Noninvasive surveillance for cardiac allograft vasculopathy following heart transplantation: One of several emerging clinical applications for cardiac positron emission tomography with assessment of myocardial blood flow reserve

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Cardiac positron emission tomography (PET) with assessment of myocardial blood flow reserve (MBFR) has matured over several decades and is now widely recognized as a powerful tool for the diagnosis of obstructive coronary artery disease (CAD), for the assessment of prognosis in patients with known or suspected CAD, and for informing decisions for revascularization.¹ In addition to the assessment of obstructive epicardial coronary artery atherosclerosis, cardiac PET with assessment of MBFR is capable of comprehensively evaluating all levels of the vascular supply to the myocardium (large conduit epicardial arteries, resistance arterioles, and the microvasculature) and has demonstrated the potential to provide useful information in other clinical scenarios.

- (1) Identification of coronary microvascular disease as an etiology for anginal symptoms in the absence of obstructive CAD.²
- (2) Assessment of patients with hypertrophic cardiomyopathy³ and other nonischemic cardiomyopathies.⁴

- (3) Assessment of patients with asymptomatic aortic stenosis with potential to inform decisions regarding timing of valve interventions.⁵
- (4) Assessment of patients with cardiac amyloidosis with potential to determine likelihood of response to medical therapy.⁶
- (5) Noninvasive diagnostic and prognostic assessment of cardiac allograft vasculopathy (CAV) following heart transplantation (HTx).^{7–12}

Cardiac PET with assessment of MBFR seems to be ideally suited for the evaluation of CAV. CAV is a diffuse process affecting the epicardial coronary arteries and the microvasculature resulting in reduced vasodilatory capacity. Cardiac PET with assessment of MBFR is noninvasive, safe in patients with renal failure, feasible in patients with arrhythmias or elevated resting heart rates, feasible in patients with implanted pacemakers or defibrillators, and capable of detecting diffuse reductions in coronary vasodilatory capacity due to CAV.

The study by Nelson and colleagues in this issue¹³ adds to the existing literature supporting the clinical utility of cardiac PET with assessment of MBFR for the noninvasive assessment of CAV following HTx. The diagnosis of CAV can be challenging due to the diffuse (rather than focal) luminal narrowing characteristic of this condition and the lack of typical anginal symptoms in patients with denervated hearts following cardiac transplantation. The diagnosis of CAV is critically important due to the availability of treatments and the poor prognosis of CAV if unrecognized and untreated. Invasive coronary angiography (ICA) with intravascular ultrasound (IVUS) has traditionally been used for routine surveillance, though this procedure is invasive and

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is associated with a small but finite risk for complications including contrast-induced nephropathy (CIN) and vascular injury. Similarly, coronary computed tomography angiography (CCTA) is contraindicated in the setting of renal dysfunction and is unable to assess the functional significance of diffuse coronary arterial narrowing. Conventional stress imaging modalities such as single-photon emission computed tomography (SPECT) myocardial perfusion imaging and stress echocardiography are not ideally suited for assessment of CAV due to the diffuse (rather than regional) abnormalities of myocardial blood flow in this condition.

The study by Nelson and colleagues was a retrospective single-center study involving 50 patients who had PET MBFR measurements performed for routine surveillance at a median of 10 (6.7 to 16) years after HTx. Patients were grouped according to MBFR ≤ 2 ($n = 25$) or MBFR > 2 ($n = 25$). The authors found that during a median follow-up of 3.6 years, the probability of event-free survival was significantly higher in those with normal MBFR compared to those with low MBFR. The patients in the study by Nelson and colleagues were referred for cardiac PET primarily due to contraindications to ICA and IVUS (renal failure, arterial access limitations). Therefore, renal failure was common (estimated GFR < 30 in 20% of patients). The primary outcome was all-cause mortality though secondary outcomes were assessed as well (revascularization, graft failure, retransplantation, and new CAV diagnosis).

A strength of the study was the relatively long-term follow-up (median 3.6 years after PET). No patients were lost to follow-up. The median time from HTx to PET was also long at 10 (6.7–16) years.

Limitations of the study include relatively small study population compared to prior published studies of the prognostic value of PET MBFR in HTx patients and the selected patient population studied (mainly comprised of patients with renal failure or other contraindications for standard surveillance with ICA).

The main findings were that survival probability was significantly higher in the high MBFR group compared to the low MBFR group, and that MBFR remained predictive of survival in the subgroup without previously documented CAV (but not in those with previously documented CAV).

Questions remaining to be answered include

(4) Is a slight reduction in MBFR on serial surveillance testing meaningful? What percentage reduction in MBFR on serial testing should be considered predictive of the development of clinically relevant CAV?

Despite these remaining questions, it appears clear that cardiac PET with assessment of MBFR has emerged as a powerful tool for noninvasive serial surveillance of heart transplant recipients. Cardiac PET with assessment of MBFR is also widely recognized as a powerful tool for assessment of coronary microvascular disease. Given the accumulating clinical data and the outstanding safety and clinical feasibility, it seems to be only a matter of time before PET with assessment of MBFR is also used to guide patient management in hypertrophic cardiomyopathy, cardiac amyloidosis, aortic stenosis, and other clinical scenarios yet to be identified.

Disclosures

Dennis A. Calnon declares no financial conflicts of interest.

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