The Changing Face of First-Year Intravascular Ultrasonography in Heart Transplantation*

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In this issue of JACC: Heart Failure, Okada et al. (1) demonstrate paradoxical vessel remodeling of the proximal left anterior descending (LAD) coronary artery segment at 1 year to be predictive of long-term mortality in a cohort of 100 heart transplantation patients. The authors are to be congratulated in pursuing the arduous task of assessing and analyzing intravascular ultrasonography (IVUS) findings in the most recent era of heart transplantation and correlating these data to hard endpoints (death and/or retransplantation). Over the course of the past 2 decades when the original IVUS studies were performed, there have been several advances in the field of heart transplantation that have improved outcomes. These improved outcomes, in addition to improved IVUS technology, may have influenced what IVUS parameters are now most sensitive as prognostic factors.

First-year change from baseline (4 to 6 weeks after transplantation) to 1 year after transplantation, in maximal intimal thickness (MIT) was the first IVUS parameter demonstrated to be a reliable prognostic marker for long-term outcomes in heart transplant recipients. In a multicenter study, Kobashigawa et al. (4) found that MIT change of $\geq 0.5$ mm in the first year after transplantation was a reliable surrogate marker for subsequent mortality, nonfatal major adverse cardiac events (heart failure, myocardial infarction, need for percutaneous cardiac intervention, need for permanent pacemaker or stroke), and the development of angiographic cardiac allograft vasculopathy (CAV) through 5 years of follow-up. A companion study by Tuzcu et al. (5) also determined that angiographic silent early coronary intimal thickening was a powerful predictor of all-cause mortality, myocardial infarction, and angiographic abnormalities. As a result of those studies, IVUS was used in prospective clinical trials as a surrogate marker for long-term outcomes and CAV. Of importance is that the studies by Kobashigawa et al. (4) and Tuzcu et al. (5) included patients in the 1990s, when many patients were still taking cyclosporine and azathioprine therapy. A threshold of 0.5 mm for coronary intimal thickening was noted as being abnormal because this number was more than 2 SD from the average intimal thickening.
observed in young 20-year-old donor coronary arteries.

Advances in the field of heart transplantation, specifically in immunosuppression medications and IVUS technology, may have influenced and altered what IVUS measurements are now most sensitive markers for prognosis. Improved immunosuppression medications appear to have decreased the incidence of CAV in the recent era, as reflected in the International Society for Heart and Lung Transplantation registry (6). Because acute cellular rejection (ACR) has been correlated with more CAV, use of the tacrolimus/mycophenolate combination compared with cyclosporine/mycophenolate, as seen in the 3-arm trial, showed significantly reduced acute ACR compared with the cyclosporine/mycophenolate regimen (7). The more common use of tacrolimus/mycophenolate regimen may, in part, explain why there is less CAV reported in the more recent era of heart transplantation. In addition, the wider use of both statins and proliferation signal inhibitors in the more recent era have been shown to reduce coronary intimal thickening in the first year after heart transplantation in multiple randomized clinical trials (8,9). IVUS technology has also improved in the most recent era. The newer IVUS machines have better imaging resolution, and there is updated computerized software available to better analyze the IVUS images in 3 dimensions. Motorized pullback has standardized the images viewed and has allowed more precise assessments of coronary artery anatomy (10).

The findings by Okada et al. (1) are notable for the geographic location of vessel remodeling. Indeed, there are previous reports of more frequent and severe intimal thickening in the proximal coronary artery vessels post transplantation compared to distal vessels. A single-center study by Tuzcu et al. (11) that performed intravascular ultrasonography in 132 transplant patients 1 to 9 years after transplantation noted CAV in 64% of proximal, 43% of mid-, and 26% of distal segments and that overall focal and non-circumferential CAV was more frequently proximal than distal. This was observed regardless of the time from transplantation. Subsequent studies by Lin et al. (12) and Kapadia et al. (13) using IVUS in single-center transplantation populations also demonstrated numerically more severe intimal thickening in proximal segments post-transplantation than distal segments, although this was not statistically significant (12,13). However, these studies did not discuss vessel remodeling.

The paradoxical negative remodeling seen in the study by Okada et al. (1) consists of a shrinkage in vessel size in combination with increased intimal thickening, thus compromising vessel lumen volume. This finding is notable for the absence of Glaov’s phenomenon, seen in native atherosclerosis, where arteries positively remodel (dilate, increasing vessel size) to maintain constant flow despite increases in atherosclerotic lesion mass. Previous studies demonstrate an inflammatory Th1 and Th2 cytokine component in this remodeling process (14). Similarly, other studies have demonstrated that other inflammatory markers such as C-reactive protein are associated with progressive luminal obstruction in transplantation patients (15), which supports the role of inflammation in negative remodeling.

Progression of intimal thickening has also been associated with the development of myocardial fibrosis, as demonstrated by serial endomyocardial biopsy results (16). Through recent greater understanding of the extracellular matrix and new advances in immunohistochemical analysis, myocardial fibrosis is noted to be one of the diverse morphologic manifestations of CAV (17). In turn, myocardial fibrosis has been implicated as a contributor to restrictive physiology. In a recent study by Kobashigawa et al. (18), a retrospective review of 30 patients who underwent retransplantation was conducted. The cohort with restrictive physiology preceding heart retransplantation had significantly more patients exhibiting myocardial fibrosis as determined by pathology of the explanted donor hearts than with the nonrestrictive physiology group. It was noted that the coronary artery adventitia and adjacent tissues around the heart were involved in an intense inflammatory process that could contribute to negative remodeling of the coronary vasculature. In another study by Yamani et al. (16), heart transplantation patients with fibrosis in whom heart biopsies were performed were noted to have greater coronary intimal thickening by first-year IVUS and worse 7-year survival than patients without fibrosis (16). Thus, cardiac fibrosis with pericardial inflammation may be implicated with CAV as well as play a role in negative remodeling of the coronary arteries (inflammation of the coronary adventitia).

There was information missing from the paper by Okada et al. (1) that could have strengthened the conclusions. The paper did not include correlation of first-year IVUS data to the development of subsequent angiographic CAV and cardiac dysfunction. It would have been of great interest and reassurance that more angiographic CAV and cardiac dysfunction also correlated to more first-year IVUS abnormal findings. The cause of death would also
have been helpful, particularly those deaths due to an immune cause, which would have had a more direct connection to the presumed heightened inflammation observed in the proximal LAD coronary artery.

It is not surprising that other IVUS parameters in the current era of heart transplantation may be even more sensitive as a marker for poor outcome after heart transplantation due to advances in the field. As CAV and IVUS technology continue to evolve, different IVUS measurements may become more sensitive prognostic markers. Therefore, as Okada et al. (1) assert, combined assessment of both vessel remodeling and intimal thickening in the proximal LAD may prove even more accurate and enable refinement in predicting those patients with adverse long-term outcomes.

**REFERENCES**


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