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EDITORIAL COMMENT

# Shedding Light on Cardiac Allograft Vasculopathy

## OCT to Predict Progression of Disease*

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Although heart transplantation has become the treatment of choice for eligible candidates with end-stage cardiac failure, survival is far less than the natural life span for all except the oldest patients (1). Analysis of International Society for Heart and Lung Transplantation registry data show progressive improvements in long-term survival, mostly due to improvements in 1-year outcomes. Importantly, the slope of the International Society for Heart and Lung Transplantation survival curves haven't changed over time, and therefore, to significantly improve post-transplantation survival, it will be necessary to modify long-term hazards such as renal failure and cardiac allograft vasculopathy (CAV) (1). Indeed, CAV represents one of the major causes of late mortality following heart transplantation.

The pathogenesis of CAV is complex and is thought to reflect a form of chronic rejection (2). This is supported by the observation that more potent immunosuppressive drugs such as mycophenolate mofetil and everolimus are associated with significantly less coronary intimal thickening as assessed by intravascular ultrasound (IVUS) studies (3,4). Yet once the patient develops CAV, proliferation signal inhibitor medications such as everolimus have a variable impact on the progression of disease. This has frustrated clinicians and patients alike, and the only therapy proven to alter prognosis for transplant patients with severe CAV is retransplantation. This is not a practical solution given the chronic imbalance between donor supply and the ever expanding heart transplantation waiting list.

Although IVUS has been an invaluable tool to study CAV since the first report in 1991 (5), it is focused mainly on the size of vessel structures such as the lumen, as well as intimal and medial thickness. In the case of CAV, the use of IVUS has granted insight into the rapid growth of intimal thickness in vessels that appear angiographically normal, and this has correlated with poor patient outcomes (6,7), making this an important surrogate endpoint in heart transplantation trials (8).

More recently, optical coherence tomography (OCT) has been applied to image coronary artery anatomy given its 10-fold increased spatial resolution compared with IVUS. Beyond the improved resolution, OCT can delineate elements of the arterial wall such as microchannel vessels or collections of macrophages that cannot be detected by alternative techniques. The disadvantages of OCT include the need for steady intracoronary contrast administration during imaging and difficulties imaging the interface between the intimal and medial layers of the coronary vessel (which are more easily distinguished with IVUS).

SEE PAGE 773

In this issue of *iJACC*, Clemmensen et al. (9) report on a prospective study of 62 heart transplantation patients who underwent comprehensive multivessel optical coherence tomographic analysis and correlated the findings to the occurrence of "nonfatal coronary progression" (defined as a new coronary lesion of at least 70% or performance of percutaneous coronary intervention). They show that the presence of layered fibrotic plaques (possibly indicative of healed endothelial injuries) and "bright spots" (which are associated with macrophages) are associated with a high risk for CAV progression.

Although others have applied OCT to heart transplantation patients (10–12), this is the first study to

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correlate specific optical coherence tomographic findings to the risk for angiographic disease progression. In this study, the risk for progression of CAV was nearly 9 times higher for patients with a specified incidence of layered fibrotic plaque (>9.6%) and bright spots (>7.9%). However, when adjusted for angiographic grade of CAV and time post-transplantation, the association was weak at best ($p = 0.06$). Notably, parameters such as intimal area and intima/media ratio remained significant predictors despite adjustment for CAV grade, and these could be measured by IVUS as well. Unlike IVUS, OCT requires iodinated contrast to be injected during the acquisition of images, and this may have a significant impact in patients with chronic kidney disease. Furthermore, as with IVUS, the interpretation of OCT requires significant experience, and the figures in the paper show findings that may be challenging to discriminate for less experienced examiners. Published standards exist, but the use of OCT is not widespread compared with IVUS (13).

Taken with previous work, it is likely that the pathogenesis of CAV is more complex than we have imagined. Because all heart transplantations start with a grossly ischemic donor heart, it seems plausible that some early aggressive CAV is due to an exaggerated response to endothelial injury. In this setting, drugs such as statins and proliferation signal inhibitors are effective in reducing the incidence of intimal thickening and CAV. Late post-transplantation, perhaps the driving forces are more like traditional coronary artery disease in nontransplantation patients, whereby immune and metabolic factors lead to vessel inflammation and vulnerable plaque formation. This is consistent with the imaging findings in the present study and others (12,14), and therefore the treatment may need to be targeted accordingly. This would explain the relatively poor efficacy of proliferation signal inhibitors when initiated for established CAV and suggests a role for enhanced dosing of statins as well as use of drugs such as aspirin and clopidogrel.

Further studies using OCT will hopefully explore the differential nature of CAV at different time points. Perhaps in the future we will use intracoronary imaging to customize treatment to individual patients so that we can finally reduce the impact of CAV and increase the longevity of heart transplantation patients in a meaningful way. There are many challenges ahead, not the least of which is the risk aversion of pharmaceutical firms and transplantation programs alike as we strive to understand and prevent CAV from killing our heart transplant patients.

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