Should positron emission tomography be the standard of care for non-invasive surveillance following cardiac transplantation?

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The number of patients with end-stage heart failure has increased over the last decade and is expected to continue to rise. Cardiac transplant is the only established, cost-effective therapy for end-stage heart failure.[1] Median survival following cardiac transplant is now greater than 13 years, and as a result many patients are now surviving until they develop cardiac allograft vasculopathy (CAV).[2] In patients who survive at least 5 years after transplant, CAV accounts for over a third of deaths, many of which occur suddenly.[3] CAV is also the most common indication for re-transplantation in patients who survive at least one year.[4]

CAV is characterized by diffuse arteriopathy involving the epicardial arteries and microvasculature.[5] Traditionally the diagnosis of CAV has been made using invasive coronary angiography.[6] Since the transplanted heart is denervated, most patients with CAV remain asymptomatic until they develop late disease. Given the important therapeutic and prognostic implications, cardiac transplant programs employ routine surveillance assessments. Many transplant programs utilize serial coronary angiography which carries a risk of bleeding, stroke, and vascular injury. Intravascular ultrasound (IVUS) has been shown to be more sensitive for early disease,[5] since it can measure coronary plaque volume and maximal intimal thickness (MIT) which has been associated with an increase in sudden death, myocardial infarction, and need for revascularization.[7] However, the improved diagnostic accuracy comes at the expense of increased procedural risks and costs.[8] Due to this limitation, non-invasive monitoring of CAV is becoming a standard component of surveillance post-transplantation.

There are several modalities currently used for non-invasive surveillance in cardiac transplant patients. Single photon emission computed tomography (SPECT) is commonly used around the world to assess for CAV. However, SPECT has suboptimal sensitivity in the setting of diffuse disease which is the typical pattern seen in CAV. The diagnostic sensitivity has been reported to be as low as 14% for identifying a stenosis $\geq$ 70%.[9] Dobutamine stress echocardiogram has been used because of its wide availability and lack of ionizing radiation. However, the sensitivity is 7% for any CAV and only 28% for CAV grade 2 or 3.[10] Cardiac CT angiogram has reasonable sensitivity (81%) and specificity (75%) for IVUS-defined CAV, however there is a paucity of prognostic data available.[11] Positron emission tomography (PET) has several advantages over other non-invasive modalities. PET allows more accurate assessment of regional differences in flow by providing routine measurement of myocardial blood flow (MBF). Additionally, rest and stress MBF can be compared to determine myocardial flow reserve (MFR) which has independent diagnostic and prognostic utility. Finally, there is a growing body of evidence regarding the prognostic significance of PET findings which may help physicians identify patients who should be considered for cardiac re-transplantation.

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Table 1. Summary of diagnostic studies of PET for CAV surveillance

Author	Year	Cohort	Protocol	Results
Allen-Auerbach[14]	1999	19 patients, 18 months post-transplant	Dipyridamole stress 13-N ammonia	MFR correlates with luminal diameter and total vessel area measurements by IVUS
Chan[19]	1994	16 patients with and without rejection	Dipyridamole stress 13-N ammonia	Stress MBF and MFR significantly lower in rejection compared to patients without rejection/after successful tx
Wu[13]	2010	27 patients 2.5 years post-transplant, angiographically normal coronaries	Adenosine stress 13-N ammonia	Burden of ischemia correlated with MFR, but not with IVUS measurements of luminal stenosis or plaque volume. However, MFR correlated with plaque volume ($r = -0.40$, $P < 0.05$)
Chih[12]	2018	40 patients undergoing IVUS, 4.8 years post-tx, 29/40 surveillance	Dipyridamole stress, Rb-82	MFR correlated with invasive evaluation of flow reserve. AUC for IVUS defined CAV 0.77. MFR < 2.9 or MBF < 2.3 95% sensitive, MFR < 2.9 AND MBF < 2.3 97% specific for IVUS defined CAV
Bravo[17]	2018	66 patients with PET within 1 year of coronary angiogram	Regadenoson or adenosine stress, N-13 Ammonia	Peak MBF AUC 0.81, MBF < 1.70 to > 92% sensitive and 70% specific. Combination of abnormal perfusion, MBF and left ventricular ejection fraction AUC 0.88

AUC, area under the curve; *CAV*, cardiac allograft vasculopathy; *IVUS*, intravascular ultrasound; *MBF*, myocardial blood flow; *MFR*, myocardial flow reserve; *PET*, positron emission tomography

Table 2. Summary of prognostic studies of PET in cardiac transplant recipients

Author, year	Cohort	Protocol	Outcome	Results
McArdle (2014)[15]	140 patients, any time post-transplant	Dipyridamole stress Rb-82	Death, ACS, or HF admission	Mean MFR HR 0.25; MFR < 1.75 HR 4.41 (1.53–12.7, P = 0.006), qualitative perfusion defects were not associated with outcomes
Bravo (2018)[17]	94 patients, 12 years post-transplant	Regadenason or adenosine stress, N-13 Ammonia	Death, re-transplantation, ACS, or HF admission	Combination of abnormal perfusion, MBF and LVEF HR 5.93, peak MBF < 1.70 HR 4.05
Konerman (2018)[16]	117 patients, 6.4 years post-transplant	Regadenason stress, Rb-82	Death, ACS, revascularization, or HF admission	Unadjusted: MFR HR 0.22, MFR > 2.0 HR 0.21. MFR remained a predictor after multivariable adjustment.
Feher (2018)[18]	89 patients, 7.0 years post-transplant. 69 repeat studies at 1.9 years	Dipyridamole stress Rb-82	All-cause mortality	Higher baseline MFR associated with reduced mortality (adjusted HR 0.36 per 0.73 unit increase). Decrease in MFR ≥ 0.79 between studies associated with increased mortality (adjusted HR 4.25)

ACS, acute coronary syndrome; *HF*, heart failure; *HR*, hazard ratio; *LVEF*, left ventricular ejection fraction; *MBF*, myocardial blood flow; *MFR*, myocardial flow reserve

Table 1 outlines studies assessing the diagnostic performance of PET with MBF assessment. PET is most commonly compared IVUS since PET is capable of identifying disease that may be missed with routine invasive coronary angiography. Due to the increased sensitivity, corrected MFR, MBF, and coronary vascular resistance (CVR, stress systolic blood pressure/stress MBF) are more closely correlated with IVUS then conventional angiography with area under the curve of 0.77-0.81 vs 0.55-0.67.[12] MFR is inversely related to plaque volume as assessed by IVUS ($r = -0.40$, $P < 0.05$).[13] Additionally, baseline MFR corrected for the rate-pressure product correlates with change in lumen area observed by IVUS after 18 months of follow-up.[14] The presence of abnormal MBF or CVR results in a sensitivity of 97% for the presence of IVUS-defined CAV, and the presence of both features increases the specificity to 97%.[12] This diagnostic accuracy is superior to alternate non-invasive modalities, and may allow physicians to better target immunosuppressive adjustments in patients with early CAV.

In addition to improved diagnostic accuracy, PET may provide prognostic information as outlined in Table 2. McArdle et al. demonstrated that MFR < 1.75 was associated with a more than 4-fold increase in the risk of death, acute coronary syndrome (ACS), or heart failure (HF) admission.[15] A separate study demonstrated that MFR > 2.0 was associated with a favorable prognosis [hazard ratio (HR) 0.22] for the combined outcome of death, re-transplantation, ACS, or HF admission.[16] Combining regional perfusion abnormalities, left ventricular ejection, and MBF can stratify patients into groups with a five-fold difference in rates of death, re-transplantation, ACS, or HF admission.[17] Feher et al. investigated the prognostic significance of serial PET assessments and found that higher baseline MFR associated with reduced all-cause mortality (adjusted HR 0.36 per 0.73 unit increase).[18] However, decrease in MFR ≥ 0.79 (adjusted HR 4.25) or stress MBF ≥ 0.80 (adjusted HR 5.01) between studies had the greatest association with increased all-cause mortality suggesting a prominent role for serial assessments.[18] While external validation studies are needed, these studies demonstrate that PET offers potentially useful prognostic information which cannot be obtained with alternate modalities.

To facilitate more uniform application of PET for CAV surveillance two practical considerations require clarification. Correction of MBF for rate-pressure product (RPP) has been variably applied in published studies. While there is a close correlation between resting MBF and RPP in patients with acute rejection ($r = 0.77$),[19] the correlation between stress MBF and RPP is modest in patients without active rejection ($r = 0.25$).[18] Bravo et al. found that uncorrected MFR was numerically, but not statistically, superior to corrected MFR (area under the curve [AUC] 0.80 vs 0.72).[17] Until this question is definitively answered, it seems that utilizing uncorrected MBF may be a prudent approach.[20] Determining the optimal parameters cut-offs and combinations also requires prospective validation. One of the only studies to compare the diagnostic accuracy of MBF to MFR found superior accuracy with stress MBF (AUC 0.89 compared to 0.80).[17] Combining parameters will allow physicians to optimize either the sensitivity of specificity of the test based on the combination chosen.[12] However, both of these questions could be efficiently resolved by validation studies facilitated by the broader application of PET for CAV surveillance.

PET is clearly the most sensitive non-invasive modality for identifying early CAV, which classically has only been detected by IVUS. Additionally, the prognostic information available from PET could allow transplant programs to identify patients with CAV at the highest risk. These patients could be assessed and listed for cardiac re-transplantation, the only definitive therapy for end-stage CAV, a process which could take months or years. Early identification of those patients may prevent the development of refractory HF, requiring multiple hospitalizations with associated costs, or preempt sudden death. Given these advantages PET should become the standard of care, when available, for the non-invasive surveillance of CAV.

Disclosure

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