PET/CT imaging of myocardial blood flow and arterial calcium: Putting the pieces together

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Positron emission tomography myocardial perfusion imaging (PET MPI) has been used with increasing frequency over the last several years. The reason for this is multi-factorial and includes the increased availability of highly efficient $^{82}Sr/^{82}Rb$ generators, superior accuracy compared to SPECT perfusion imaging, and favorable reimbursement profile. Also, PET MPI allows for the assessment of absolute myocardial blood flow (MBF) and coronary flow reserve (CFR), in addition to left ventricular function and the extent and severity of myocardial ischemia.[1]

The primary strength of PET MPI has been its superior sensitivity and specificity for detection of obstructive coronary artery disease (CAD) compared to myocardial SPECT.[2] Cardiac PET imaging can be performed with a variety of radiotracers, including ^{82}Rb, ^{15}O H_2O, and ^{13}N-ammonia. PET MPI affords a lower radiation dose compared to conventional SPECT imaging, and can be used in larger patients secondary to its larger bore size. A recent advance with ^{82}Rb imaging has been the development of methods for quantification of absolute MBF and CFR, which was originally studied with ^{15}O H_2O, and NH_3 tracers. CFR is the ratio of MBF during adenosine stress to that at rest. There are several clinical scenarios in which assessment of absolute MBF or CFR evaluation may be particularly useful. For example, in patients with multi-vessel CAD, there is potential for underestimation of ischemia using qualitative MPI assessment, as qualitative analysis of myocardial perfusion images relies on identification of relative differences in blood flow from rest to stress perfusion. Therefore, only the areas of most significant relative coronary flow impairment are visually apparent. Measurement of absolute MBF or CFR limits the risk of underestimating disease severity, as areas with low MBF or CFR will be identified as being abnormal regardless of the flow in other myocardial regions.

The measurement of CFR provides additional opportunities for the assessment of coronary disease. For example, patients with no significant epicardial coronary disease may still have decreased CFR, consistent with impaired endothelial function or ''small-vessel'' disease. It has been shown that PET-derived CFR is reduced in diabetic patients without known CAD, implying underlying vascular dysfunction, and also is an independent predictor of cardiac events in this population.[3] The detection of reduced CFR in either of these scenarios could result in a change in clinical management. In the patient with probable multi-vessel CAD, there is a lower threshold for consideration of invasive catheterization for confirmation of diagnosis and subsequent revascularization. In the latter case, aggressive risk factor modification and/or medical therapy should be contemplated.

As PET MPI requires robust attenuation correction, hybrid PET/CT scanners have been developed in which the CT scan provides an accurate anatomic attenuation map. Although hybrid scanners were originally developed for CT attenuation correction and oncologic applications, there has been great interest in establishing whether non-contrast CT acquisition of calcium scoring data (which can be readily obtained during the same patient sitting) has an incremental benefit in risk stratification or cardiac event prediction. Before discussing the role of this form of ''hybrid'' imaging, it would be useful to first review the role that calcium scoring independently has in risk profiling and coronary event prediction.

Coronary artery calcium (CAC) scoring has historically been used in asymptomatic, intermediate risk patients for assessment of cardiovascular risk. It has been shown to be a powerful marker of cardiovascular risk in intermediate risk populations and provides incremental value beyond traditional Framingham risk factors, C-reactive peptide, and carotid intimal medial thickness for prediction of cardiovascular events and

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mortality.[4] The detection of an elevated coronary calcium score has been shown to have favorable effects on both initiation of preventive medical therapies, and also on downstream clinical events as seen in the St. Francis Heart Study.[5-7] There is limited data, however, on calcium scoring in symptomatic populations, but a zero calcium score appears to have excellent negative predictive value in ruling out acute coronary syndromes in patients presenting with acute chest pain.[8] For example, it is notable that in the Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT) trial, only one patient of 368 low-intermediate risk patients presenting to the emergency department had an acute coronary syndrome with zero calcium score.[9]

As coronary artery calcification is only one manifestation of arterial calcification, recent interest has arisen in establishing the role that thoracic aortic calcification plays in risk factor assessment and cardiac outcomes. Prior studies have found a strong correlation between CAC and thoracic aortic calcium (TAC). TAC can predict cardiac events, albeit not as robustly as CAC. Interestingly, in the MESA cohort TAC was found to be an independent predictor (beyond CAC) of future coronary events in women but not in men.[10]

A theoretical advantage of hybrid PET/CT cardiac imaging is that it could provide comprehensive data regarding CFR, CAC, and TAC in addition to data on the extent and severity of myocardial ischemia. It is conceivable that combining anatomical information (CAC and TAC) with comprehensive functional information (MPI, CFR, and stress LVEF) may increase diagnostic test accuracy, improve risk stratification, decrease downstream testing by improving selection criteria for revascularization, and help with prediction of clinical outcomes. However, limited evidence is available on whether such a hybrid approach can result in improvement in risk classification and downstream clinical outcomes. Furthermore, the relationship among CAC, TAC, and ^{82}Rb PET-derived CFR and whether they truly represent independent information has been incompletely explored in patients with abnormal myocardial perfusion.[11]

Therefore, the work by Kim and colleagues in this issue of the *Journal* presents itself at an opportune time. Kim and colleagues performed a retrospective analysis of 75 patients with intermediate risk of coronary artery disease referred for pharmacologic ^{82}Rb PET/CT MPI on clinical grounds. Their main purpose was to examine the associations and the predictive capacity of qualitative myocardial ischemia, CFR, CAC, and TAC. *The key findings of their study are that*: (1) CAC correlated with TAC, (2) CFR was inversely related to both CAC and TAC, and (3) CFR was the most powerful predictor of an ischemic MPI study.

Kim et al furthermore determined the diagnostic performance of CAC, TAC, and CFR for detection of ischemic burden on myocardial perfusion imaging. They observed a correlation between each of these three parameters and the presence of ischemia. This confirms the results of prior studies that have examined the relationship between CAC and ischemia on MPI, but contributes additional knowledge to the literature regarding the strength of correlation between TAC and ischemic MPI. Intuitively, the higher CAC and TAC would identify a greater burden of CAD and therefore, a higher chance for an obstructive lesion causing myocardial ischemia. Other key findings include the high independent NPV of CAC (96% for CAC < 100), TAC (94% for TAC < 250), and CFR (95% for CFR > 1.94) for predicting the absence of moderate-severe ischemia. Overall, while the observed association between elevated CAC and myocardial ischemia is consistent with prior larger scale studies, sensitivity and specificity of each of these parameters for detection of ischemia were only modest, and positive predictive value was poor in this study. Kim et al additionally observed that CFR correlates strongly with the presence of ischemia on MPI, a finding that adds to a growing evidence base for CFR measures derived from ^{82}Rb PET MPI.

One important question that was not addressed by this study, however, is whether the combination of calcium data to MPI data provides incremental value for prediction of angiographic stenosis over and above the measurement of either of these imaging parameters on their own. Moreover, the question remains whether a hybrid approach combining anatomic and functional parameters actually improves patient management and results in reduction of downstream cardiovascular events. Indeed, the authors' work provides additional impetus for a large-scale prospective comparative effectiveness imaging trial analogous to the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in CAD (SPARC) trial and ongoing PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial to specifically evaluate the potential benefit of hybrid anatomical/functional imaging using calcium scores and CFR in conjunction with PET MPI compared to conventional strategies.[12] The extreme case would be evaluating the combination of PET/CFR and coronary CTA, which would provide superior anatomic information regarding the coronary arteries over calcium scoring. However, with each additional test component, we need to consider potential risks and consequences including radiation exposure, contrast toxicity, downstream testing for incidental findings, and over-all cost efficacy.

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