Coronary Computed Tomography Angiography

Is it Time to Replace the Conventional Coronary Angiogram in Heart Transplant Patients?*

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In this issue of the Journal, Wever-Pinzon et al. (1) performed a meta-analysis on prospective trials assessing cardiac allograft vasculopathy (CAV) using coronary computed tomography angiography (CCTA). They find that CCTA is a reliable noninvasive imaging alternative to coronary angiography with excellent sensitivity, specificity, and negative predictive value (NPV) for the detection of CAV.

The authors are to be congratulated on bringing this timely issue of a noninvasive imaging modality to detect CAV to the forefront. To judge the need for this newer technology, there are several questions to be asked. Is there a need for frequent CAV monitoring and with what method? What is the efficacy of this modality compared to coronary angiography? What are the disadvantages with CCTA? Other issues of cost and quality of life should also be considered.

Is there a need for frequent CAV monitoring and with what method? CAV affects over 50% of heart transplant recipients within 10 years after transplant. For those patients with severe 3-vessel CAV, 1-year mortality following diagnosis can be as high as 90% (2). Once detected, the progression of CAV is variable with some disease accelerating over months. Therefore, the need for CAV monitoring is warranted, especially as interventions are available such as coronary artery stenting, bypass surgery (in rare cases), and change in medical management.

Routine periodic screening of CAV is necessary due to absent or atypical symptomatology in the majority of cardiac transplant recipients. It is essential that every patient undergo coronary angiography at 1 year after cardiac transplant. An early angiogram, with or without intravascular ultrasound (IVUS), 1 month after transplant may be considered to establish a baseline assessment. Abnormal findings at that time are unlikely to represent CAV but rather donor coronary artery disease. After the first annual study coronary angiography is recommended on at least an every other year basis in patients without CAV and on an annual basis in those with CAV. In patients who are found to have normal coronaries on serial coronary angiography, the surveillance interval may be increased. Many heart transplant centers alternate coronary angiography with noninvasive stress testing such as dobutamine stress echocardiography or myocardial perfusion imaging. Cardiac magnetic resonance does not currently have the resolution to adequately define coronary anatomy as does CCTA.

A major limitation of these noninvasive tests is that they do not reliably detect early stage or limited disease, particularly in the small coronary artery vessels. Coronary artery distal pruning of the epicardial vessels may represent small vessel disease. This small vessel disease has been associated with the subsequent development of restrictive cardiac physiology, which is diagnosed with hemodynamic measurements routinely obtained at the time of coronary angiography (3). This entity of restrictive cardiac physiology and small vessel disease has been recognized in the recent International Society for Heart and Lung Transplantation (ISHLT) CAV nomenclature scale and represents the most severe CAV category as CAV-3, which has been associated with subsequent poor survival. This underscores the importance of recognizing CAV small vessel disease.

What is the efficacy of CCTA compared to coronary angiography? CCTA is a relatively new modality. The earlier generation technology (16-slice) with single detector has limited use in heart transplant patients due to high resting heart rates and low resolution. The accuracy (spatial resolution) of even the most recent multislice scans may overlook short lesions, ostial lesions and coronary fistulae (4). Secondary branch vessels <1.5 mm diameter are not well analyzed. In addition, given that coronary branch vessel assessment is not adequate with CCTA, the ISHLT Working Group does not recommend use of CCTA for CAV classification. However, CCTA appears relevant to exclude significant CAV on clinically significant coronary arteries suitable for coronary stenting. Thus, the high NPV of CCTA for significant stenosis on main branches may avoid unnecessary invasive coronary angiograms.

CCTA has the potential of recognizing CAV in earlier stages compared to coronary angiography. Similar to IVUS, CCTA can measure intimal thickness >0.5mm (5). However, the prognostic value of early CAV detected by CCTA has not been systematically studied. IVUS is the most sensitive method to assess CAV as it measures intimal thickening of the coronary artery wall. In a multicenter study, the change in first-year IVUS was found to provide prognostic information (6). The change in first year maximal

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intimal thickness >0.5 mm was associated with increased mortality, nonfatal major adverse cardiac events and angiographic detected CAV at 5 years post-transplant. Interestingly, an increase in IVUS intimal thickening in other studies has been correlated to the presence of small vessel disease (7). In the more recent clinical trials of newer immunosuppression agents, first-year IVUS has been used as a marker for drug efficacy to prevent CAV (8). At this time, CCTA is not as sensitive as IVUS to accurately measure coronary artery intimal thickness but may prove useful with advancing technologies.

What are the disadvantages of CCTA? The study by Wever-Pinzon et al. (1) is weakened by the relatively small number of patients in this meta-analysis. There also appears to be patient selection bias, as the study participants compared to national averages were slightly younger, had relatively slower heart rates, were of normal body mass index, and had acceptable renal function (creatinine <1.7 mg/dl). The latter 2 patient characteristics limit extrapolation of these data to many heart transplant patients. From the 2013 ISHLT Registry data, 15.1% of heart transplant patients develop abnormal creatinine (i.e. >2.5 mg/dl) within 5 years after heart transplant. For CCTA, iodinated contrast is still a prerequisite, which limits its use in patients with renal insufficiency.

Until recently, CCTA was associated with significant radiation exposure. A prospective electrocardiogram-gated axial technique now allows radiation dose reduction by 80% to a level lower than conventional coronary angiography but does require slower heart rates (9). Exposure to radiation is a great concern to heart transplant patients as prolonged use of immunosuppression translates into an increased risk of cancer in this patient population. Cancer rates are estimated to be approximately 15% at 5 years after heart transplant. CCTA has exposed patients to similar or more radiation compared to the coronary angiogram. Over time, exposure to radiation for heart transplant patients is considerable due to the repetitive need for annual monitoring and other testing. However, the increased cancer risk attributable to cumulative radiation exposure appears to remain very low (0.34% additional risk in nontransplant patients) compared with cancer linked with immunosuppression and has to be balanced with the diagnostic interest of the ionizing procedures.

Conclusions. CCTA does offer advantages over the gold standard coronary angiography in that it is noninvasive, less costly, and less resource intensive. Similar to coronary angiography, it uses iodinated dye (running the risk for renal failure) and subjects the patient to repeated radiation exposure, thus potentially increasing malignancy risk in a patient population that is already at increased risk for this complication. What is needed is an accurate imaging modality that can be used in all patients (even those with renal insufficiency) and does not have adverse risks such as radiation exposure. For now, the use of the CCTA, although not ideal, may be reasonable in stable heart transplant patients as a screening tool to exclude significant CAV.

In the future CCTA may be used to assess intimal thickness similar to IVUS. With continued technological advances, improvement in the ability of CCTA to assess the arterial wall and distal small vessels, while requiring less contrast and radiation, may allow it to play an increasing role in this arena.

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