EDITORIAL COMMENT

Virtual Histology Intravascular Ultrasound

Assessing the Risk of Cardiac Allograft Vasculopathy*

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Heart transplantation offers a means to improve longevity and quality of life in patients with end stage heart failure. Although survival following cardiac transplantation improved significantly following the advent of calcineurin inhibitors, the development of vascular disease within the arterial system of the grafted heart, known as cardiac allograft vasculopathy, is a major cause of morbidity and mortality (1,2). Graft vasculopathy, defined by an angiographically determined stenosis >50% in an epicardial coronary artery, is present in 40% to 50% of patients by 5 years post-transplant and is the leading cause of death in recipients who survive past the first year (3,4). Unfortunately, ischemic symptoms in cardiac transplant patients are often nonspecific, and a common presentation of cardiac allograft vasculopathy is that of sudden cardiac death. Indeed, far too often, transplant cardiologists receive the most dreaded of phone calls from a bereaved spouse, child, or parent reporting the sudden death of a transplant recipient. Any modality that can increase our awareness of patients at high risk for developing progressive graft vasculopathy would be a welcome addition to the available tools for monitoring patients after cardiac transplant.

In this issue of the Journal, Raichlin et al. (5) of the Mayo Clinic explore the utility of virtual histology intravascular ultrasound (VH-IVUS) to carefully examine coronary lesion morphology of transplant recipients and identify which type of coronary lesions may predict progression of allograft vascular disease. They examined the frequency and significance of coronary plaques containing both necrotic core and calcification from VH-IVUS exams performed a mean of 3.6 years following transplant in 86 recipients. A subgroup of patients (n = 38) had a follow-up study after 12 months to explore the rate of progression of these necrotic core/dense calcium containing lesions. The investigators defined “noninflammatory” plaque as being composed of <30% by volume of the combination of both necrotic core and calcium and “inflammatory” plaque as that composed of ≥30% necrotic core and calcium. They first compared these data to the total rejection score defined as the average rejection score of biopsies over 6 months using the revised histologic grading scheme. They observed more inflammatory plaques in patients with a total rejection score ≥0.3 than in those with a total rejection score <0.3, supporting the idea that early rejection may contribute to inflammatory plaque development. In patients having inflammatory plaque identified in the initial study, there was a significant increase in plaque volume over 1 year compared with those without inflammatory plaque at the initial VH-IVUS examination. The investigators concluded that this coronary imaging modality may hold promise in identifying transplant patients who are at high risk of developing progressive graft vasculopathy.

This retrospective analysis of compiled VH-IVUS (see review in Sangiorgi et al. [6]) as a tool to predict progression of graft vascular disease has inherent weaknesses that the investigators emphasize in the discussion. The rather arbitrary cutoff of 30% for plaque content of combined necrotic core and calcium to define an inflammatory plaque is based on prior autopsy data from nontransplanted hearts with coronary artery disease and not from coronaries of transplanted hearts. Given the differences in pathophysiology between allograft vasculopathy and atherosclerosis, it remains unclear that this VH-IVUS morphology represents inflammation. A dataset obtained in transplanted hearts at autopsy would be required to explore this further. Inherent in this retrospective analysis is the significant variability with which the timing of VH-IVUS was performed following transplantation. Nonetheless, data obtained by VH-IVUS presented by Raichlin et al. (5) represent a novel and potentially important approach for the early identification of patients at risk of developing graft vasculopathy. Nearly all patients after cardiac transplant are treated with 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, antihypertensive medications, and aggressive diabetes control to combat treatable coronary artery disease risk factors. More recently, the addition of rapamycin to the immunosuppressive regimen of transplant recipients diagnosed with graft vasculopathy has been shown to stabilize the progression of vascular disease in many patients (7,8). This, in appropriately selected transplant recipients, the identification of high-risk coronary morphology might be an impetus to use earlier, more potent antiproliferative

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therapy such as rapamycin. Ultimately, earlier intervention may lead to improved survival in allograft vasculopathy patients.

How this new imaging technology compares with stand-alone IVUS is not known. A multicenter consortium (9) performed IVUS at baseline in the early period following heart transplantation (4 to 6 weeks) with a repeat IVUS exam 1 year later. Kobashigawa et al. (9) reported that patients whose maximal intimal thickness increased >0.5 mm over the first 12 months had a markedly higher mortality and graft loss than those whose maximal intimal thickness increased <0.5 mm. Moreover, patients with greater maximal intimal thickness increases had double the incidence of angiographically determined graft vasculopathy at 5 years (65% vs. 32%).

Before any striking conclusions can be drawn from the data presented in this novel study by Raichlin et al. (5), more clinical data must be collected to help strengthen (or refute) these preliminary observations. The most rapid means of gathering such data would be in the formation of a multicenter consortium to collect data prospectively and compare the predictive utility and prognostic value of intravascular ultrasound versus VH-IVUS from consistently timed, consecutive examinations following cardiac transplantation. These data may contribute importantly to our understanding of the pathophysiology underlying this progressive vasculopathy in cardiac transplant recipients. Moreover, with these data in hand, it may then be feasible to draw more definitive conclusions about the ability of this new technology to predict patients at risk of developing cardiac allograft vasculopathy.

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