Allograft Vasculopathy
Diagnosing the Nemesis of Heart Transplantation
James B. Young, MD

Remarkable progress has been made with respect to cardiac transplantation over the past 3 decades.1 Few dramas are as compelling as a successful heart transplant in a patient who otherwise would die of cardiogenic shock. Improved outcomes relate to our greater (but yet incomplete) insight into the pathophysiology of allograft rejection. Still, the transplanted heart is not normal, and it is subjected to chronic immunologic assault. The long-term function of cardiac allografts is related primarily to the integrity of the organ at the time of transplantation and to rejection. More general systemic pathological processes, such as hypertension, lipid perturbation, diabetes, and infection, are also likely to take their toll.2 Although with contemporary immunomodulating strategies, cardiac allografts may perform satisfactorily for ≥20 years, a more reasonable expectation of the half-life of these organs is between 7 and 10 years. It is disturbing to note that the long-term survival of cardiac allografts has changed little over the past 2 decades. Obviously, there is a complicated interplay between immunologic and nonimmunologic factors that determine the long-term function of the transplanted heart, but so-called chronic rejection dictates outcome in large part. This process (at times rapid) is a diffuse, obliteratorative atherosclerosis, also referred to as allograft arteriopathy or vasculopathy (veins rarely can be involved as well). The pathophysiology of chronic cardiac allograft rejection is probably analogous to that of chronic nephrosclerosis of transplanted kidneys, biliary atresia of liver allografts, and bronchiolitis obliterans after lung transplantation. Interestingly, we still rather crudely separate rejection episodes into hyperacute, acute, and chronic classifications. Although these different categories probably have, at root, common intertwining immunologic themes, we believe that hyperacute rejection is mediated by a rapid humoral immune response, with complement activation noted immediately after organ reperfusion. Myocyte dysfunction occurs immediately in this setting, and allografts become nonfunctional over the course of minutes or, at the most, hours. Acute cardiac allograft rejection generally refers to T-cell lymphocyte–mediated processes manifested by cellular cardiac muscle infiltration over hours or days. Resultant ventricular dysfunction can be rapid and profound, particularly when effective immunosuppressive therapies have not been prescribed; but more commonly, acute rejection is slower to evolve and leads to cardiac dysfunction over a longer period of time. Acute cell-mediated rejection can often be treated effectively, with subsequent satisfactory ventricular performance.

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Chronic rejection, with its endothelial dysfunction and concentric, diffuse narrowing of the coronary arteries, occurs later after heart transplantation and is problematic to diagnose and treat. Indeed, this diffuse atherosclerotic process may be the leading cause of death during long-term follow-up of heart transplant recipients. It is a complicated process and needs to be studied in light of the fact that older donor hearts are being used more frequently, with the risk that preexisting atherosclerotic lesions will be transported as passive passengers during the transplant surgery. Although this passenger atherosclerosis can have important consequences and sequelae, the pathophysiology, propensities to progress, and response to therapy are different from those of allograft vasculopathy. Nonetheless, the chronic immunologic assault directed at coronary endothelium, vascular wall more generally, and myocytes, in conjunction with nonimmunologic issues, such as lipid perturbation, hypertension, viral infection, and possibly donor genetic predisposition to the development of atherosclerosis, leads to coronary flow perturbation, particularly when preexisting atherosclerosis is present.3–7

Interestingly, pathological processes associated with transplantation of arterial conduits and vascularized organs have been observed for many decades. In a landmark series of experiments on arterial vessel allograft preservation, Alexis Carrel,8 in 1910, reported that canine carotid artery allografts in place for 90 days demonstrated an abnormally thickened intima, degenerated muscle fibers of the media, and muscle cells invading the intima more often than not. Carrel also noted that in 1 transplant experiment, the carotid artery was yellow only over the segment that had been transplanted. Carrel speculated that if insight into this vessel transplant–related process could be gained, a more general understanding of the pathogenesis of atherosclerosis would accrue. Atherosclerotic disease generally was a great enigma at that time, with the term “atherosclerosis” just coming into more general use.9 The significance of cardiac allograft vasculopathy was first emphasized by the Stanford University team when they reported coronary intimal proliferation and obliteratorative changes in the epicardial coronary arteries of long-

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term canine and human heart transplant recipients. Indeed, allograft vascular disease in humans after heart transplantation was first reported in a short-term transplant survivor from Christiania Barnard’s Capetown experience. Thompson\(^{11}\) detailed the anatomic findings of an autopsy of the longest surviving heart transplant recipient at the time, noting that the coronary arteries had an unusual atheromatous appearance, with symmetrical, diffuse involvement of all vessels and in particular, small, more distal intramyocardial vessels.

As our awareness of this problem has grown, we have focused largely on diagnosing and staging the severity of allograft arteriopathy.\(^{12,13}\) Most patients undergo routine coronary angiographic study (often with intravascular ultrasound, usually referred to as IVUS) shortly after transplantation to determine baseline atherosclerotic burden, with subsequent annual evaluations done to give clinicians objective information regarding progression of the difficulty. This practice is costly and repeatedly exposes patients to cardiac catheterization risk.

Recently, the largest experience with post–heart transplantation coronary angiography was reported.\(^{14}\) As part of the ongoing Cardiac Transplant Research Database (CTRD) project, a multi-institutional registry study was carried out to analyze incidence, implications, and preoperative donor and recipient risk factors for the development of allograft arteriopathy. Costanzo and colleagues\(^{14}\) evaluated 5963 postoperative angiograms performed in 2609 heart transplant recipients from 39 institutions who underwent surgery between January 1990 and December 1994. Angiographic diagnosis of allograft arteriopathy was classified as mild, moderate, or severe on the basis of degree of left main involvement, primary-vessel stenosis, or branch-vessel stenosis. After 5 years of follow-up, coronary artery disease was present in 42% of the patients (mild in 27%, moderate in 8%, and severe in 7%). The frequency of the difficulty was stunning in view of the fact that coronary angiograms are insensitive in this setting and disease incidence is therefore underestimated. Coronary artery disease–related events (death or retransplantation) had an actuarial incidence of 7% at 5 years. In this analysis, recipient risk factors for vasculopathy included the presence of diabetes, peripheral vascular disease, dyslipidemia, and elevated creatinine levels as well as native heart disease. Donor-recipient mismatch variables included in the multivariable analysis were sex, race, age, body surface area, blood type, and number of histocompatibility locus mismatches. Donor age, medical history, and cause of death were also taken into account. By multivariable logistic analysis, risk factors for donor coronary artery disease included older donor age and donor hypertension. By multivariable analysis in the hazard-function domain, risk factors identified for the earlier onset of allograft coronary disease included older donor age, donor male sex, donor hypertension, recipient male sex, and recipient black race. The actuarial incidence of severe coronary artery disease was 9% at 5 years. This database suggested that angiographic coronary disease is very common after heart transplantation and that its presence is highly predictive of subsequent coronary disease–related events. It is interesting that lipid perturbation and immunologic status did not, in this study, correlate with presence of allograft arteriopathy by coronary angiography. Other observations have demonstrated that elevated triglycerides and lipid abnormalities in general, particularly when associated with histocompatibility mismatch and a significant number of rejection episodes, relate to the development of allograft arteriopathy.

In the past, noninvasive studies in heart transplant recipients to detect allograft arteriopathy have been hampered by diagnostic insensitivity and lack of specificity, particularly when used in routine surveillance screening fashion.\(^{12}\) Fang et al\(^{12}\) reviewed programs of yearly noninvasive evaluation of transplant recipients (gated radionuclide wall motion exercise studies, 24-hour ambulatory arrhythmia monitoring, resting 2D echocardiograms with Doppler imaging, and routine exercise ECGs) and compared angiographic evidence of allograft arteriopathy with routine noninvasive studies. In these reports, 26% of transplant recipients developed allograft arteriopathy over a 5-year period, but no noninvasive test had specificity >75%. Although the studies generally demonstrated negative predictive values of >75%, sensitivity and positive predictive value ranged only from 21% to 53% for the individual tests. Of course, the sensitivity and specificity of any noninvasive diagnostic test done in a population at risk for coronary artery disease depend on the incidence of disease and its functional significance. Most noninvasive diagnostic tests rely on the induction of ischemia (with stress of one sort or another) manifested by relative regional wall-motion abnormalities or asymmetrical myocardial radionuclide uptake. Lack of sensitivity of echocardiographic and radionuclide studies after transplantation have therefore been thought to be due to the diffuse nature of allograft arteriopathy and its presence in small intramyocardial vessels. This characteristic might produce abnormalities more generally, and when studied by techniques that use regional myocardial motion or scintigraphic comparisons, may fail to suggest the presence of significant findings.

Reported in this issue of Circulation is a large and thorough study from the University of Munich, Germany, that gives more insight into the diagnostic and prognostic values of serial dobutamine stress echocardiography after heart transplantation.\(^{15}\) The report amplifies this group’s previous experience.\(^{16–19}\) Spes and associates prospectively evaluated heart transplant recipients with serial dobutamine stress echocardiography and compared their findings with results from coronary angiography and IVUS in 109 heart transplant recipients followed up for up to 5 years. Although resting 2D echocardiograms were often suggestive for allograft arteriopathy (defined by IVUS and angiography) because of wall motion abnormalities, the overall sensitivity was only 57% (but specificity was 88%). Dobutamine stress echocardiography increased the sensitivity to 72% without changing specificity. Possibly more important is the fact that cardiac events occurred in only 1.9% of patients who had a normal stress test, compared with 6.3% of patients with normal resting studies. Increasing the abnormalities noted by use of dobutamine stress echocardiography identified a group with higher risk of subsequent adverse events compared with patients without such findings (risk ratio increased to 7.26).
The study by Spes et al should be put into perspective with previous reports using dobutamine stress echocardiography as a means to diagnose occult allograft arteriopathy. As recently summarized by Fang et al, studies by Derumeaux et al, Herrengods et al, and Aksah et al previously suggested that the sensitivity for detecting significant allograft arteriopathy by dobutamine stress echocardiography can be as high as 80% or 90%, with up to 100% specificity. Furthermore, dobutamine echocardiography may be better than radionuclide scintigraphy, even when coronary artery disease definition is liberalized to include angiographic stenosis <50%, diffuse distal tapering, or intimal thickening by IVUS.

Although Spes et al demonstrate that dobutamine stress echocardiography is important with respect to prognostication after transplantation, I do not believe that it should replace routine serial coronary artery evaluation by IVUS, because early vasculopathy not associated with myocardial flow abnormalities will probably be missed. Identification of chronic cardiac allograft rejection at the earliest presentation is critical if long-term prognosis is to be improved. Although the best treatment of allograft arteriopathy is not known, there is some justification for intensification of disparate treatment strategies when it is diagnosed. Although we have no firm guidance, it has been suggested that diltiazem therapy, administration of pravastatin, and intensification of immunosuppression can attenuate adverse outcome and limit progression of allograft arteriopathy. Also, the new immunosuppressive agent mycophenolate mofetil has been suggested to have antiproliferative effects that may be important in limiting allograft vasculopathy. If clinicians are of the opinion that development or progression of allograft arteriopathy mandates a change in medication, knowing that vasculopathy is present is vastly more important than determining whether perfusion abnormalities that cause wall motion impairment have ensued. By the time wall motion abnormalities secondary to coronary flow perturbation can be noted, it is probably too late to get maximum benefit from “preventive” therapeutics. There is no doubt that IVUS is the best tool for identification of these problems. Nonetheless, as Spes et al demonstrate, serial dobutamine stress echocardiographic evaluation after heart transplantation is valuable. Even more important, though, is the fact that more work must focus on strategies to prevent allograft vasculopathy and, when present, to better define effective treatment.

References

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