Cardiac Allograft Vasculopathy
Recent Developments
Daniel Schmauss, MD; Michael Weis, MD

Abstract—Cardiac allograft vasculopathy (CAV) continues to limit the long-term success of cardiac transplantation. Recent insights have underscored the fact that innate and adaptive immune responses are involved in the pathogenesis of CAV. Vascular lesions are the result of cumulative endothelial injuries induced both by alloimmune responses and by nonspecific insults (including ischemia-reperfusion injury, viral infections, and metabolic disorders) in the context of impaired repair mechanisms. Intravascular ultrasound is the most sensitive method for detection of CAV, and progressive intimal thickening in the first posttransplant year identifies patients at high risk for future cardiovascular events. Encouraging results with regard to the detection of CAV by noninvasive methods should be an incentive to apply routine noninvasive imaging during mid- to long-term follow-up. Improved immunosuppressive drugs, including mycophenolate mofetil and proliferation signal inhibitors, as well as statins (in part via immunomodulation), have beneficial effects on CAV progression, although there is still a need to confirm the impact of vasodilators in improving outcome after heart transplantation. Coronary revascularization for CAV is only palliative, with no long-term survival benefit. Three main strategies for CAV prevention are currently under investigation: inhibition of growth factors and cytokines, cell therapy, and tolerance induction. However, because individual responses to an allograft change over time, assays to monitor the recipient’s immune response and individualized methods for therapeutic immune modulation are clearly needed. (Circulation. 2008;117:2131-2141.)

Key Words: coronary disease ■ immunology ■ inflammation ■ microcirculation ■ transplantation

Although major improvements have been made in the prevention and treatment of acute transplant rejection, accelerated cardiac allograft vasculopathy (CAV) still limits the long-term success of heart transplantation (HTx). On the basis of the registry of the International Society of Heart and Lung Transplantation (ISHLT), CAV is detectable by angiography in 8% of survivors within the first year, in 32% within the first 5 years, and in 43% within the first 8 years after HTx.1 Patient survival after report of CAV is diminished significantly,1 and CAV and graft failure (most likely undetected CAV) are, in addition to malignancy, the most important causes of death in patients who survive the first year after transplantation.1 Undetected CAV may also present as heart failure due to global ischemia without documented infarction by ECG or pathology.

Early after HTx, focal and noncircumferential donor-transmitted epicardial intimal thickening is detectable, whereas later after HTx, focal atherosclerotic plaques, diffuse intimal thickening, or a variable mixture of both may be found.2 The progression of donor-derived lesions is comparable to de novo lesions,3 and the diffuse and progressive nature of CAV is one of the factors responsible for the poor success of interventional therapies.3,5 The importance of smooth muscle cell infiltration versus matrix formation in the development of CAV is quite debatable. Intima thickening might be caused indirectly by cell infiltration, which in turn is responsible for the production of cytokines, growth factors, and matrix deposition (collagen I and fibroblasts).4 Intimal T cells have an activated helper-1 phenotype, induce cytokines, and are most likely responsible for the induction of the intimal proliferation.6

Pathophysiology
Adaptive and Innate Immune Responses
The trigger to cell-mediated rejection is allorecognition, in which non-self-antigens are detected by the host immune system.7 This occurs by 3 distinct mechanisms, called the direct, indirect, and semidirect pathways. The direct pathway results from the recognition of foreign major histocompatibility (MHC) molecules on the surface of donor cells by recipient dendritic cells (DCs).7 Indirect allorecognition occurs when donor antigens are internalized, processed, and presented as peptides by host DCs.8 The impact of the recently described semidirect pathway of immune recognition9 (recipient’s DCs acquire donor MHC through cell-to-cell contact, which stimulates a T-cell response) for CAV is unknown.

Current concepts suggest that direct allorecognition mediates acute rejection, whereas indirect allorecognition mediates...
chronic rejection/transplant arteriosclerosis. In addition, human graft endothelial cells can directly activate allogeneic host T cells through direct presentation of foreign human leukocyte antigen (HLA) molecules and costimulators.

Severe CAV is positively correlated with persistent inflammation and a higher degree of HLA mismatch. In recent studies, it has been shown that activation and deposition of the complement degradation product C4d is correlated with the presence of circulating alloantibodies specific for donor HLA molecules, which subsequently leads to enhanced cardiovascular events. In line with this, de novo recipient-specific HLA-directed antibodies are associated with poor allograft outcome, and HLA-DR matching is a strong and independent predictor of outcome. In particular, the combination of antibodies and complement may play an important role in the development of CAV.

Independent of the specific antigen, host DCs frequently adhere to allograft endothelial cells, invade the tissue, capture foreign antigens, and present alloantigens to naive host T cells. Activated T cells invading the graft contribute to the ongoing smoldering subendothelial immune activation and endothelial dysfunction via cytokine activation. Interferon-γ, in part through induction of the inducible nitric oxide (NO) synthase, is a critical determinant linking early vascular dysfunction with later structural changes in graft arteriosclerosis.

In addition to the impact of adaptive immune responses in chronic allograft dysfunction, there is accumulating evidence that the innate immune response via toll-like receptor (TLR) signaling is involved in the immune recognition of allografts. For example, ischemia-reperfusion injury and the subsequent reactive oxygen species–mediated allograft injury lead to the release of innate immune ligands (eg, heat shock proteins [HSPs]), which may be detected by TLR-4 on mononuclear cells. Increased TLR-4 gene expression in circulating monocytes was associated with allograft coronary endothelial dysfunction. TLR ligation mediates maturation of DCs and may therefore contribute to excessive adaptive immune responses. Future studies are warranted to elucidate which ligands activate different innate immune pathways after HTx and whether these pathways participate in CAV or tolerance. However, different alloantigen-independent factors may indirectly enhance alloimmune responses by mediating endothelial dysfunction and vascular inflammation.

**Interaction Between Alloantigen-Independent Factors and Alloimmune Response**

According to the “immunologic view,” centered on the overwhelming importance of alloimmunity, CAV has long been referred to as “chronic rejection.” However, this term is misleading because it does not adequately take into account alloantigen-independent factors. Alternatively, the “response to injury” concept may provide a theoretical framework for understanding CAV as well. This concept dictates that vascular lesions are the result of cumulative endothelial (vessel) injury induced both by alloimmune responses and by nonspecific “alloimmune-independent” insults.

A variety of nonalloimmune insults, including brain death, organ preservation, surgical trauma, ischemia-reperfusion, cytomegalovirus (CMV) infection, hypertension, hyperlipidemia, and glucose intolerance, have been associated with immune activation, endothelial dysfunction, and CAV (Figure). As a consequence of endothelial activation, endothelial adhesion molecule and chemokine expression is upregulated, vascular growth factors and thrombogenic molecules are expressed, and immune cells invade the graft (Figure).

One good example of how increased graft immunogenicity induces a host alloimmune response even in the absence of non-self-antigens is brain death–induced immune activation. After brain death, a series of neural, hormonal, and molecular changes occur that result in cellular stress and an inflammatory response. The induced expression of (endothelium-derived) MHC molecules and costimulatory signals activates the different pathways of allorecognition. Nonspecific inflammation, derived from the ischemia-reperfusion injury or metabolic dysregulation, further promotes the shedding of intact, soluble HLA, which again might prime the indirect allorecognition pathway.

The classic cardiovascular risk factors, such as hypertension, hyperglycemia, and dyslipidemia, may enhance vascular inflammation by inducing endothelial dysfunction. Furthermore, LDL and oxidized LDL are able to upregulate levels of HLA-DR and the costimulatory molecule CD86 in immature DCs. Moreover, lipids may sequester activated DCs in the allograft, where they aggravate local immune responses. Thus, alloantigen-independent factors might indirectly or directly trigger alloimmune responses by inducing endothelial dysfunction, activating complement and coagulation pathways, recruiting inflammatory cells, promoting trafficking of DCs into the allograft, and regulating T-cell differentiation (Figure).

On the basis of the ISHLT registry, risk factors for CAV within 3 years are as follows: era of HTx, donor history of hypertension, donor gender as an interaction with donor age, recipient body mass index, and infection requiring intravenous drug therapy within 2 weeks of HTx. Kobashigawa et al detected that hypercholesterolemia and diabetes mellitus are risk factors for nonfatal major adverse cardiac events, whereas high serum creatinine levels and body mass index >33 kg/m² were associated with graft death. Ultimately, alloimmune-dependent and -independent injuries in the context of impaired/heightened repair mechanisms (reduced activity of endothelial cell progenitors, enhanced smooth muscle cell progenitors) control the progression of CAV (Figure).

**Endothelial Replacement in the Transplanted Heart**

Although endothelial cell replacement after transplantation has been suggested to have a role in graft adaptation (Medawar’s hypothesis), endothelial cell replacement by host-derived endothelial cells is actually a response to vascular damage. Hu et al provided evidence that endothelial cells of neointimal lesions in allografts are derived from circulating progenitor cells and that bone marrow–derived progenitors are responsible for angiogenesis of the allograft. Indeed, extracardiac progenitor cells are capable of repopu-
lating most major cell types in the human transplanted heart. Endothelial progenitors are significantly decreased in the circulation, and recipient endothelial cells are enriched in coronary arteries with CAV, which further supports the concept that donor-derived progenitor cells participate in cardiac transplant vascular biology.

Diagnosis

Early diagnosis of CAV in humans is limited by the lack of clinical symptoms for ischemia in the denervated allograft, by the insensitivity of coronary angiography, which frequently underestimates the extent and severity of the disease, by the involvement of small intramyocardial vessels, and by the occurrence of functional coronary alterations independent of morphological changes.

Invasive Detection of CAV

**Intravascular Ultrasound**

Intravascular ultrasound (IVUS) is the most sensitive tool for the diagnosis of CAV. IVUS allows a reproducible view of both actual lumen diameter and the appearance and thickness of the intima and media. Typically, serial IVUS allows assessment of the percentage change in atheroma volume, with considerable statistical power to detect small changes. Most large multicenter studies assessing new treatment regimens use IVUS to assess the drug’s efficacy in reducing the development of CAV.

The most rapid rate of progression of intimal thickening occurs during the first year, followed by slow but inexorable progression over time. The presence of moderate to severe intimal thickening by IVUS is predictive of the future development of angiographically apparent CAV. Rapidly progressive CAV, defined as an increase of greater than 0.5 mm in maximal intimal thickness within the first year after HTx, is associated with a significantly increased risk of all-cause death, myocardial infarction, and the subsequent development of angiographically severe CAV (Table 1). Therefore, the performance of IVUS at 1 and 12 months after HTx is an important approach to identify patients at high risk for future cardiovascular events, with subsequent consequences for therapeutic alterations.

**Coronary Angiography**

Coronary angiography is still the standard for the diagnosis of CAV in most transplant centers, and the angiographic detection of significant epicardial coronary stenoses conveys a poor prognosis. CAV is detectable by angiography in 30% to 50% of HTx survivors after 5 years.

The relative insensitivity of coronary angiography in the diagnosis of CAV, except for significant focal stenoses, has
been demonstrated by histopathological studies and by comparison with IVUS. In line with this, the positive predictive power of coronary angiography (compared with IVUS as the “gold standard”) is 44%. Using sophisticated statistical strategies, Sharples et al detected a high specificity (98%) and moderate sensitivity (79%) of coronary angiography to detect CAV. Ongoing studies are evaluating the safety of performing coronary angiography only in patients with a high score for probability of CAV.

**Detection of Coronary Vasomotor Alterations**

Activation of allograft endothelium predicts development of CAV and increased risk of graft failure. Specifically, the time of appearance and the proportion of endothelial activation during the first 3 months after HTx were associated with progression of CAV. Epicardial and microvascular endothelium-dependent and -independent vasomotor dysfunction are frequently observed after HTx. Coronary allograft endothelial dysfunction is associated with circulating endothelin levels, enhanced graft cytokine activation, and CMV infection, whereas statin treatment reduces the progression of epicardial and microvascular dysfunction.

Coronary endothelial dysfunction predicts the development of intimal thickening and predicts cardiovascular end points after HTx. These data implicate endothelial dysfunction in the development of clinically significant CAV.

Assessment of microvascular function has been shown to be of predictive value after HTx in some but not all studies. Predominant allograft microvascular dysfunction is detectable in ~15% of patients after HTx. Very recently, stenotic microvasculopathy (detected in biopsy samples) has been characterized as a prognostic factor for long-term survival after HTx. The ability to detect and distinguish changes in epicardial and microvascular function may aid in identifying modifiable factors that lead to CAV.

**Molecular Analysis of Myocardial Biopsy Specimens**

Recent studies have focused on the role of endothelial markers, matrix proteases, chemokines, and stress proteins in CAV. Endomyocardial biopsy specimens taken in the first 3 months after HTx reveal arteriolar/arterial endothelial changes (ie, expression of HLA-DR or intercellular adhesion molecule-1 and depletion of tissue plasminogen activator) that are strongly associated with the development of CAV and outcome. Anti-thrombin III staining was shown to be an independent predictor of CAV with high discriminative power. Analysis in sequential myocardial biopsy samples revealed a strong association between persistent elevation of the antiangiogenic glycoprotein thrombospondin-1 and the development of CAV. Moreover, CXCR3 chemokines are induced in cardiac allografts and are differentially associated with CAV. Using a global proteomic approach, De Souza et al detected that the expression of a specific diphosphorylated form of HSP-27 is lost in patients with CAV, thereby limiting the vascular stress response to alloimmune-dependent and -independent signals.

<table>
<thead>
<tr>
<th>Study and End Points</th>
<th>Timing of IVUS</th>
<th>Definition of Rapidly Progressive CAV</th>
<th>Follow-Up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kobashigawa et al17 (n=125)</td>
<td>4 to 6 wk and 12 mo after HTx</td>
<td>Change of MIT ≥0.5 mm in any matched site (increase from baseline to 1 y)</td>
<td>5 y</td>
<td>MIT &lt;0.5 mm MIT ≥0.5 mm P &lt;3.5 mm² MIA ≥3.5 mm² P &lt;20% ≥20% P</td>
</tr>
<tr>
<td>Death or graft loss</td>
<td></td>
<td></td>
<td></td>
<td>6% 21% 0.007 6% 28%</td>
</tr>
<tr>
<td>NFMACE or death/graft loss</td>
<td></td>
<td></td>
<td></td>
<td>17% 46% 0.003 19% 44%</td>
</tr>
<tr>
<td>Angiographic luminal irregularities</td>
<td></td>
<td></td>
<td></td>
<td>33% 65% 0.004 34% 71%</td>
</tr>
<tr>
<td>Tuzcu et al20 (n=143)</td>
<td>4 ±2 wk and 12 ±1 mo after HTx</td>
<td>Change of MIT ≥0.5 mm in any matched site (increase from baseline to 1 y)</td>
<td>5.9 y</td>
<td>11% 26% 0.03 NA NA NA NA NA</td>
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<tr>
<td>All-cause mortality (PEP)</td>
<td></td>
<td></td>
<td></td>
<td>16% 51% &lt;0.0001 NA NA NA NA NA</td>
</tr>
<tr>
<td>Mortality and nonfatal MI (SEP)</td>
<td></td>
<td></td>
<td></td>
<td>NA NA NA NA NA NA</td>
</tr>
</tbody>
</table>

MIT indicates maximal intimal thickness (first-year change in MIT from baseline); MIA, maximal intimal area (first-year change in MIA from baseline); PAS, percent area of stenosis (first-year change in PAS from baseline); NFMACE, nonfatal major adverse cardiac events; PEP, primary end point; NA, data not available; and SEP, secondary end point.
Noninvasive Screening
Noninvasive screening of allograft vasculopathy has been discussed in detail very recently by Kass et al.60

Dobutamine Stress Echocardiography
The sensitivity of dobutamine stress echocardiography compared with coronary angiography is ~80%.61,62 When intimal thickening by intravascular ultrasound is taken as the “gold standard,” dobutamine stress echocardiography shows specificities of up to 88%.63,64 Moreover, a predictive value of dobutamine stress echocardiography for development of future CAV and outcome has been described.64,65

Single-Photon Emission CT
Annual myocardial single-photon emission CT (SPECT) has a high negative predictive value and appears to be well suited to screening for significant CAV.66,67 The surveillance intensity of coronary angiography might be designed reasonably and safely on the basis of noninvasive monitoring of dobutamine 201TI SPECT testing67 or on the basis of the combination of resting echocardiography and quantitative stress 99mTc sestamibi SPECT.68 The latter strategy reserves coronary angiography for patients with resting wall-motion abnormalities or perfusion defects.

Multidetector CT
Romeo et al69 reported a sensitivity of 83% and a specificity of 95% for 16-slice multidetector CT (MDCT) compared with conventional coronary angiography and a negative predictive value of 95%. In agreement with this, MDCT with adaptive multisegment reconstruction has a sensitivity and specificity of 86% and 99%, respectively.70 In addition, 64-slice MDCT provides good to excellent image quality and has moderate to excellent test characteristics for the detection of CAV.41 Iyengar et al71 found a good overall agreement of conventional catheter-based angiography and 64-slice MDCT, with MDCT eventually being superior to identify nonobstructive vessel wall disease.

Concerns with respect to the routine use of MDCT after HTx include the high heart rate of patients even when treated with β-blockers and the obesity of many heart transplant recipients, which might compromise imaging quality; distal pruning of small coronary arteries due to diffuse concentric vessel involvement of CAV; contrast media as a risk for worsening renal insufficiency; and radiation, which is still higher than with cardiac catheterization. Importantly, significant wall or lumen changes detected in annual MDCT should be further investigated by angiography.

The encouraging results of dobutamine stress echocardiography, SPECT, and CT should be an incentive for more transplant centers to begin using parallel routine noninvasive imaging with one of the above-mentioned techniques. If the good results of noninvasive imaging are confirmed, routine care for the transplant patient may become less of a burden both for the patients and for society.72

Emerging New Noninvasive Technologies for Detecting CAV
Myocardial contrast echocardiography has demonstrated good accuracy (89%) for detecting the presence of CAV, but it failed to identify the extent of the disease.73 The measurement of a lower coronary flow rate with contrast-enhanced transthoracic echocardiography has been shown to be a reliable marker for CAV-related major cardiac events,52 but this may not be assessable in all patients.

Another new option for noninvasive detection of CAV might be 31P magnetic resonance chemical shift imaging, which detects the potential modifications of high-energy phosphates related to CAV.74 Further longitudinal outcome studies with larger patient cohorts must be performed before the widespread adoption of these new methods may be advocated.

Biomarkers and Gene Profiling
Elevated C-reactive protein concentrations are associated with progression of CAV,75,76 whereas persistently elevated levels of troponin I are associated with a significantly increased risk for subsequent development of CAV.77 The clinical use of brain natriuretic peptide (BNP) levels as a predictor of survival after HTx remains controversial.78,79 Mehra et al79 described elevated BNP concentrations as being associated with molecular patterns that point to ongoing active cardiac structural remodeling, vascular injury, and inflammation. BNP levels <250 pg/mL (N-terminal pro-BNP levels <800 pg/mL) predict significantly better survival after HTx.80,81 Besides CAV, elevated BNP levels may derive from acute rejection episodes or from diastolic and systolic dysfunction after HTx.

Cellular assays have been developed to test for various effector, cytotoxic, and regulatory functions of T cells.82 One goal of these cellular studies has been to determine whether posttransplant changes in the donor antigen-specific cellular response could predict good and poor graft outcome, thereby allowing for individualization of immunosuppression.82 Given the impact of antidonor cellular immunity, enzyme-linked immunospot (ELISPOT)–based antidonor T-cell immunity combined with flow cytometer–based antidonor alloantibody might be useful in detection of CAV.83

The AlloMap gene-expression test, initially validated for the detection of acute rejection episodes, has recently been evaluated for its association with CAV.84 In this retrospective analysis, CAV was associated with an increased AlloMap gene-expression score.84 Prospective studies will be required to determine the predictive capacity of the biomarker/gene-profiling approach.

Therapeutic Options
Rapidly progressive CAV within the first year after HTx strongly predicts all-cause mortality, myocardial infarction, and the subsequent development of angiographically severe CAV.35 Accordingly, prophylactic strategies must be implicated very early to induce significant improvements in long-term prognosis.

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors (Statins)
Different statins have been associated with reduced progression of CAV, and simvastatin improved 8-year survival in heart transplant recipients.85 The vasculoprotective effects of
statins are probably mediated by multiple immunogenic effects. Simvastatin over 12 months reduced cardiac cytokine activity (interleukin [IL]-6 and tumor necrosis factor-α), improved coronary endothelial function, and increased coronary lumen area.48 It is noteworthy that regular doses of statins may cause side effects such as myositis and rhabdomyolysis if used concomitantly with calcineurin inhibitors owing to drug-drug interactions.

**Vasodilators**

Calcium channel blockers appear to slow the progression of CAV86 and enhance coronary vasodilatation.87 ACE inhibitors partially improve allograft microvascular endothelial dysfunction, oxidative stress, and endothelin activation88 and have been associated with plaque regression89 and improved graft survival.29 Recently, a synergistic beneficial effect of a calcium channel blocker and an ACE inhibitor on the development of CAV independent of their antihypertensive efficacy has been described.90 There is still a need for larger prospective trials to confirm the impact of vasodilators for improving outcome after HTx.

**Endothelial Protection**

Strategies to improve the endothelial NO pathway resulted in early gene expression sufficient to reduce ischemia-reperfusion injury by inhibiting nuclear factor-kB activation, adhesion molecule expression (intercellular adhesion molecule-1, vascular cell adhesion molecule-1), and leukocyte infiltration.91 Recently, Lim et al92 have demonstrated that oral l-arginine (a precursor of NO synthase) therapy reverses endothelial dysfunction and attenuates high blood pressure after HTx. Excess endogenous NO from l-arginine supplementation may buffer increased vascular oxidant stress in the allograft.93 However, the effectiveness of L-arginine in the prevention of CAV needs to be confirmed in larger randomized, prospective trials.

Other drugs that might have the potential to restore allograft endothelial function include antioxidants such as vitamins C and E94 and flavonoids.95,96 Fang et al94 performed a prospective, randomized study in 40 HTx patients (0 to 2 years after HTx) who received vitamin C 500 mg plus vitamin E 400 IU, each twice daily (n = 19), or placebo (n = 21) for 1 year. The average intimal index measured by IVUS increased in the placebo group by 8% but did not change significantly in the vitamin group. Therefore, supplementation with the antioxidant vitamins C and E might retard the early progression of CAV.94 Riboflavin significantly reduced the oxidant production and inflammatory mediator production induced by ischemia-reperfusion injury, suppressed T-cell infiltration and donor-reactive alloantibody formation, and improved graft survival by decreasing the severity of CAV in animal models.96

**Infection and CAV**

CMV, the single most frequent infecting organism after HTx, may directly (eg, by dysregulation of the NO pathway25) or indirectly (eg, via cytokine activation) affect allograft endothelial function.47 One important indirect effect of CMV infection that results in acceleration of CAV is the increase in the host immune response to the allograft and the virus that results in recruitment of inflammatory cells and inflammatory effectors such as chemokines and cytokines, including interferon-γ, tumor necrosis factor-α, IL-4, IL-18, RANTES, monocyte chemotactic protein-1, macrophage inflammatory protein-1α, IL-8, and interferon-inducible protein-10.97 CMV also encodes CC and CXC chemokine homologs that recruit a multitude of host cellular infiltrates.97 CMV infection promotes mononuclear adhesion and transmigration within the allograft vasculature, induces a procoagulant state, and affects factors involved in angiogenesis, smooth muscle cell migration, and vessel remodeling.97 Ganciclovir treatment appears to reduce the progression of CAV,23 whereas lack of aggressive CMV prophylaxis is correlated with greater lumen loss.98 Importantly, the early control of subclinical CMV replication after transplantation by T-cell immunity may limit cardiac allograft rejection and vascular disease.99

**Immunosuppression**

**Calcineurin Inhibitors**

The high prevalence of CAV with cyclosporin A (CyA)-based immunosuppressive regimens implies that CyA is not effective in preventing CAV.100 Recently, several trials revealed that tacrolimus-based immunosuppression provides superior prevention of acute rejection compared with CyA-based therapy.101–103 Five-year survival and angiographic CAV were similar between microemulsion CyA- and tacrolimus–treated groups in a study by Kobashigwa et al.104 A more pronounced intimal proliferation in the group treated with CyA and mycophenolate mofetil (MMF) than in the tacrolimus-MMF–treated group was noticed during the first year in a study by Meiser et al.105 Moreover, microvascular endothelial function deteriorates more in CyA-treated patients than in tacrolimus-treated patients, which correlates with the enhanced endothelin-1 concentration and reduced vascular remodeling.105

**Mycophenolate Mofetil**

The combination of CyA and MMF was associated with a 35% reduction in 3-year mortality or graft loss106 compared with patients treated with CyA and azathioprine. No significant differences between treatments were observed in quantitative coronary angiographic measurements of CAV. However, the change in mean maximal intimal thickness tended to be less for the MMF group than for the azathioprine group (P = 0.056).106 Reanalysis revealed a significant decrease in the number of patients with first-year maximal intimal thickness ≥0.3 mm (a primary end point) in the MMF group.107 Moreover, the first-year decrease in mean lumen area and the decrease in vessel area in the azathioprine group was significantly greater than in the MMF group.107 These results were confirmed by Kaczmarek et al,108 who detected (using multivariate Cox regression analysis) that MMF decreased the incidence of CAV significantly (P = 0.041).

**Proliferation Signal Inhibitors**

Proliferation signal inhibitors inhibit T-cell and B-cell proliferation driven primarily by interleukins.109 Sirolimus has...
been shown to slow the progression of CAV in nonrandomized\textsuperscript{109} and randomized\textsuperscript{110} clinical trials. Mancini et al\textsuperscript{109} performed a study with 46 patients who were randomly assigned to treatment with sirolimus (n = 22) versus continued current immunosuppression (azathioprine or MMF; n = 24). Primary end points of that study were death, need for angioplasty or bypass surgery, myocardial infarction, and a >25% worsening of the catheterization score (graded with the use of a semiquantitative scale and repeated annually). Three patients in the sirolimus group reached primary end points compared with 14 in the control group (P < 0.001). A study by Keogh et al\textsuperscript{110} showed that intimal progression was absent for up to 2 years in de novo HTx patients who received sirolimus. Importantly, the studies on sirolimus were done in comparison to azathioprine, which is no longer used in many programs compared with MMF.

The use of everolimus from the time of HTx has shown to preserve the coronary artery lumen at 1 year.\textsuperscript{111} The latter study was the most robust in demonstrating that all first-year IVUS parameters were reduced in those patients treated with everolimus versus azathioprine. The incidence of vasculopathy was significantly lower in the 1.5-mg group (35.7%, P = 0.045) and the 3.0-mg group (30.4%, P = 0.01) than in the azathioprine group (52.8%).\textsuperscript{113} These initial findings were confirmed by a 2-year follow-up IVUS substudy.\textsuperscript{100,112} Interestingly, administration of everolimus was associated with a lower incidence of acute rejection and fewer episodes of CMV infection, 2 well-known risk factors for CAV.\textsuperscript{100,112} The 4-year follow-up of this study showed that patients who were treated with everolimus experienced significantly fewer CAV-related events or revascularization than those in the azathioprine group (7.9% versus 13.6%, P < 0.033).\textsuperscript{100,112}

### Coronary Revascularization

The impact of coronary revascularization in patients with severe CAV has been discussed in detail elsewhere.\textsuperscript{100} Revascularization procedures for CAV are only palliative, with no long-term survival benefit. In contrast to native atherosclerosis, stented and reference-vessel nonstented lesions in CAV appear to progress indefinitely with time,\textsuperscript{5,113} which reflects the more aggressive and dynamic nature of CAV.

#### Percutaneous Interventions

The restenosis rate after percutaneous coronary intervention in patients with CAV is high\textsuperscript{4,5,114–118} (Table 2). Stent placement reduced early and midterm restenosis compared with percutaneous coronary intervention; however, late restenosis was comparable to the late restenosis of percutaneous coronary intervention\textsuperscript{5} (70%; Table 2). Multivariate predictors of freedom from restenosis were the use of stents and a higher antiproliferative immunosuppressant dose.\textsuperscript{113} Especially in the setting of 3-vessel disease at first intervention, the 2-year freedom for death or graft loss is very low (27% compared with 74% and 75% for 1- and 2-vessel disease, respectively).\textsuperscript{113} Most recently, drug-eluting stents have been shown to have a tendency to lower restenosis rates compared with bare-metal stents (15% versus 31%)\textsuperscript{119} at 40 months’ follow-up (Table 2). It might be appropriate to perform stenting only in patients with discrete lesions who have an abnormal stress test or symptoms suggestive of myocardial ischemia.

#### Bypass Grafting

Bypass grafting is associated with a high periprocedural mortality of up to 40% and with limited midterm success\textsuperscript{115,120,121} (Table 3). Therefore, the indication of surgical revascularization should be evaluated very carefully.

#### Retransplantation

Retransplantation is the only definitive treatment for CAV; however, survival is lower than after primary HTx\textsuperscript{122,123} (Table 3). The optimal patient for retransplantation (with a comparable survival to primary HTx) is young and has an intertransplant interval >2 years.\textsuperscript{122} In practice, retransplan-

### Table 2. Long-Term Results of Nonsurgical Revascularization Procedures After HTx

<table>
<thead>
<tr>
<th>Nonsurgical Revascularization</th>
<th>n</th>
<th>6 mo</th>
<th>12 mo</th>
<th>5 y</th>
<th>Death or Graft Loss (Time of Follow-Up)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioplasty</td>
<td>33</td>
<td>67</td>
<td>53</td>
<td>68</td>
<td>NA</td>
<td>Simpson et al\textsuperscript{6}</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>25</td>
<td>35</td>
<td>43</td>
<td>39% (19 mo)</td>
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<tr>
<td></td>
<td>66</td>
<td>25</td>
<td>35</td>
<td>43</td>
<td>56% (60 mo)</td>
<td>Benza et al\textsuperscript{13}</td>
</tr>
<tr>
<td>Angioplasty × stenting</td>
<td>62</td>
<td>25</td>
<td>35</td>
<td>43 (4 y)</td>
<td>17% (4 mo)</td>
<td>Schnetzler et al\textsuperscript{116}</td>
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<tr>
<td></td>
<td>29</td>
<td>25</td>
<td>35</td>
<td>43</td>
<td>48% (52 mo)</td>
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<td></td>
<td>25</td>
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<td>35</td>
<td>43</td>
<td>54% (24 mo)</td>
<td>Fernandez et al\textsuperscript{18}</td>
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<tr>
<td>Stenting (BMS)</td>
<td>13</td>
<td>38</td>
<td>36 (33 mo)</td>
<td>43</td>
<td>54% (24 mo)</td>
<td>Jonas et al\textsuperscript{4}</td>
</tr>
<tr>
<td>DES vs BMS</td>
<td>15</td>
<td>38</td>
<td>36 (33 mo)</td>
<td>43</td>
<td>54% (24 mo)</td>
<td>Simpson et al\textsuperscript{6}</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>38</td>
<td>36 (33 mo)</td>
<td>43</td>
<td>54% (24 mo)</td>
<td>Redonnet et al\textsuperscript{14}</td>
</tr>
</tbody>
</table>

NA indicates not available; BMS, bare-metal stent; and DES, drug-eluting stent.

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tation is a real solution for only highly selected patients with CAV.

**Emerging New Strategies for the Prevention/Treatment of CAV**

Three different strategies for CAV are emerging: (1) inhibition of growth factors, cytokines, and circulating antibodies; (2) cell therapy; and (3) tolerance induction. New therapeutic strategies should be directed against matrix formation. Possible targets for this therapeutic approach may be chemokines, cytokines produced by T cells, the infiltration of these T cells in the intima, or stimulation of anti-inflammatory pathways via IL-10 induction. Sensitive methods for detecting circulating antibodies and improved therapeutic strategies (e.g., photophoresis) against these antibodies are currently under investigation.

Strategies targeted to homing, differentiation, and proliferation of hematopoietic and vascular progenitors (e.g., by modulating intragraft angiogenesis and inflammation) may diminish the progression of CAV. Administration of autologous IL-10–engineered hematopoietic stem cells before HTx prolonged allograft survival. Induction of hematopoietic chimerism is associated with immune tolerance and lack of CAV. Chimerism found on the graft endothelia may have a protective effect against CAV. However, although cell therapy research is promising, there is still a need to understand the mechanisms and long-term consequences of endothelial chimerism, as well as to characterize the impact of differentiated stem cells for vascular protection.

Pharmacological induction of tolerance by the targeting of local or circulating DCs (e.g., silencing nuclear factor-kB protein RelB), induction of alloantigen-presenting plasmacytoid DCs, or by modulation of T-cell costimulation pathways is under investigation. Finally, a number of regulatory T cells, including CD4+CD25+ T cells, natural killer T cells, and anergic CD4+ T cells, play an important role in maintaining transplantation tolerance; however, enthusiasm for tolerance induction has been tempered by the realization that it is more difficult to achieve clinically than predicted by experimental models. As individual responses to an allograft change over time, we need to develop assays to monitor the recipient immune response, as well as individualized methods for therapeutic immune modulation.

**Disclosures**

None.

**References**


Cardiac Allograft Vasculopathy: Recent Developments
Daniel Schmauss and Michael Weis

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