PET for Assessment of Cardiac Allograft Vasculopthy

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Approximately six million people are diagnosed with heart failure in United States of America with over 600,000 new cases annually. The gold standard treatment for end stage heart failure is heart transplantation. The median survival post-transplant is 12 years. Cardiac Allograft Vasculopathy (CAV) is the cause for up to 33% of all deaths 5 years post transplantation and 60% by 10 years' post-transplantation. Compared to those without CAV, patients with mild CAV have a two-fold risk of death, while patients with severe CAV have a 15 times greater risk of death. CAV is also the most common indication for re-transplantation in patients who survive at least one year. In CAV there is abnormal proliferation of smooth muscle and fibrosis leading to decreased blood flow from a diffuse circumferential thickening of the coronary arteries. This is quite different from traditional atherosclerosis. Most patients with CAV remain asymptomatic until they develop late disease. [1, 2]

CAV is present in approximately 25% of patients with in 4 years of transplant. The current methods to diagnose CAV are insufficient[3] (Figure 1). The guidelines recommend invasive coronary angiography for annual screening. Angiography detects impaired filling of the artery lumen, frequently missing the circumferential thickening of the vessel wall in CAV.

	Sensitivity	Specificity	PPV	NPV
PET w/Flow	83%	93%	71%	96%
Dobutamine Stress Echo	72%	83%	71%	62%
SPECT	56%	89%	70%	81%
CTA	81%	75%	93%	50%
CMR w/Flow	78%	76%	78%	76%

Figure 1. Noninvasive Diagnostic Test Comparison for the Detection of CAV. Surveillance techniques for the detection of CAV (stenosis = to <50%)

Intra coronary imaging allows for direct measurement of arterial wall thickening allowing for detection of CAV earlier. However, the improved diagnostic accuracy comes at the expense of increased procedural risks and costs. Coronary blood flow is another alternative and is measured invasively via fractional flow reserve (FFR), index of microcirculatory resistance (IMR) and non-invasively by myocardial flow reserve (MFR) using cardiac positron emission tomography (PET) stress testing. The MFR predicts adverse CAV related events including death (Figure 2). [4,5,6,7,8]

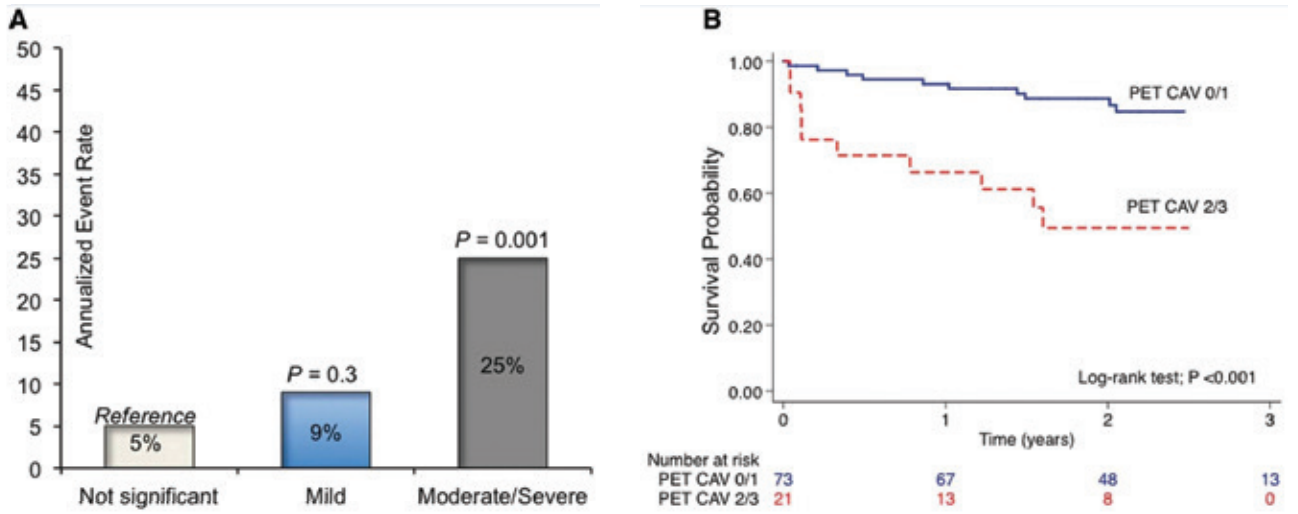
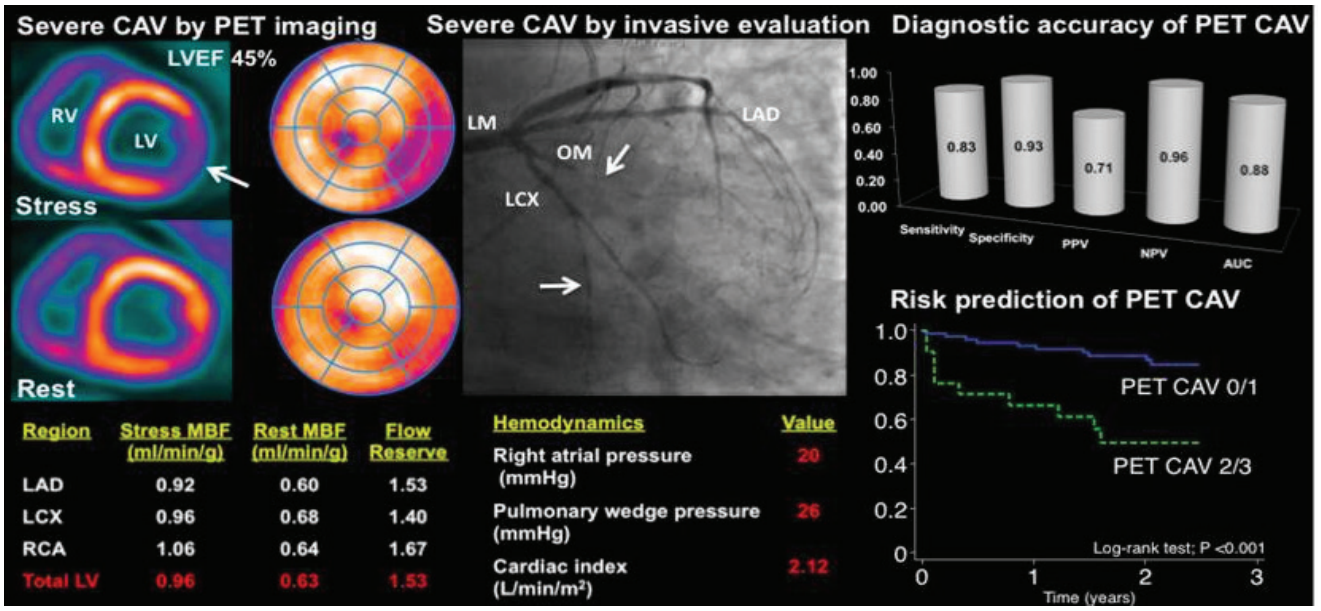


Figure 2. Annualized event rates (A) and event-free survival curves (B) of major adverse events according to positron emission tomography cardiac allograft vasculopathy severity.

The International Society of Heart and Lung Transplantation (ISHLT) guidelines assign a Class I recommendation for coronary angiography and a Class IIa recommendation for non-invasive dobutamine stress echocardiography. Coronary angiography is limited to detect CAV as it detects luminal disease, but as previously mentioned the disease in CAV is in the vessel wall. Studies have shown that when compared to intracoronary imaging, conventional angiography had a sensitivity of only 44% to detect CAV. Similarly, two recent studies have shown that DSE has a sensitivity of 0-28% to detect any CAV. The commonly used modalities for noninvasive surveillance in cardiac transplant patients are Single photon emission computed tomography (SPECT) and dobutamine stress echocardiogram to assess for CAV. The SPECT and dobutamine stress echocardiogram have suboptimal sensitivity for CAV. [9]

Using a radiolabeled isotope, myocardial perfusion and blood flow are measured before and after administration of a coronary vasodilating agent. This results in information analogous to FFR and also provides a non-invasive measurement of CFR. While this test does involve radiation exposure, on average it is 1.6 mSv; half the annual background radiation one receives living at sea level or the equivalent of two mammograms. Among non-transplant patients a decreased CFR measured by PET is associated with increased mortality with up to ten years of follow-up.

Two single center studies of PET to screen for CAV have shown an association with future adverse cardiac events. This will help physicians identify patients who should be considered for medical intervention or cardiac re-transplantation. [10,11,12]



(Figure 3) Diagnostic and prognostic value of myocardial blood flow quantification as non-invasive indicator of cardiac allograft vasculopathy. Multiparametric myocardial perfusion positron emission tomography imaging score including absolute flow quantification is a versatile and powerful tool for the diagnosis and risk stratification of individuals with suspected cardiac allograft vasculopathy (CAV).

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