coronary angiogram has long been considered the gold standard for diagnosing CAV. Dobutamine stress echocardiography is the most sensitive noninvasive alternative, detecting CAV with 92% sensitivity and 86% specificity versus angiography.8 Other noninvasive tests that have been compared directly to coronary angiography include single-photon emission computed tomography (CT) with 89% sensitivity and 71% specificity,9 and multidetector CT with 86% sensitivity and 99% specificity.10

Although coronary angiography remains the most widely used screening test for vascular disease, this technique highlights only the luminal diameters and therefore, often misses the intimal thickening associated with early CAV. This is because the coronary artery in CAV often dilates in a compensatory response to the thickening. In addition, because early CAV tends to appear diffusely throughout the entire coronary tree rather than in more intense focal lesions, angiography may also tend to obscure any narrow points of constriction. This inability to detect early CAV is critical in transplanted patients with denervated hearts because these patients fail to display the classic accompanying warning signs of angina.

Because it provides a cross-sectional image of the wall structure itself rather than just the lumen, IVUS offers a potentially more sensitive technique for detecting CAV than angiography. As shown in Figure 2, IVUS often reveals intimal thickening that might be missed by angiography. Objective measurement of the

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**Figure 1. Proposed Mechanisms in the Development of Allograft Vasculopathy**

![Diagram of proposed mechanisms in the development of allograft vasculopathy]


**Figure 2. Comparison of Angiography and IVUS in Detecting Intimal Thickening with Compensatory Dilatation**

![Comparison of angiography and IVUS images](image-url)

On the left, coronary angiography suggests minimal or no luminal narrowing; evaluation of same patient with IVUS at distal point (lower right) also shows an open artery; IVUS imaging at proximal point (upper right) shows an identical luminal diameter but also reveals a large crescent area within the right side of the vessel wall that represents significant intimal thickening. IVUS has detected vasculopathy with compensatory dilatation that would have been missed by angiography alone. (Note: the small white circle in the center of the IVUS image is a catheter artifact.) IVUS = intravascular ultrasound. Courtesy of Tuzcu EM and Starling RC, Department of Cardiovascular Medicine, Cleveland Clinic Heart and Vascular Institute, Cleveland, OH.
intima with IVUS has now been used to screen for CAV in large populations. One large study (N = 262) found more than 50% of patients to have vasculopathy by IVUS as soon as 1 year after transplantation—more than 5 times the rate of luminal irregularities found angiographically in the same patients. Although IVUS studies using different thickness thresholds to define CAV have produced different results, the superior sensitivity of ultrasound is clear and the potential value of early IVUS results in predicting long-term morbidity and mortality has now been established.

In one of these validation studies, researchers from several heart centers reviewed IVUS data from 125 patients who had been transplanted before 1998. The IVUS examinations had been performed 4 to 6 weeks after transplantation and then again at 1 year after the surgery. Patients were separated into 2 groups: those with first-year maximal intimal thickness (MIT) at or above 0.5 mm and those with MIT lower than 0.5 mm. The prognostic significance of IVUS findings were tested by analyzing their associations with 5-year outcome data abstracted from the medical records.

The results showed that patients at or above the 0.5-mm cutoff had a higher incidence of eventual death or graft loss (20.8% vs 5.9%, P = .007); more nonfatal major adverse cardiac events and/or death or graft loss (45.8% vs 16.8%, P = .008); and more newly occurring angiographic luminal irregularities (65.2% vs 32.6%, P = .004). This study indicates that first-year IVUS data are a surrogate marker for 5-year outcomes after heart transplantation. As discussed next, some newer immunosuppressive agents appear to diminish CAV, and therefore, this study also implies that first-year IVUS data may predict longer-term outcomes with these agents after transplantation.

TREATMENT APPROACHES

In addition to improved handling, storage, and transport of grafts, the main approaches for managing CAV include modification of cardiovascular risk factors (such as control of hypertension and diabetes, cessation of smoking, and weight loss), medical therapies, revascularization, and retransplantation.

MEDICAL THERAPIES

Several studies have evaluated the short-term impact of medical therapies on CAV (Table). Unfortunately, none of these agents have been shown to completely prevent or directly reverse development and progression of the disease process. Most current therapies are aimed at specific elements of suspected pathogenesis, such as those outlined in Figure 1. Selected studies focused on prevention of CAV—including several that have employed IVUS—are discussed here.

In terms of antihypertensive therapy, one randomized study of 104 heart transplant patients showed that the calcium channel blocker diltiazem led to a greater average coronary luminal diameter at 1 to 2 years versus controls. Another study in 32 transplant patients showed that calcium channel blockers and/or angiotensin-converting enzyme inhibitors led to reduced IVUS intimal thickness at 1 year versus untreated controls.

Antioxidants also may reduce development of CAV. In one study, 40 heart transplant patients (0–2 years postoperative) were randomized to vitamin C 500 mg twice a day plus vitamin E 400 IU twice a day or to placebo for 1 year. Over this period, the IVUS intimal index (plaque area divided by vessel area) increased by 8% in the placebo group versus 0.8% in the treatment group (P = .008) leading to the conclusion that supplementation with vitamins C and E retards early progression of transplant-associated coronary atherosclerosis.

Cytomegalovirus (CMV) is associated with development of CAV, most likely through direct and indirect cell endothelial damage. Specific mechanisms may involve upregulation of proinflammatory adhesion molecules in CMV-infected endothelial cells and

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CAV = cardiac allograft vasculopathy.
cytokines in infected T cells; inhibition of apoptosis in infected smooth muscle cells; and elevations in antiendothelial cell antibodies in infected individuals. Retrospective studies indicate that prophylaxis with ganciclovir with or without CMV hyperimmune globulin early after transplantation may reduce the risk of CAV.

In terms of immunosuppressive agents, 3 multicenter trials and 1 single-center trial provide evidence suggesting that specific agents slow CAV progression. In a multicenter randomized trial involving 650 heart transplant patients, those receiving mycophenolate mofetil (MMF) had clear survival and rejection benefits versus those receiving azathioprine but there was no significant difference in the baseline-to-1-year IVUS scores between treatment groups. However, when the 10 IVUS images from each patient were reanalyzed by matching site-to-site comparisons rather than averaging the 10 readings (which can mask the progression of intimal thickening at any one vessel site), patients in the MMF group had significantly less progression of first-year intimal thickening. Only 23% of those in the MMF group had a first-year change in MIT at or above 0.3 mm versus 43% of those in the azathioprine group (P = .005).

In a multicenter randomized trial (N = 136) comparing sirolimus to azathioprine, rejection rates were lower and serum creatinine higher in the sirolimus groups at 6 months. No differences in mortality were noted at 1 year. Results from IVUS taken at 6 weeks, 6 months, and 2 years showed that CAV had progressed markedly in azathioprine-treated patients. By comparison, sirolimus was associated with a significant absence of progression in intimal and medial proliferation at 6 months and 2 years.

The other proliferation inhibitor, everolimus, was also evaluated recently for its impact on CAV. In this randomized multicenter trial (N = 634), the combined primary end point, including rejection, graft loss, and death, was significantly lower in the everolimus group versus the azathioprine group. The 12-month IVUS results showed that the average MIT increase and the overall incidence of vasculopathy were significantly less in the everolimus groups versus the azathioprine group (Figure 3). A 4-year follow-up of this study showed that everolimus led to significantly less efficacy failure (ie, biopsy-proven rejection, graft loss, and death) (P < .05) and significantly less intimal thickening (P ≤ .01) over this period. In addition, those patients in the everolimus group had less CAV and fewer major adverse cardiac events, including revascularizations, compared with those in the azathioprine group over this long follow-up period.

One single-center study (N = 46) also found that sirolimus may slow disease progression in patients with existing CAV. After discovery of CAV at routine catheterization 3 to 5 years posttransplantation, patients were randomized to sirolimus or continued current immunosuppression. Two years later, only 3 of 22 patients taking sirolimus had achieved the primary end point (ie, death, need for revascularization, myocardial infarction, and >25% worsening of catheterization score) versus 14 of 24 patients in the control group (P < .001).

Finally, in terms of immunosuppression, note that photopheresis, a procedure in which pheresed white blood cells are treated with 8-methoxy-psoralen and given ultraviolet irradiation and then reinfused, has been shown in a small study to cause an unspecified immunomodulating effect that decreased CAV. The use of 3-hydroxyl-3-methylglutaryl coenzyme reductase inhibitors (statins) has also demonstrated benefit in transplant patients. In a study of 97 heart transplant patients randomized to pravastatin or no pravastatin, not only did the active treatment group have lower mean cholesterol (193 ± 36 mg/dL vs 248...

Figure 3. Impact of Everolimus Versus Azathioprine on CAV: Percentage of Patients with Change in IVUS MIT ≥ 0.5 mm at 12 Months

Pairwise comparison with Wilcoxon’s rank sum test. CAV = cardiac allograft vasculopathy; IVUS = intravascular ultrasound; MIT = maximal intimal thickness.
± 49 mg/dL, \( P < .001 \)) at 1 year, they also demonstrated less frequent cardiac rejection accompanied by hemodynamic compromise (3 vs 14 patients, \( P = .005 \)), better survival (94% vs 78%, \( P = .025 \)), and a lower incidence of CAV as determined by angiography and at autopsy (3 vs 10 patients, \( P = .049 \)). In an IVUS substudy, intimal thickness showed 50% less progression in the pravastatin group (\( P < .04 \)). A 10-year follow-up study of these patients showed that the early benefits associated with pravastatin treatment persisted in terms of survival and lower incidence of CAV (Figure 4). Ten-year survival in the statin group was 68% versus 48% in the control group (\( P = .028 \)).

**CORONARY REVASCULARIZATION AND RETRANSPLANTATION**

Percutaneous transluminal coronary angioplasty is used extensively as palliative treatment for CAV. In a single-center study of 29 heart transplant recipients, 50 of 53 lesions (94.3%) were successfully opened (<50% stenosis) with angiography; restenosis (≥50%) was seen at 14 of 43 (32.5%) sites at 6 months. In a study of drug-eluting stents, there was a trend toward lower restenosis rates (2 of 13, 15%) compared to bare metal stents (20 of 65, 31%) at 40 months. And in a study of 62 transplant patients who received angioplasty for CAV, freedom from restenosis (seen in 81% of patients at 3 months and 57% at 6 months), the multivariate predictors of success were use of stents and high antiproliferative immunosuppressant doses. Outcomes with coronary artery bypass after heart transplantation have been generally poor, with small studies indicating high rates of perioperative and 1-year mortality.

Retransplantation is the only effective manner of therapy for severe CAV. Rates of survival are acceptable if retransplantation is performed after the first year and if patients with acute rejection are excluded. Registry data indicate that 1-year patient survival rates reach 70% to 80% in patients retransplanted after 12 to 24 months. However, the ethical dilemma of retransplantation in these patients is considerable due to the scarcity of donor organs.

**CONCLUSIONS**

The pathogenesis of CAV includes immune and nonimmune factors. First-year IVUS data can provide an early marker for long-term outcomes. The proliferation inhibitors, sirolimus and everolimus, and the statins show clinical benefit in preventing CAV. For patients with existing CAV, revascularization is effective palliative therapy and retransplantation offers a more definitive solution but is limited by organ shortages.

**DISCUSSION**

*Dr Eisen:* Diagnosing transplant coronary disease is complicated. At Hahneman, the procedure we use most frequently, despite its flaws, is coronary angiography. Usually, we do not employ IVUS unless it is part of a clinical trial because it is not reimbursed. On occasion, we convince payers to pay for IVUS in selected patients. For patients at high risk, we will sometimes perform either dobutamine stress echocardiography or pharmacologic stress testing with nuclear imaging. But noninvasive tests are limited, thus we depend on angiography.

*Dr Rogers:* We take a similar approach at Duke, with annual screens primarily with coronary angiography for the first 5 years and then less frequent angiography after that. In years without angiography, we typically perform a pharmacologic stress test, usually dobutamine stress echocardiography.

*Dr Eisen:* Our angiographers use vasodilators, usually intracoronary nitroglycerin, as part of the standard procedure but we do not attempt quantitation because it is so much more time consuming and requires special expertise.
Dr Russell: Let me ask a radical question: Why do we cath people at all? There is increasing evidence that patients do not benefit greatly from stenting asymptomatic lesions. In fact, changing therapy rarely alters disease progression and, at any rate, we rarely act until the ejection fraction drops.

Dr Kobashigawa: In certain patients, we do pick up isolated lesions amenable to angioplasty. But it is true that we still need a randomized trial of non-left main, nonproximal left ventricular assist device lesions to see if angioplasty has a benefit. The COURAGE trial [Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation]19 showed no benefit here, but we have not yet tested this in cardiac transplant patients. The outcome might be similar in the transplant setting because the disease process is diffuse. Studies show that cardiac transplant patients with restenosis after angioplasty have further progression over the rest of the coronary arteries—that is, it is a homogeneous disease.

Dr Eisen: The other factor that might make it imperative to identify those with coronary disease is the preliminary evidence presented by Dr Kobashigawa29 showing that altering immunosuppression, in this case with sirolimus, may favorably affect outcomes. We need a much larger clinical trial with either sirolimus or everolimus to build on this Mancini data.

Dr Rogers: Statins have immunomodulatory effects and improve long-term outcomes in transplant patients. But are all statins alike in heart transplantation?

Dr Kobashigawa: I believe it is a class effect in transplant and nontransplant populations. We have found that various statins depress natural killer cell (NKC) activity to similar degrees but we have also found that the immunomodulatory impact on NKC activity becomes even more striking when the statin is combined with a calcineurin inhibitor. This occurs because calcineurin inhibitors increase statin levels by approximately 20-fold while, conversely, the statin increases the enzyme inhibitor concentration levels by approximately 8-fold. This boosts the bioactivity of the drug. That is why the immunomodulatory effect of statins is magnified in transplant patients compared to nontransplant patients on statins but not cyclosporine or tacrolimus. It is also why opportunistic infections are not a problem in those millions of individuals on statins.

Dr Rogers: Does this change in pharmacokinetics also account for the increased statin-related side effects seen in this population—effects such as increased muscle pathology, myalgias, and elevated creatinine kinase levels?

Dr Kobashigawa: Yes. But it also depends on the statin’s lipophilicity and hydrophilicity. Hydrophilic drugs, such as pravastatin and rosvastatin, have a lower incidence of myalgias and rhabdomyolysis. With simvas-tatin, especially when you go from 5 mg or 10 mg up to 20 mg, which is an average dose, there are more problems with myositis. This is less of a problem with pravastatin.

Dr Conte: How do you manage a patient who receives a donor heart with a low level of native coronary disease? Other than considering a back table bypass graft on an organ before implantation, are there any management differences?

Dr Eisen: We might consider sirolimus, the currently available proliferation signal inhibitor (PSI). The potential problem with sirolimus in these patients is wound healing, thus we might start the PSI approximately 3 months out once the wound has healed. However, there are no data on this approach.

Dr Kobashigawa: This is a common problem. The registry data show that both older age and preexisting coronary disease in the donor are risk factors for the development of transplant vasculopathy. Up to 80% of the older general population will show intimal thickening on IVUS—and that is about what you will see on transplant patients at baseline or 1 year.

Dr Eisen: Even the younger donor hearts—and keep in mind older is defined as over 40 years—are at higher risk for developing de novo diseases after transplant.

Dr Rogers: Are you using antioxidants?

Dr Kobashigawa: Yes. We routinely use vitamin C and vitamin E based mainly on the IVUS data I discussed.16 There also appears to be a beneficial interaction of these agents in combination with the calcineurin inhibitors. We do not yet know if the other antioxidant agents, such as coenzyme Q10 or vitamin A, will be helpful.

REFERENCES


