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EDITORIAL COMMENT

Early Detection of Cardiac Allograft Vasculopathy and Long-Term Risk After Heart Transplantation*

Ahmed Tawakol, MD,[a] Jean-Claude Tardif, MD[b]

Since the first successful transplantation of a human heart in 1967, scientific advances have transformed cardiac transplantation such that it is now an important therapeutic option for many individuals with severely symptomatic heart failure despite maximal medical therapy. Although survival in the early days of heart transplantation was poor because of high rates of early acute rejection, contemporary immunosuppressive therapies now allow individuals to live decades after the initial surgery. However, with the major improvement of medical management—including the success of immunosuppressive techniques and the resultant higher survival—has come new complications, including a high rate of cardiac allograft vasculopathy (CAV). In fact, CAV is the leading cause of late morbidity after heart transplantation (1) and, unfortunately, often requires repeat transplantation, leading to intense interest in developing better methods to identify, treat, and perhaps even prevent CAV during its earliest phases. Detection of CAV in a relatively early stage has long been an important goal, with hopes that it would result in more timely treatment and improved outcomes.

Some of the biological processes that lead to CAV are similar to those promoting native coronary atherosclerosis, whereas others are distinctly different. The presence of atherosclerotic risk factors, such as hypertension, dyslipidemia, diabetes, obesity, and smoking associate with an increased risk of CAV. Yet, perhaps unsurprisingly, immunobiological events appear to play the predominant role in the initiation and progression of CAV, a largely alloimmune process that affects the donor but not recipient arteries. The histopathological hallmark of CAV is diffuse, progressive concentric intimal smooth muscle hyperplasia involving much of the major epicardial vessels, along with abnormalities of the cardiac microvasculature. Notably, CAV is marked by an abundance of inflammatory cells in association with the donor vessels.

The standard approach to imaging CAV has long been invasive coronary angiography, which can detect several characteristic anatomic abnormalities, including gradual, distal "pruning" and lumen stenoses of the major epicardial arteries and obliteration of the small branching vessels. These anatomical luminal findings characterize very late-stage CAV. In contrast, intravascular ultrasonography (IVUS) imaging of the coronary arterial wall has proven to be much more informative and sensitive than the 2-dimensional silhouette of the coronary lumen depicted by angiography. More than 20 years ago, IVUS taught us that some of the atherosclerotic disease detected early after transplantation actually represents angiographically silent plaques transferred from the donor (2). Diffuse concentric intimal thickening after heart transplantation is also readily detected by IVUS, but not by angiography if this

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From the [a]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; and the [b]Montreal Heart Institute, Université de Montréal, Montreal, Canada. Dr. Tawakol has received research funding from Actelion, Genentech, and Takeda; and modest consulting fees from Actelion, Amgen, and Takeda; none of those activities relate to the subject of this paper. Dr. Tardif has received research support from Amarin, AstraZeneca, Cymabay, DalCor, MedImmune, Merck, Pfizer, Roche, Sanofi, and Servier; has received honoraria (mostly to his institution) from DalCor, Pfizer, Sanofi, and Servier; and holds the Canada Research Chair (tier 1) in translational and personalized medicine and the University of Montreal Pfizer endowed research chair in atherosclerosis.

extraluminal disease is relatively symmetric. Even more sensitive IVUS parameters that could help to detect CAV earlier, identify patients at risk of related serious clinical manifestations, and determine the vascular consequences of rejection episodes, would be highly desirable.

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In this issue of the *Journal*, Okada et al. (3) report the findings of a retrospective study that evaluated the association between coronary attenuated signal plaques (ASP) and both long-term mortality and the need for retransplantation. The authors performed serial coronary IVUS imaging in 105 heart transplant recipients and assessed ASP within the proximal 50 mm of the left anterior descending artery early (at approximately 6 weeks) and 1 year after transplantation. All-cause death and retransplantation were evaluated, with a median follow-up of 4.6 years. ASP progressed from baseline to 1 year post-transplantation in approximately 10% of patients. Patients with ASP progression at 1 year had a nearly 3-fold increased incidence of acute cellular rejection within the first 12 months post-surgery. Indeed, the occurrence of acute cellular rejection during the first year after transplantation was independently associated with ASP progression at 1 year. Patients with ASP progression also had a significantly increased prevalence of coronary atherosclerosis transmitted from the donor. Furthermore, in a multivariate analysis, ASP progression at 1 year was associated with a substantially elevated risk (hazard ratio: 5.72) of long-term mortality or retransplantation. In contrast, IVUS-determined coronary intima-media thickness did not predict long-term mortality risk.

The study's finding of an association between acute cellular rejection and ASP progression during the first year further implicates immune-related inflammation as a key culprit underlying CAV progression. Additionally, ASP emerged from this study as a potentially important measure that may help identify patients who are at the highest risk of developing cardiovascular complications after heart transplantation. Because these results are on the basis of a retrospective single-center study of 105 patients in whom approximately 10% ($n = 11$) had ASP progression, larger prospective studies are warranted. Additional parameters (like low-density lipoprotein cholesterol, which was not measured in the current study) could also be taken into account in future multicenter studies.

Although the mechanisms leading to ultrasound signal attenuation in coronary ASP are not entirely clear, a prior, fairly large investigation convincingly showed that the histopathological substrate is a relatively large lipid/necrotic core (4), which represents features of high-risk coronary atheroma. ASP has also been reported to predict complications associated with percutaneous coronary interventions such as distal embolization (5) and no reflow (6). Although ASP on coronary IVUS has shown promise for indicating clinical risk in native atherosclerotic disease, its role had not been well defined for the evaluation of risk after heart transplantation prior to the study by Okada et al. (3).

Pushing this concept further, a question raised by these data is whether a more direct assessment of coronary inflammation could enable the diagnosis of even earlier forms of CAV. To that end, novel intravascular imaging methods are currently in development (7–10). In pre-clinical studies, the emerging technique of near-infrared fluorescence imaging has been used to image atherosclerotic inflammation using protease or macrophage-targeted agents (7). Moreover, the inflammatory process associated with CAV may one day be assessed noninvasively. Indeed, there has been substantial experience in assessing arterial inflammation using ^{18}fluoro-^{2}deoxyglucose and positron emission tomography (PET). Arterial inflammation, as measured with PET, predicts the development of cardiovascular events (11). However, this approach has, thus far, been applied primarily to large, noncoronary vessels, because technical issues have limited the use of ^{18}fluoro-^{2}deoxyglucose-PET for assessing coronary inflammation. Conversely, several novel PET tracers targeting inflammation are currently in development and might eventually prove useful for assessing the inflammation associated with CAV.

The findings of Okada et al. (3) provided important new data strongly suggesting that IVUS assessment of ASP allows the identification of high-risk CAV and the prediction of long-term mortality or retransplantation. Once this observation is replicated in a larger multicenter setting, the logical next step will be to assess whether early detection of echo-attenuated plaques and CAV will trigger changes in treatment that result in improved clinical outcomes.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Ahmed Tawakol, Division of Cardiology, Massachusetts General Hospital, 165 Cambridge Street, Suite 400, Boston, Massachusetts 02114. E-mail: atawakol@mgh.harvard.edu.

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