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## EDITORIAL COMMENT

# Cardiac Allograft Vasculopathy in Heart Transplant Patients

## Pathologic and Clinical Aspects for Angioplasty/Stenting*

Jon A. Kobashigawa, MD, FACC
*Los Angeles, California*

The paper by Jonas et al. (1) in this issue of the *Journal* illustrates the inflammatory nature of cardiac allograft vasculopathy (CAV) in heart transplant recipients. The authors report that heart transplant patients who undergo coronary artery angioplasty/stent and subsequently develop in-stent restenosis correspondingly develop worsening disease in other areas of the coronary artery tree. Therefore, in heart transplant patients, in-stent restenosis appears to be representative of a heightened immune response. In accordance with this finding, heart transplant patients with in-stent restenosis, compared to those patients without restenosis, have increased subsequent mortality.

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Cardiac allograft vasculopathy is one of the major factors limiting long-term survival in recipients of a heart transplant. The disease has many features similar to non-transplant atherosclerosis, but there are important differences in both pathology and distribution of the disease. Cardiac allograft vasculopathy is thought to result from an initial injury to the allograft endothelium ensuing in a chronic inflammatory state. Principal determinants contributing to this endothelial cell inflammation include preservation injury, alloimmune response (cellular and humoral rejection), and possibly chronic cytomegalovirus infection, in addition to the conventional risk factors for atherosclerosis, such as hyperlipidemia. The general distinguishing feature of CAV compared with conventional atherosclerosis is its more diffuse nature, with frequent involvement of large- and medium-sized vessels as well as the microvasculature. With CAV, lesions also tend to be concentric, limiting detection by conventional angiography. For the most part, lesions tend to be lipid-poor, and calcification seems to occur relatively late. The disease not only affects the intima but also the media and adventitia, frequently undergoing fibrous infiltration. As a consequence, compensatory remodeling of the artery is inhibited (the Glagov phenomenon), and the artery may even undergo constriction (2). Intravascular thrombus is also a frequent finding at autopsy, which may explain why this disease is associated with sudden death. Clinical presentation of CAV is also atypical because of surgical denervation. Diagnosis and monitoring of disease depends mostly on invasive techniques. One of the more sensitive means to detect CAV is the use of intravascular ultrasound (IVUS), which assesses intimal thickening and is performed at the time of coronary angiography.

The finding by Jonas et al. (1) that more inflammation in the donor coronary arteries is associated with poor outcome in heart transplant patients is exemplified in IVUS studies. A recent multicenter study of first-year IVUS data in heart transplant patients validated the use of first-year intimal thickening as a surrogate marker for poor outcome after heart transplantation (3). Development of intimal thickening >0.5 mm in the first year after transplant conferred poor survival, more non-fatal major adverse cardiac events, and more angiographic CAV in 5-year follow-up. The rapid progression in first-year intimal thickening as detected by IVUS appears to represent the cumulative effects of adverse events that cause damage and inflammation to the coronary artery endothelial cells, which ultimately lead to poor clinical outcome.

In order to effectively treat CAV, as suggested by Jonas et al. (1), a global approach to reducing inflammation in all areas of the donor coronary artery tree is essential. This will involve newer immunosuppressive agents that can alter the immune response in the heart transplant recipient. Many of the heart transplant multicenter, randomized trials testing these newer immunosuppressive agents have utilized first-year IVUS intimal thickening as a study end point to predict the development of CAV and long-term outcomes. Recently, newer antiproliferative agents, including sirolimus (4), everolimus (5), and mycophenolate mofetil (6), have been demonstrated to significantly reduce first-year rejection and IVUS intimal thickening in large, multicenter, randomized trials involving heart transplant patients. Longer follow-up of these study populations will be needed to confirm the actual efficacy of these antiproliferative agents in reducing angiographic CAV.

Hyperlipidemia is a well-established risk factor for non-transplant atherosclerosis. Both clinical and experimental observations suggest that it may be important in the development of CAV (7). Interestingly, a randomized trial reported that treatment initiated within 2 weeks of transplantation with an inhibitor of the rate-limiting enzyme in the cholesterol biosynthetic pathway, hydroxymethylglutryl coenzyme A (HMG Co-A) reductase, is associated not only with decreased development of coronary artery intimal thickening, but also with decreased clinically severe rejection, decreased development of angiographic CAV, and

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From the Division of Cardiology, Department of Medicine, The David Geffen School of Medicine at the University of California, Los Angeles, California. Dr. Kobashigawa has received research grants for clinical trials from Novartis, Roche, and Astellas Pharmaceuticals, has served on advisory boards for Novartis, Roche, and Astellas, and has received honoraria for lectures from these companies.

improved survival (8). These agents likely have an anti-inflammatory and/or immunosuppressive effect in addition to their lipid-lowering activity (9). Moreover, HMG Co-A reductase inhibitors have been demonstrated to reduce high-sensitivity C-reactive protein, a known marker of inflammation that has been associated with both non-transplant and transplant atherosclerosis (10). As hyperlipidemia is so common after transplantation, these findings suggest that all cardiac transplant recipients should receive HMG Co-A reductase inhibitors where tolerated.

It is clear that angioplasty/stenting can be performed with a high success rate in heart transplant patients. However, from the results of the Jonas et al. (1) study, the long-term benefit of performing angioplasty/stenting for all CAV lesions amenable to this procedure is not clear. Does this procedure prolong survival or decrease non-fatal major adverse cardiac events? Are there subgroups of specific CAV lesions, such as left main or proximal left anterior descending artery stenoses, where benefit is greater? If in-stent restenosis is a marker for a heightened inflammatory state of the donor coronary artery tree, is it worth redoing this procedure, especially since worsening CAV occurs in other areas and subsequent mortality is high? It might be time to perform a randomized trial of angioplasty/stenting in heart transplant patients with significant CAV.

Given the relatively poor prognosis of CAV, prevention remains an important strategy. Greater understanding of the pathology of CAV will offer more promising immunosuppressive regimens and improved methods of organ preservation in the near future. It is hoped that this will have a significant impact on the development of CAV in the heart transplant population. In the meantime, those with established disease have conventional revascularization techniques available to them for palliation, and retransplantation may be a consideration for a few.

**Reprint requests and correspondence:** Dr. Jon A. Kobashigawa, 100 UCLA Medical Plaza, #630, Los Angeles, California 90095. E-mail: jonk@mednet.ucla.edu.

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