EDITORIAL

Direct myocardial ischemia imaging with exercise ^{18}FDG

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Myocardial perfusion imaging (MPI) using SPECT or PET tracers has dominated the field of non-invasive evaluation and work-up of patients with known or suspected coronary artery disease (CAD).[1-3] This technique has been around for over four decades now. This longevity of MPI is perhaps the most important testimonial of the versatility, robustness, reliability, and safety of this technique. Constant refinements, innovations, research and development in the fields of perfusion tracers, pharmacological stress agents, instrumentation and software for analysis, and interpretation have contributed to MPI remaining relevant to the rapidly progressing field of CAD. Databases including hundreds of thousand of patients spanning over several decades have been used to probe its diagnostic and prognostic utility in a variety of patient populations.[3,4] MPI provides very powerful diagnostic as well as prognostic information in a very wide spectrum of patients: patients with clinically suspected CAD, patients with established CAD, patients with recent or prior myocardial infarction, patients who have undergone revascularization procedures, patients with heart failure as well as patients with multiple co-morbidities and organ failures and those unable to exercise.[3,4] The success of scintigraphic MPI has encouraged all other imaging modalities: echocardiography, magnetic resonance imaging, and CT angiography to follow its footprint to develop their MPI techniques.[5,6] Although all of these imaging modalities have succeeded to some extent in developing techniques for MPI, yet these techniques remain somewhat cumbersome, complicated, technically challenging, limited only to very carefully selected patient populations and are far from being ready for routine clinical use. But most importantly, none of these techniques are currently able or likely to overcome the limitations of scintigraphic MPI.

Although, the sensitivity and specificity of scintigraphic stress-rest MPI are good, yet they are not ideal. The sensitivity of MPI for the detection of individual vessels with significant CAD is suboptimal. Artifacts due to attenuation, tracer activity in the adjoining organs and other technical factors remain important causes for suboptimal image quality and false positive studies. So what else can be done to overcome these limitations?[7] Perhaps, it is time to think beyond the paradigm of MPI: After all, MPI is based upon the concept of imaging myocardial perfusion at rest or baseline and again after maximum coronary hyperemia induced by exercise or pharmacological stress. The areas of relative hypoperfusion on stress in comparison to rest represent myocardial ischemia. So why not image myocardial ischemia directly?[8] In fact, a major strength of scintigraphic imaging is its ability to image a very wide array of biological, metabolic, and biochemical processes, cell membrane receptors and transporters in intact organisms under various physiological conditions. This requires an intricate understanding of the biological process under evaluation and development and radiolabeling of suitable ligands to investigate this process. Using this principle, investigators have been able to image apoptosis, necrosis, angiogenesis, matrix metalloproteinases, and gene expression in experimental animal models as well as in human.[9-15] The same principles can be applied for myocardial ischemia imaging as well. Myocardial

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ischemia is associated with very distinctive and profound changes in local and regional pH, pO_2, substrate utilization, and metabolism. Some of these changes are evanescent, whereas some others persist long enough to facilitate imaging. Normal myocardium can utilize a wide spectrum of substrates for energy production such as free fatty acids, glucose, lactate, ketone bodies, amino acids, etc. with the free fatty acids and glucose being the predominant components. The relative proportion of free fatty acids and glucose uptake and utilization varies with their blood levels, metabolic milieu (fed or fasting state), insulin, and catecholamine levels.[16-18] Free fatty acid metabolism is obligatory aerobic. Glucose metabolism is a two-stepped process, the first step (glycolysis) where glucose is converted to pyruvate is anaerobic, whereas the second step whereby pyruvate enters Kreb's cycle and is metabolized to carbon dioxide and water is aerobic. Under normal conditions, free fatty acids are the predominant source of energy production, but with the onset of myocardial ischemia, free fatty acid uptake diminishes substantially, and glycolysis becomes the predominant source of energy. However, glycolysis being a relatively inefficient source of energy production, only a multifold increase in glucose uptake and glycolysis can sustain ischemic myocardium. This is mediated by an immediate translocation of highly specialized glucose transporters (GLUTs) from cytosol to the cell membrane with the onset of ischemia. Interestingly, once translocated to the cell membrane, GLUTs persist in the cell membrane for several hours or even longer even after the resolution of ischemia.[19] Therefore, the metabolic accompaniments of myocardial ischemia can potentially be used as surrogates for imaging myocardial ischemia. The ultimate success of imaging a biological phenomenon by scintigraphic imaging is dependent upon a number of factors such as the abundance of the target signal, specificity of this signal for that particular biological phenomenon, duration for the expression of this signal, and availability of suitable and specific ligands or probes and radiolabeling of such probes with commonly available radiotracers. Whereas, any number of factors may preclude a successful and clinically usable and relevant imaging of a biological phenomenon, it is definitely worth a try. ^{18}FDG, a radiolabeled glucose analogue has been evaluated is several relatively small experimental animal as well as clinical studies as a potential myocardial ischemia imaging agent with highly encouraging results.[20-32] Although earlier studies indicated its feasibility, the clinical potential of this technique was appreciated only after it was possible to precisely localize any observed or perceived increased ^{18}FDG uptake to the myocardium either by simultaneous perfusion and ^{18}FDG imaging using PET imaging capable gamma cameras or by PET-CT imaging.[24,28]

In this issue of the journal Sasikumar et al have presented their preliminary data on successful use of ^{18}FDG PET-CT for imaging of exercise-induced myocardial ischemia.[33] They performed exercise-rest SPECT MPI and exercise ^{18}FDG PET-CT imaging and coronary angiography in 45 patients with suspected CAD. Of these, 27 patients had $\geq$50% narrowing of $\geq$1 coronary artery and the remaining 18 had no significant CAD. The overall sensitivity and specificity of MPI were 56% and 72% compared to 96% and 44% for exercise ^{18}FDG ($P = .0004$). This difference narrowed when the threshold of significant CAD was changed to $\geq$70 narrowing (MPI sensitivity and specificity 90% and 72% vs 100% and 44%, respectively, for exercise ^{18}FDG, $P =$ ns). Furthermore, the sensitivity of MPI for the detection of individual vascular territories with $\geq$50% narrowing was 24% for LAD, 27% for LCx, and 86% for the RCA, whereas the corresponding sensitivities for exercise ^{18}FDG were 71%, 80% and 57%, respectively.

Despite the limitations of relatively small sample size, this study adds significantly to the extant literature on exercise ^{18}FDG for the detection of CAD. Once again, this study confirms the previous observations of significantly higher sensitivity of exercise ^{18}FDG for the detection of CAD compared to exercise-rest MPI. However, this study also raises several important questions and issues. The overall sensitivity of exercise MPI was substantially lower compared to the published literature in this study. The authors have not provided any explanation for this. A low specificity of exercise ^{18}FDG (44%) is also very concerning. Notably 10/18 patients with no significant CAD had increased regional myocardial ^{18}FDG uptake. This requires a very careful thinking. A small proportion of these false positive cases also had reversible perfusion abnormalities, and/or ST segment depression on exercise. Nine of the ten patients had hypertension. This may highlight the limitations of using 50% luminal narrowing on coronary angiography as the gold standard for comparing other diagnostic modalities. Nevertheless, this still indicates an unacceptably low specificity of exercise ^{18}FDG imaging. Interestingly, nearly all these false positive exercise ^{18}FDG studies were due to increased ^{18}FDG uptake in the lateral wall. The authors performed a semi-quantitative visual scoring of the intensity of myocardial ^{18}FDG uptake, similar to what was performed by Dou et al while performing ^{18}FDG SPECT imaging.[29] They did not perform quantitative imaging readily available with PET imaging. Perhaps, a simple standardized uptake value (SUV) may be able to define a threshold

above which the uptake in the lateral wall is indeed indicative of ischemia.

Despite the limitations of a small sample size and a lack of quantitative analysis, the current study greatly enhances our understanding of the concept of direct myocardial ischemia. Direct myocardial ischemia imaging with exercise ^{18}FDG can be a very useful and highly promising diagnostic option, at least in a subgroup of patients with CAD. Perhaps, it is the right time for considering a large multicenter study to evaluate the role of exercise ^{18}FDG imaging in the management of patients with CAD. A lot more information is needed about its specificity and any confounding effects of the presence of hypertension, diabetes, other myocardial diseases, and treatment with cardiac as well as noncardiac medications. An ability to image myocardial ischemia does indeed represent a unique and major strength of the molecular cardiovascular nuclear imaging surpassing all other imaging modalities.

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