Cardiac ^{18}F -FDG imaging for direct myocardial ischemia imaging

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Coronary artery disease (CAD) continues to be the leading cause of death worldwide.¹ There is an ever expanding armamentarium of modalities to diagnose CAD. Patients with acute coronary syndrome or those with a very high clinical suspicion of obstructive CAD are usually best served by invasive angiography of the coronary arteries, whereas non-invasive imaging modalities are preferred in patients with a low to intermediate probability of CAD. Multiple non-invasive imaging modalities are available and there is no clear consensus about the best approach for the non-invasive evaluation of patients with suspected CAD.²

Non-invasive anatomic testing with coronary computed tomography angiography (CCTA) is being increasingly used to identify and define the extent and severity of CAD, and also provides useful information about plaque composition and high-risk features. However, CCTA imaging is usually suboptimal in patients with uncontrolled heart rate, extensive coronary artery calcifications, prior coronary stents and bypass grafts, and may adversely affect renal function in patients with pre-existing renal disease. Fractional flow reserve with

computed tomography (CT-FFR) tries to estimate the lesion specific ischemia³, but lacks widespread clinical use till date. The hemodynamic significance of intermediate coronary artery lesions seen on CCTA remains uncertain, calling for the need of functional ischemia testing.

Hemodynamically significant coronary artery stenosis results in the myocardial ischemic cascade which proceeds from subclinical to clinical manifestations (Figure 1). Coronary hypoperfusion leads to changes in myocardial metabolism, followed by diastolic dysfunction, systolic dysfunction, and ECG abnormalities, before clinical presentation with anginal symptoms.^{4,5} Ischemic cascade provides the rationale for the development of various non-invasive modalities for diagnosing CAD. Coronary hypoperfusion and metabolic changes are the earliest events in the cascade, and therefore stress-rest myocardial perfusion imaging (MPI) and myocardial metabolism-based ischemic tests are expected to have the highest sensitivity. Wall motion abnormality-based stress imaging like exercise or dobutamine echocardiography follow in sensitivity.^{5,7} As the ischemic cascade progresses, ECG abnormalities manifest. Stress ECG abnormalities have a relatively low diagnostic accuracy due to several factors including resting ECG abnormalities and treatment with several pharmacotherapeutic agents.^{5,8} Addition of cardiac imaging improves the diagnostic performance of exercise ECG.

Radionuclide MPI is the most widely studied and clinically used non-invasive modality for the diagnosis and risk stratification of patients with known or suspected CAD. Conventional testing with ^{201}Tl or $^{99\text{m}}\text{Tc}$ -labeled perfusion tracers or PET perfusion tracers

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Figure 1. The Ischemic Cascade-Progressive myocardial oxygen supply and demand mismatch from coronary hypoperfusion results in a series of events, starting with metabolic abnormalities, sequentially followed by diastolic dysfunction, systolic dysfunction (wall motion abnormalities), ECG abnormalities, and angina.

depends upon flow heterogeneity induced by exercise or pharmacologic stress. Myocardial regions receiving diminished blood supply show reduced radiotracer uptake than the normally perfused myocardial regions. However, this “cold spot” imaging technique has several limitations. Although the sensitivity and specificity are high, they are far from being perfect. The sensitivity of MPI for detecting individual coronary vessels with significant obstructive disease is low. Perfusion abnormalities may be relatively unimpressive or even absent in patients with multi-vessel CAD, due to balanced ischemia. Artifacts due to attenuation, extracardiac radiotracer uptake, scatter, partial volume effect, and relatively poor spatial resolution are some of the technical issues that limit an accurate interpretation of MPI studies. These drawbacks of MPI warrant consideration of alternative modalities for direct imaging of myocardial ischemia.⁹⁻¹⁴

Unique changes in myocardial metabolism with the onset of myocardial ischemia make this an interesting target for direct myocardial ischemia imaging.^{10,11,15-20} Myocardium has an extremely high metabolism to generate energy for its pumping function that requires a constant supply of oxygen and substrates. Normal myocardium preferentially uses free fatty acids over glucose as the source of energy production. The proportion of their relative contribution to energy production is variable and varies with the metabolic milieu: fasting vs fed state, insulin level, circulating catecholamines, and most importantly oxygen availability. In the fasting state, glucose and insulin levels are low, while free fatty acid levels are high; hence, free

fatty acids constitute the majority of energy production, with a low glucose uptake by the myocardium. In contrast, after a carbohydrate-rich diet, the levels of blood glucose and insulin are high; therefore, the myocardial glucose uptake is higher and glucose contributes to a higher percentage of energy production. Exercise increases catecholamines and free fatty acid levels, and a higher fraction of energy is from free fatty acid metabolism. However, myocardial ischemia results in profound changes in substrate utilization. Oxidation of free fatty acids, being an obligatory aerobic process, is extremely sensitive to low oxygen availability. Myocardial ischemia results in an impairment of free fatty acid uptake and oxidation. Glucose metabolism is a 2-step process: initial glycolysis is anaerobic that occurs in the cytosol, and results in conversion of glucose to pyruvate. In the anaerobic milieu, pyruvate is converted to lactate and is released from the cells. However, under normoxia, pyruvate gets converted to acetyl co-enzyme A, and enters the Krebs cycle in the mitochondria which is an obligatory aerobic process resulting in its conversion to water and carbon dioxide after a chain of oxidative reactions. In the setting of myocardial ischemia, glycolysis is the predominant source of energy production. But glycolysis is inefficient and produces only 2 molecules of ATP per molecule of glucose (compared to 30 molecules of ATP per molecule of glucose through oxidative metabolism). Hence, ischemic myocardium needs a very large supply of glucose and this is brought on by the immediate translocation of specialized glucose transporters (GLUT-4 and GLUT-1) from the sarcoplasm to the sarcolemma. These glucose transporters function independent of insulin, and are highly efficient in transporting glucose across the cell membrane. It is also interesting that the impairment in free fatty acid metabolism, overexpression of GLUT receptors, and increased glucose uptake persist for some time even after the resolution of ischemia, thereby providing a metabolic memory of myocardial ischemia. So, a significant metabolic differential exists between the ischemic and the normal myocardium on exercise in fasting state. Deoxyglucose is a glucose analog which enters the glycolytic pathway similar to glucose. Deoxyglucose gets phosphorylated to deoxyglucose-6-phosphate by the enzyme hexokinase, but unlike glucose does not undergo any further phosphorylation and is trapped in the cell. ^{18}F Fluorine-labeled fluorodeoxyglucose (^{18}F -FDG) is classically used to image malignant tumors and to look for myocardial viability^{21,22}. However, ^{18}F -FDG is also promising as a “hot spot” imaging agent for exercise-induced myocardial ischemia.

Camici et al²³ reported increased myocardial ^{18}F -FDG uptake in 9 of 10 patients in regions with decreased

exercise ^{82}Rb uptake. Abramson et al²⁴ noted ^{18}F -FDG uptake in 8 out of 9 women in myocardial segments with reversible perfusion defects. Araujo et al²⁵ found significantly increased ^{18}F -FDG uptake after dipyridamole in diseased vascular territories. Abbott et al²⁶ observed high ^{18}F -FDG uptake in one third of vascular territories with reversible perfusion abnormalities when ^{18}F -FDG was injected 1-1.5 hour after treadmill exercise. All of these studies used PET imaging. He et al²⁷ performed simultaneous myocardial perfusion and ischemia imaging by injection of ^{18}F -FDG and $^{99\text{m}}\text{Tc}$ -sestamibi in 26 patients with suspected CAD and without prior myocardial infarction, using a SPECT camera capable of imaging PET as well as SPECT tracers to permit simultaneous perfusion and ischemia imaging. Out of the 22 patients with at least 50% narrowing in at least 1 coronary artery, 18 had perfusion abnormalities on MPI (sensitivity 82%), while 20 had abnormally high ^{18}F -FDG uptake (sensitivity 91%). Myocardial perfusion abnormalities were observed in 25 vascular territories out of total 51 vessels with at least 50% narrowing (sensitivity 49%), whereas increased ^{18}F -FDG uptake was viewed in 34 vascular territories (sensitivity 67%, $p < 0.01$). Arun et al²⁸ performed exercise-rest SPECT MPI and exercise ^{18}F -FDG PET imaging on different days in 45 patients with suspected CAD and found similar results. Dou et al²⁹ performed exercise $^{99\text{m}}\text{Tc}$ -sestamibi and ^{18}F -FDG imaging, followed by ^{18}F -FDG and $^{99\text{m}}\text{Tc}$ -sestamibi perfusion imaging at rest, 24 hours after exercise. Of the 18 patients with significant CAD on coronary angiography, 15 (83%) showed increased regional ^{18}F -FDG uptake after exercise, whereas only 11 (61%) had perfusion abnormalities. Out of the 15 patients with high ^{18}F -FDG uptake after exercise, 8 (53%) had no ^{18}F -FDG uptake, 5 (33%) had somewhat reduced ^{18}F -FDG uptake, and 2 (13%) had persistent ^{18}F -FDG uptake on rest imaging 24 hours later. In another study, Dou et al³⁰ performed two ^{18}F -FDG PET imaging sessions within two hours after a single administration of ^{18}F -FDG (dual-time-point imaging), and an exercise test after the first imaging. $^{99\text{m}}\text{Tc}$ -sestamibi was injected at peak exercise, and MPI was performed after ^{18}F -FDG imaging. Based on the classification of the ^{18}F -FDG distribution pattern, exercise ^{18}F -FDG was found to have high sensitivity of 81% (compared to MPI sensitivity of 65%), and high specificity (95%).

In the study published in the current issue of this journal, Zampella et al³¹ aimed to assess the utility of ^{18}F -FDG cardiac PET imaging after dobutamine stress echocardiography (DSE) in predicting myocardial ischemia on ^{82}Rb -PET imaging. Forty-one patients with suspected CAD underwent cardiac rest-stress ^{82}Rb -PET, and DSE followed by ^{18}F -FDG cardiac PET within 7

days. Ischemia was detected in 22 (54%) patients on DSE, 21 (51%) patients on ^{18}F -FDG PET, and 20 (49%) patients on ^{82}Rb -PET imaging. ^{18}F -FDG PET was found to be a statistically significant predictor of ischemia on ^{82}Rb -PET on both univariate and multivariate analysis. Similar result was also observed on analysis by vascular territory. The authors concluded that ^{18}F -FDG PET can be used after DSE and provides incremental value to the latter in the diagnosis of stress-induced myocardial ischemia. Previous studies used ^{18}F -FDG after exercise stress or vasodilator agents for myocardial ischemia imaging. This is the first study to describe the use of ^{18}F -FDG for myocardial ischemia imaging after dobutamine stress. While the study design is straightforward, study population is small, variables to compare are relatively few, and all three diagnostic tests yielded very comparable findings, yet for unclear reasons, the authors chose a relatively complex approach for analyzing and describing their results. They chose to determine the incremental value of dobutamine stress FDG-PET imaging over DSE for predicting perfusion abnormalities observed on ^{82}Rb -PET imaging. The study results and discussion are enveloped in the predictive models using univariate and multivariate analysis. The results when interpreted in light of the previous studies suggest that stress ^{18}F -FDG imaging (whether using exercise or pharmacological stress) is highly sensitive and a useful modality for diagnosing myocardial ischemia. The addition of stress echocardiography to dobutamine ^{18}F -FDG PET imaging did not add any utility in the detection of myocardial ischemia in this study. It would be prudent to consider exercise ^{18}F -FDG imaging for patients who are able to exercise, and dobutamine stress ^{18}F -FDG imaging in those unable to exercise, but otherwise suitable for dobutamine stress.

The advantages of myocardial ischemia imaging with ^{18}F -FDG over rest-stress MPI are quite evident. The sensitivity of ^{18}F -FDG myocardial ischemia imaging is higher than stress-rest MPI for the diagnosis of CAD. It is also more sensitive than MPI for detecting ischemia in the individual coronary vascular territories, which highlights its utility in patients with multivessel CAD where abnormally high ^{18}F -FDG can be seen in all affected vascular territories. Differentiation of inferior wall perfusion abnormalities from diaphragmatic attenuation artifacts can at times be challenging on MPI. However, uptake of ^{18}F -FDG due to inferior wall ischemia is not affected by the diaphragmatic attenuation. Furthermore, stress ^{18}F -FDG imaging reduces the radiation dose and imaging time.

However, several unresolved issues with ^{18}F -FDG for myocardial ischemia imaging were not addressed by this study.^{10,18-20} Firstly, how to distinguish ischemic ^{18}F -FDG myocardial uptake from non-specific uptake by

the normal myocardium that can be observed in some cases? Regional variability of myocardial ^{18}F -FDG uptake has also been reported in the fasting state.³² These issues may be resolved by implementing strict patient preparation successfully used in cardiac inflammation imaging with ^{18}F -FDG.³³ Secondly, would ^{18}F -FDG imaging for myocardial ischemia be useful in diabetic patients? Due to the complexity of glucose metabolism in diabetics, they are not included in some of the studies. But it has been postulated that ischemia triggered increased myocardial glucose uptake is independent of insulin triggered pathways.³⁴ This suggests that ischemic myocardium would have high ^{18}F -FDG uptake in diabetic patients similar to non-diabetic subjects. Thirdly, there are questions about patient preparation prior to ^{18}F -FDG myocardial ischemia imaging. In contrast to ^{18}F -FDG imaging for myocardial viability, the aim of ischemia imaging is to suppress glucose uptake by the normal myocardium so that only the ischemic myocardium lights up. Low carbohydrate diet and prolonged fasting should be followed prior to stress ^{18}F -FDG imaging. It remains unclear if left ventricular hypertrophy, and other myocardial diseases and medications confound the results of ^{18}F -FDG myocardial ischemia imaging. Additional studies with larger number of patients are required to further evaluate the role of stress ^{18}F -FDG myocardial ischemia imaging in clinical practice.

Author contributions

All authors contributed to the manuscript.

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Declarations

Disclosures

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Ethical approval

Not applicable.

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Not applicable.

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