Circulation: Heart Failure

EDITORIAL

Predicting the Future of Cardiac Allograft Vasculopathy With Cardiac Positron Emission Tomography

Ready for Prime Time?

See Article by Konerman et al

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Over the last 5 decades, significant advances in the care of heart transplant recipients have improved long-term survival. However, cardiac allograft vasculopathy (CAV) remains a significant problem with incidence varying from 30% at 5 years to 50% at 10 years. CAV is one of the leading causes of death after heart transplantation and accounts for ≈12% of deaths starting at 1 to 3 years posttransplant.[1] CAV affects both epicardial and microvascular coronary vasculature. The microvascular dysfunction associated with CAV can result in early endothelial vasoreactive abnormalities which can reduce myocardial flow reserve (MFR). The pathogenesis of CAV is multifactorial and is influenced by both alloimmune dependent and independent factors.[2]

Because of denervation of the transplanted heart and absence of typical anginal symptoms, surveillance coronary angiography is recommended for CAV surveillance. Periodic screening is important for prognosis and management (ie, adjustment of cardiovascular and immunosuppressive therapies).[3] Coronary angiography may not identify early small vessel or advanced diffuse CAV.[4] Intravascular ultrasonography (IVUS) is more sensitive than angiography for CAV detection and has prognostic value with >0.5 mm intimal thickening in the first year posttransplant associated with increased risk of death and angiographic CAV development.[5] Although considered the gold standard, IVUS has limitations. It is only able to image larger epicardial vessels and is better at identifying focal eccentric narrowing of the vessel lumen rather than the more diffuse pattern typically found in CAV. Invasive methods, in general, have significant limitations associated with procedural- and contrast-related complications as well as reduced sensitivity for detection of early-stage CAV.[6]

Stress echocardiography and single-photon emission computed tomography myocardial perfusion imaging have reasonable sensitivity and negative predictive value for the detection of significant obstructive disease. However, these modalities have limited sensitivity for detection of limited or early-stage disease (<50% stenosis), with sensitivity as low as 56%, as they rely on heterogeneity of perfusion or contractility.[6] As such, current guidelines recommend these noninvasive imaging methods in recipients who are not candidates for invasive evaluation (Class IIa).[3] Recently, it has been demonstrated that when dynamic cadmium-zinc-telluride-single photon emission computed tomography myocardial perfusion imaging with ^{99m}Tc-sestamibi is used to measure MFR the values obtained are similar to those obtained using ^{15}O-water positron emission tomography (PET). With further validation dynamic single-photon emission computed tomography may become a valuable tool for CAV detection when PET is not available.[7]

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PET is a very useful tool for assessing coronary physiology. It can quantify absolute myocardial blood flow (MBF) in addition to MFR. Quantification of absolute MBF with PET is advantageous in the assessment of coronary artery physiology. Rest/stress PET can allow quantification of MFR which incorporates assessment of both macro- and microvascular function. It is especially valuable in the assessment of CAV because of the diffuse nature of CAV and associated endothelial dysfunction may result in a homogeneous reduction in blood flow that is not detectable by conventional single-photon emission computed tomography. MFR is the ratio of MBF during maximal coronary vasodilatation to resting MBF.[8] In a study by Wu et al,[9] MFR using ^{13}N-ammonia PET was inversely associated with plaque volume index by IVUS in heart transplant recipients (n=27) with normal angiography suggesting utility for early CAV detection. This may be important prognostically. Additionally, PET has demonstrated the presence of coronary endothelial dysfunction in heart transplant recipients, some of which may be temporary.[10,11]

A prospective registry of 140 heart transplant recipients (average 8.2 years posttransplant) assessed the role of dipyridamole rubidium-82 PET. In this cohort, patients with MFR ≤1.75 had a higher rate of cardiovascular events and death than patients with MFR >1.75. These differences were observed in the presence of preserved systolic function and normal perfusion in the majority of patients with adverse outcomes. Rubidium-82 PET was demonstrated to have predictive value for adverse outcomes and overall mortality. However, although prognostic value was demonstrated with MFR the association of these outcomes with either the presence or degree of CAV is uncertain as angiography was not routinely performed in this study.[12] More recently, Chih et al[13] prospectively evaluated 40 heart transplant recipients with PET, IVUS, and intracoronary hemodynamics. In this cohort, patients with reduced MBF and increased coronary resistance measured by PET had high likelihood of CAV (specificity >96%). These findings of these studies suggest PET imaging may provide a reliable tool for detecting early CAV and identifying high-risk patients with the potential to avoid coronary angiography and IVUS in a low-risk group.

In this issue of *Circulation: Heart Failure*, Konerman et al[14] retrospectively assess the prognostic and diagnostic implications of MFR assessed by a rubidium-82 cardiac PET in heart transplant recipients. The first cardiac PET, occurring at any time point after transplant, was utilized for analysis. The primary composite outcome of cardiovascular death, acute coronary syndrome, coronary revascularization, and heart failure hospitalization was assessed. MFR was assessed in a subset of patients who had undergone coronary angiography within 1 year of PET imaging.

During the study period, 117 recipients were included with a median time from heart transplant to cardiac PET of 6.4 years. Of these 117 patients, 19% experienced the primary composite outcome after a median of 1.4 years (2 cardiovascular deaths; 5 with acute coronary syndrome; 8 underwent revascularization; 15 with heart failure hospitalization). Median global MFR was 2.31 (interquartile range, 1.84–2.72) with 28% with MFR <2.0. MFR and stress MBF were associated with the primary composite outcome in unadjusted analyses: hazard ratio, 0.22 per unit increase in MFR (95% confidence interval, 0.09–0.50); hazard ratio, 0.48 per unit increase in stress MBF (95% confidence interval, 0.29–0.79). MFR remained a predictor with adjusted analyses, whereas stress MBF did not on all adjusted analyses. Additionally, MFR <2.0 was associated with increased risk of the primary composite outcome (hazard ratio, 4.76).

Additional analysis was performed on a subset of 42 patients who underwent cardiac PET within 12 months of coronary angiography to assess MFR. Almost half of patients in this group (48%) had moderate to severe CAV (International Society of Heart and Lung Transplantation grade 2 or 3). Median global MFR was 2.18 in this cohort (interquartile range, 1.62–2.60). MFR and stress MBF, with or without adjustment, were significantly correlated with severity of CAV as assessed by International Society of Heart and Lung Transplantation grade. However, moderate to severe CAV was not found to be associated with other assessed parameters (sum stress score, sum rest score, left ventricular ejection fraction, or rest MBF).

There are several notable limitations of this study. Notably, the sensitivity of invasive coronary angiography without IVUS to detect early-stage CAV may be limited raising concerns of its use in this study to confirm the presence or absence of CAV. Additionally, as this study was retrospective, there was considerable variability in time from transplant to first cardiac PET limiting early assessments after heart transplant. Donor coronary artery disease incidence was not reported which may limit the prognostic implications about transplant-related coronary vasculopathy in this cohort. Finally, reference standards have not been well established with variability between studies.

The majority of studies utilizing cardiac PET for CAV assessment, while largely retrospective, have demonstrated promise for earlier detection.[9–12,15,16] The current study is an important step forward in identifying a noninvasive modality with the ability to detect CAV at earlier stages as well as offering prognostic data. It remains to be seen if targeted therapies at this earlier

stage can impact CAV progression and long-term outcomes of these heart transplant recipients. Larger prospective studies are needed to validate cardiac PET for CAV detection and prognosis.

ARTICLE INFORMATION

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Disclosures

None.

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