Defining the role for PET myocardial blood flow early post cardiac transplant

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With advances in the care of cardiac transplant patients over the last 50 years, cardiac allograft vasculopathy (CAV) has become an increasingly important long-term complication.¹ CAV is the most common indication for re-transplantation in patients who survive at least one year and is a leading cause of graft failure and death in patients who survive at least 3-year post-transplant.² While many transplant programs perform surveillance invasive coronary angiography (ICA), often with intravascular ultrasound, there is mounting evidence for non-invasive monitoring with positron emission tomography (PET).^{3–8} PET with myocardial blood flow (MBF) measurement for CAV surveillance has a strong pathophysiologic rationale since it can detect the diffuse epicardial and microvascular disease characteristic of CAV.

In this issue, Wiefels et al. evaluated the clinical utility of serial PET myocardial blood flow (MBF) measurements in 121 patients early post-transplant.⁹ The authors demonstrate that patients with an abnormal stress MBF (defined as < 2.1) on the baseline PET study and those with persistently elevated coronary vascular resistance (defined as > 76) were more likely to experience adverse cardiovascular events.⁹ This study suggests that PET has a clinical role for CAV diagnosis

and risk stratification early post-transplant and also confirms the potential benefits of serial PET measurements. Feher et al. recently demonstrated that serial evaluation of coronary flow reserve (CFR), with abnormal defined as < 1.5 , resulted in a significant reclassification in risk of all-cause mortality.⁸ Additionally, baseline CFR and change in CFR between PET studies were the only significant predictors of all-cause mortality in multivariable analysis.⁸

The most important, novel aspect of the study by Wiefels et al. was the early nature of the PET assessments. PET studies were performed at a mean of 1.4 and 2.6 years post-transplant for baseline and follow-up studies, respectively. Previous studies have investigated patients between 4.8 and 12.5 years post-transplant.^{3–8} Prior to the current study, the utility of PET early post-transplant represented an important knowledge gap because proliferation signal inhibitors (PSI) may be more effective in patients with early CAV. In a prior study of 402 patients post cardiac transplant, transition to PSI in the first two years post-transplant was associated with slower progression of CAV and reduced all-cause mortality compared to later transition.¹⁰ However, PSI is not typically initiated immediately post-transplant due to delayed wound healing and infections.¹¹ Additionally, routine transition to PSI is problematic because many patients are unable to tolerate chronic therapy.¹¹ The results from Wiefels et al. support a role for PET MBF early post-transplant to target PSI therapy for patients who are at higher risk of progressive CAV or adverse events.

There are a few important limitations to the study by Wiefels et al. The study was not adequately powered to assess multiple variables, such as regional perfusion abnormalities, and used a composite outcome which included diagnostic (progressive CAV) and prognostic endpoints. Studies were collected during routine clinical care, and there was most likely ascertainment bias due to

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patients with abnormal PET parameters being preferentially referred for ICA. Lastly, the authors only demonstrated significant results with new PET thresholds, but not with several previously described values. While this could reflect a need for different thresholds early post-transplant, it could also simply reflect the lack of statistical power. Importantly, we recently validated the diagnostic and prognostic utility of previously defined thresholds in a study of patients later post-transplant.⁶ Currently, a lack of standardization for diagnostic or prognostic thresholds is a barrier to broader implementation of PET for CAV surveillance.

There is mounting evidence that PET may be a superior modality for CAV surveillance. Dobutamine stress echocardiography has limited sensitivity for detecting mild CAV and inducible ischemia is not associated with cardiovascular events.¹² The diagnostic accuracy of SPECT MPI has been variably reported, with sensitivity and specificity ranging from 13 to 92% and 55%-98%, respectively, due to differences in patient populations and definitions of CAV.^{13–15} Additionally, the prognostic utility of SPECT in cardiac transplant patients is unclear.^{16,17} Cardiac computed tomography angiography has good diagnostic accuracy for mild CAV (sensitivity 97%, specificity 81%),¹⁸ which can potentially be improved by including quantitative assessment of plaque volumes.¹⁹ However, its prognostic value has not been defined and accuracy may be lower in non-expert centers, due to the technical challenge inherent in imaging cardiac transplant patients who have high resting heart rates.

Surveillance for CAV is typically performed to diagnose patients with early stages of CAV or to risk-stratify patients with known CAV. Current evidence supports the use of PET MBF, and potentially CCTA in experienced centers, to identify patients with early CAV who may benefit from PSI therapy. Additionally, there is robust evidence for using PET MBF to risk-stratify patients with established CAV to potentially guide decisions regarding revascularization or re-transplantation.²⁰ Large, multicenter efforts are needed to more rapidly advance the field and provide clarity regarding optimal implementation of PET for CAV surveillance.

Disclosures

Dr. Daniel Berman receives royalties for QPS software at Cedars-Sinai. Dr. Miller has no relevant conflicts of interest.

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