Reviews

Direct Myocardial Ischemia Imaging: a New Cardiovascular Nuclear Imaging Paradigm

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ABSTRACT

Myocardial perfusion imaging (MPI), using radiotracers, has been in routine clinical use for over 40 years. This modality is used for the detection of coronary artery disease (CAD), risk stratification, optimizing therapy, and follow-up of patients with CAD. Molecular cardiovascular imaging using targeted radiotracers provides a unique opportunity for imaging biochemical and metabolic processes, and cell membrane transporter and receptor functions at a cellular and molecular level in experimental animal models as well as in humans. Cardiac imaging using radiolabeled free fatty acid analogues and glucose analogues enable us to image myocardial ischemia directly as an alternative to stress-rest MPI. Direct ischemia imaging techniques can avoid and overcome some of the limitations of standard stress-rest MPI. This article describes recent studies using ^{18}F-fluorodeoxyglucose (^{18}FDG) for myocardial ischemia imaging.

Introduction

The diagnostic evaluation and management of patients with coronary artery disease (CAD) has undergone major new advances in the last few decades. These new developments have resulted in a dramatic decrease in the morbidity and mortality from CAD. Routine availability of safe, simple and reliable noninvasive modalities for the diagnosis, risk stratification, and follow-up of a wide range of patient populations with established or suspected CAD has greatly facilitated the development and appropriate use of a very wide array of therapeutic options. Myocardial perfusion imaging (MPI) using radiotracers is a notable development in this field.[1–3] Introduction of a new generation of radiotracers for MPI, agents for pharmacological stress test, and advances in gamma imaging cameras and image processing have resulted in its wide clinical acceptance.[4–8] MPI has played an important role in large clinical trials, which resulted in the evolution of the current therapy of CAD.[1,8] Despite all of these strengths, MPI does suffer from several drawbacks. The sensitivity and specificity of MPI for the diagnosis of CAD are relatively suboptimal.[4] Furthermore, the sensitivity of MPI for detecting individual coronary vessels with significant obstructive disease is quite low. Abnormalities on MPI can sometimes be unimpressive or even absent despite the presence of significant underlying multivessel disease. Attenuation artifacts, artifacts due to extracardiac radiotracer activity, and technical issues are relatively common. These artifacts are sometimes indistinguishable from true perfusion abnormalities. These artifacts cannot be adequately corrected or prevented using current technology. Some of these drawbacks are as a consequence of the "cold-spot" nature of this imaging, where the target abnormality (myocardial ischemia) appears as an area of deficient or reduced radiotracer uptake. A wide variety of artifacts can also mimic cold-spot abnormality. These drawbacks of MPI warrant consideration of alternative imaging modalities for detecting CAD.[4,9,10]

Molecular Cardiovascular Imaging

The repertoire of radionuclide imaging includes tools for noninvasive imaging of biochemical and metabolic phenomena, cell membrane receptors, and transporters in humans. This permits the development of highly innovative, targeted molecular imaging techniques for clinical use. Molecular imaging of the myocardium with ischemia can overcome the drawbacks of MPI.[10,11] The Table 1 provides a list of the established nuclear imaging modalities as well as the investigational modalities in various stages of development. Molecular imaging techniques are under development for studying myocardial metabolism and

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Table 1. Established and Experimental/Investigational Scintigraphic Cardiovascular Imaging Techniques

Indication	Technique	Radiotracers	Current Status
Established nuclear imaging techniques			
Myocardial perfusion imaging	SPECT	Tl-201	Less commonly used
		^{99m}Tc-sestamibi (Cardiolite)	In extensive clinical use
		^{99m}Tc-tetrofosmin (Myoview)	In extensive clinical use
	PET	^{82}Rb	In frequent clinical use
		^{13}N ammonia, ^{15}O-water	Rarely used
		^{18}F-flupiridaz	Investigational, not FDA approved
Cardiac adrenergic neuronal imaging	SPECT	^{123}I-MIBG	Only recently FDA approved
Myocardial necrosis imaging	SPECT	^{111}In-antimyosin	Not in clinical use anymore
Experimental/investigational nuclear imaging techniques			
Myocardial apoptosis imaging	SPECT	^{99m}Tc-Annexin	Investigational, not FDA approved
Myocardial necrosis imaging	SPECT	^{99m}Tc-glucarate	Investigational, not FDA approved
Fatty acid metabolism imaging	SPECT	^{123}I-BMIPP	Investigational, not FDA approved
Glucose metabolism/imaging, myocardial ischemia imaging	PET	^{18}FDG	Investigational
Vascular calcification imaging	PET	^{18}F-NaF	Investigational, not FDA approved
Hypoxia imaging	PET	^{18}F-fluoromisonidazole	Investigational, not FDA approved

Abbreviations: ^{18}FDG, ^{18}F-fluorodeoxyglucose; ^{99m}Tc, technetium-99 m; ^{123}I-BMIPP, ^{123}I-labeled β-methyl iodophenyl pentadecanoic acid; FDA, Food and Drug Administration; PET, positron-emission tomography; SPECT, single-photon emission computed tomography.

imaging atheroma, apoptosis, and angiogenesis. This review is focused on molecular imaging techniques for imaging myocardial ischemia.

Myocardial Ischemia Imaging

Direct imaging of myocardial ischemia can be accomplished by targeting regional myocardial hypoxia, which parallels regional myocardial ischemia, or by targeting metabolic accompaniments of myocardial ischemia, which can act as signature of myocardial ischemia.

Hypoxia Imaging

The partial pressure of oxygen, or oxygen tension (pO_2), inside the cells in normally oxygenated and adequately perfused tissues ranges from 30 to 50 mm Hg. The pO_2 inside the hypoxic cells is substantially lower. pO_2 in the hypoxic tumors can be as low as 3 to 10 mm Hg.[12,13] Nitroimidazoles are compounds that have a core nitroimidazole ring with an NO_2 moiety and varying side chains.[12,13] Nitroimdazoles are freely diffusible across the cell membranes. Inside the cells with normal pO_2, nitroimdazoles undergo a reversible reduction to a reduced moiety (NO_2^-). The reduced and nonreduced moieties exist in equilibrium. Under hypoxia, reduced nitroimidazole undergoes further reduction to NO_2^{--} moiety. This reaction is irreversible. NO_2^{--} is a highly reactive species that reacts indiscriminately with intracellular macromolecules and binds with them. Thus, NO_2^{--} is trapped inside the hypoxic cells. Several radiolabeled nitroimidazole derivatives have been used for imaging tissues or organs with hypoxia.[12,13,18] F-fluoromisonidazole is a commonly used positron-emission tomography (PET) imaging agent for imaging tumors that are hypoxic.[12,13] These compounds can be used for imaging tumor hypoxia, but they are not suitable for imaging stress-induced myocardial ischemia because of the evanescent nature of the later phenomenon.

Metabolic Imaging

An understanding of myocardial energetics and metabolism can provide imaging tools for targeting myocardial ischemia. Cardiac metabolism and its alteration in the ischemic milieu provides possible targets for imaging exercise-induced myocardial ischemia.[13–22] Myocardium has an extremely high metabolic demand to meet the energy needs of its contractile function. Approximately 90% of the cardiac energy requirement is for its pumping function. Myocardial oxygen consumption is in the range of 8 to 15 mL/min/100 g at rest. This increases to 60 to 70 mL/min/100 g of tissue at a high workload.[22] The heart requires a steady supply of energy substrates and oxygen for supporting its metabolism. Normal myocardium extracts and metabolizes a variety of energy substrates such as glucose, pyruvate, lactate, free fatty acids, ketone bodies, and amino acids. Of these substrates, free fatty acids and glucose are the largest substrates for energy production (Figure 1). The relative uptake and proportional contribution of these substrates to cardiac metabolism varies widely and depends on a multitude of factors such as a fed or a fasting state, plasma insulin and catecholamine levels, oxygen

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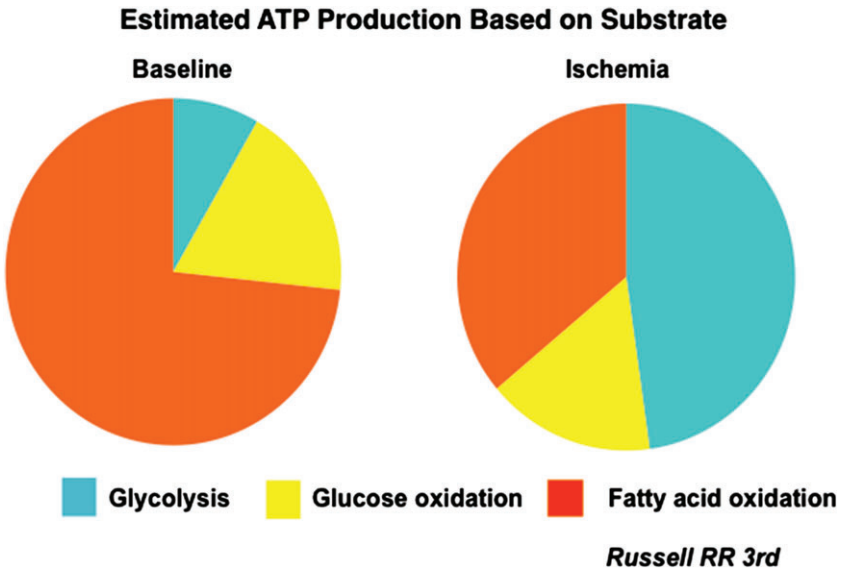

Figure 1. A diagrammatic representation of the relative proportion of myocardial substrate utilization. Under resting conditions, fatty acid metabolism contributes to nearly 70% to 75% energy generation, whereas the remaining comes from glucose metabolism (approximately 8% from glycolysis and 18% from oxidative metabolism). Myocardial substrate utilization changes dramatically with the onset of myocardial ischemia, with glycolysis contributing to nearly 50% of the energy production and a significant reduction in fatty acid uptake and metabolism. Courtesy of Dr. Raymond R. Russell, III, Yale University School of Medicine. Abbreviations: ATP, adenosine triphosphate.

availability, and the circulating levels of these substrates in the plasma. While fasting, the insulin and glucose levels are low, and free fatty acid levels are high. Therefore, under conditions of fasting, free fatty acids are the main contributors to energy production. The contribution of glucose metabolism is relatively low. In contrast, blood glucose and insulin levels rise following a carbohydrate-rich meal. Therefore, glucose contributes to a greater fraction of energy production in the postprandial state. Exercise increases catecholamines and free fatty acid levels, and free fatty acids contribute to a higher proportion of metabolism during exercise. However, free fatty acid metabolism is an obligatory aerobic and is highly sensitive to reduced oxygen tension. Myocardial ischemia profoundly alters myocardial metabolism and substrate utilization (Figure 1). The ischemia-induced suppression of free fatty acid metabolism persists significantly longer than the duration of ischemia. This provides a signature of myocardial ischemia. Glucose metabolism is a 2-step process: glycolysis and oxidative phosphorylation. The first step, glycolysis, is an anaerobic process that converts 1 molecule of glucose to 2 molecules of pyruvate in the cytosol. Pyruvate is reduced to lactate under hypoxia. Under normal oxygen tension, pyruvate enters the Krebs' cycle, an obligatory aerobic process. This process occurs in the mitochondria and through a long sequence of oxidative reactions, pyruvate is converted to carbon dioxide and water. Glycolysis becomes the predominant source of energy production, which sustains the myocardium under hypoxia or ischemia. However, glycolysis is a relatively inefficient source of energy production. One mole of glucose generates only 2 net moles of adenosine triphosphate (ATP) through glycolysis. In comparison, oxidative phosphorylation yields approximately 38 moles of ATP. Ischemic myocardium, therefore, requires a large supply of glucose for surviving through glycolysis. An increased glucose uptake by the ischemic myocardium is facilitated by an immediate translocation of highly specialized and efficient glucose transporters GLUT-4 and GLUT-1 (GLUT) from cytosol to the sarcolemma with the onset of ischemia.[19] An interesting feature of this process is that once GLUT transports are translocated to the sarcolemma, they persist in the sarcolemma significantly longer than the duration of myocardial ischemia.[19] Thus, the glycolysis as a signature of myocardial ischemia persists longer than the duration of actual ischemia, providing us with an opportunity to image myocardial ischemia.

The analogues of free fatty acids and glucose can be used for imaging myocardial ischemia after suitably radiolabeling them. The radiolabeled free fatty acid analogues show a reduced uptake (cold spot), whereas radiolabeled glucose analogues show an enhanced uptake (hot spot) in myocardial regions following an episode of myocardial ischemia. These metabolic changes are instantaneous with the onset of myocardial ischemia, but persist for a significantly longer than the duration of myocardial ischemia. This article reviews the concept and basic principles of scintigraphic imaging of myocardial ischemia imaging.

^{18}F-Fluorodeoxyglucose for Imaging Myocardial Ischemia

Myocardial ischemia is associated with a significant and persistent upregulation of regional glucose uptake in comparison to the normally perfused myocardium.[15–19] Normal myocardium has a lower glucose uptake on exercising under fasting milieu and a higher uptake of free fatty acids. Therefore, a significant metabolic differential separates the normal from the ischemic myocardium. Deoxyglucose is a glucose analogue, and tracks cellular glucose uptake and initial metabolic steps in the tissues.

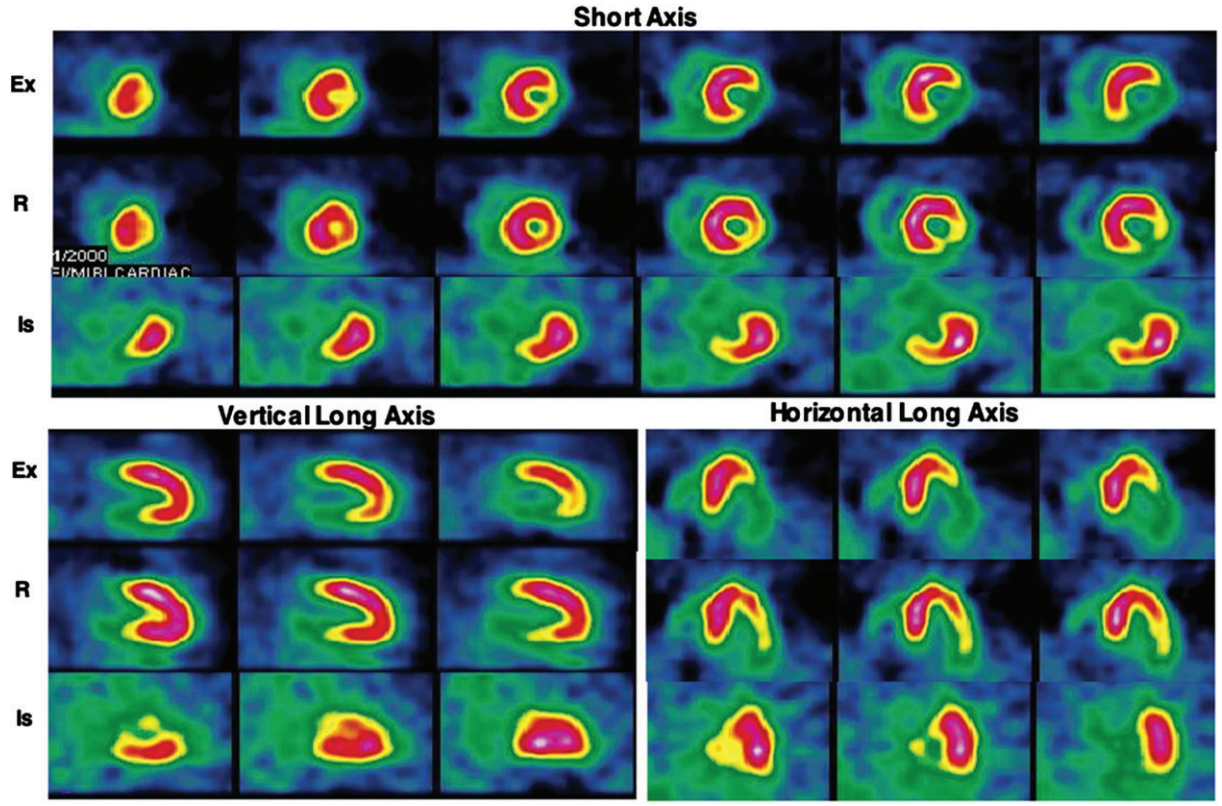

Figure 2. Representative exercise (Ex) and rest (R) technetium-99 m-sestamibi and exercise ^{18} F-fluorodeoxyglucose (^{18}FDG) images of a patient with angina in the short axis, and vertical and horizontal long axes. This patient had no history of myocardial infarction. A large area of partially reversible perfusion abnormality involving the inferior and lateral walls is seen on the perfusion images. Intense ^{18}FDG uptake is seen in the areas corresponding to the perfusion abnormalities. On coronary angiography, 100% occlusion of the right coronary artery and a 50% narrowing of the left anterior descending coronary artery were observed. Reproduced with permission from Jain and He.[34]

^{18} F-fluorodeoxyglucose (^{18}FDG) is a commercially available radiotracer that is used for imaging glucose uptake and metabolism. ^{18}FDG is used for imaging a wide variety of malignant tumors that show chronic hypoxia and increased glucose uptake.[23] ^{18}FDG is also useful for detecting viable or hibernating myocardium.[24,25] ^{18}FDG can also be used for imaging exercise-induced myocardial ischemia. The profound metabolic differential between the normal and the ischemic myocardium on exercise permits the use of ^{18}FDG for myocardial ischemia imaging.[26–35] ^{18}FDG is imaged using dedicated PET imaging cameras. However, specially designed single-photon emission computed tomography (SPECT) cameras with modified sodium iodide detectors and thicker collimators suitable for high-energy radioisotopes can also be used for ^{18}FDG imaging.[29,32,36]

The potential of ^{18}FDG as a myocardial ischemia imaging agent has been evaluated in several small studies by Abramson et al,[26] Camici et al,[27] and Araujo et al.[28] These investigators observed increased ^{18}FDG uptake in myocardial segments corresponding to the reversible perfusion abnormalities on MPI. Abbott et al observed increased ^{18}FDG in less than one-half of the vascular territories showing reversible perfusion abnormalities when ^{18}FDG was injected 1 to 1.5 hours following completion of treadmill exercise in CAD patients.[30] He et al performed simultaneous perfusion and ischemia imaging of the heart by injecting ^{18}FDG and technetium-99 m (^{99m}Tc)-sestamibi at peak exercise in 26 patients with angina symptoms and no previous myocardial infarction.[29] They used a SPECT camera capable of PET imaging to compare simultaneous perfusion and ischemia imaging. Coronary angiography was used to compare MPI and ischemia imaging. Twenty-two patients had $\geq$50% narrowing of $\geq$1 coronary arteries, of which 18 had abnormalities on MPI (sensitivity 82%), and 20 had abnormally increased cardiac ^{18}FDG uptake (sensitivity 91%, P = not significant). Myocardial perfusion abnormalities were seen in 25 vascular territories out of a total of 51 vessels with $\geq$50% luminal narrowing (sensitivity 49%). Abnormally increased ^{18}FDG uptake was noticed in 34 vascular territories (sensitivity 67%, $P < 0.01$). These data provided definitive proof that exercise ^{18}FDG can be used for imaging exercise-induced myocardial ischemia (Figures 2 and 3). Similar results were obtained by Sasikumar et al, who performed exercise-rest SPECT MPI and exercise ^{18}FDG PET imaging on separate days in 45 patients with suspected CAD.[37,38] They observed a significantly higher sensitivity (96% vs 56%, $P < 0.001$), but lower specificity (44% vs 72%) of exercise ^{18}FDG compared to exercise-rest SPECT MPI.

Dou and colleagues performed exercise and rest cardiac ^{18}FDG and perfusion imaging 24 hours apart in 18 patients with significant CAD.[39] Of these 18 patients, 15 showed increased regional ^{18}FDG uptake on exercise images, of

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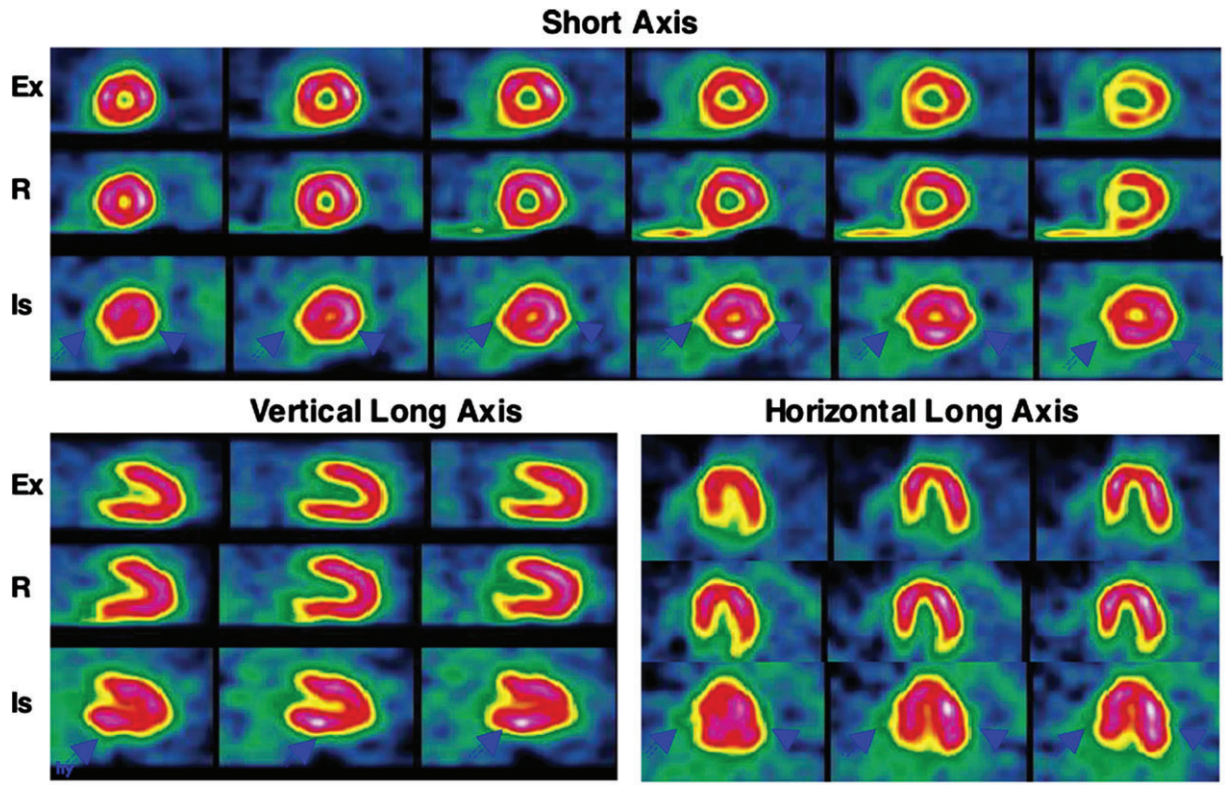

Figure 3. Representative exercise (Ex) and rest (R) technetium-99 m-sestamibi and exercise ^{18} F-fluorodeoxyglucose (^{18}FDG) images of a patient with angina in the short axis, and vertical and horizontal long axes. This patient had no prior myocardial infarction. No perfusion abnormality is observed on the stress and rest perfusion images. An intense global ^{18}FDG uptake is observed in all 3 vascular territories (solid arrowheads). On coronary angiography, 3-vessel disease was observed (70% narrowing of the left anterior descending, 60% narrowing of the left circumflex, and 60% narrowing of the right coronary arteries). Reproduced with permission from He et al.[30]

which 8 (53%) had no ^{18}FDG uptake, 5 (33%) had reduced ^{18}FDG uptake, and 2 (13%) had persistence of ^{18}FDG uptake on rest ^{18}FDG imaging 24 hours later (Figure 4). Patients with persistence of ^{18}FDG uptake on rest imaging had more extensive ^{18}FDG uptake and developed myocardial ischemia at a lower workload in comparison to the patients with no ^{18}FDG uptake at rest. These data confirm that increased regional myocardial ^{18}FDG uptake on exercise is specific for myocardial ischemia. Increased regional myocardial ^{18}FDG uptake is not observed in a majority of patients if ^{18}FDG is injected 24 hours after an episode of myocardial ischemia. Persistence of increased myocardial ^{18}FDG uptake 24 hours after exercise is a marker for severe CAD and development of high-risk myocardial ischemia at a low workload. This finding has obvious prognostic and therapeutic implications.

The strengths of myocardial ischemia imaging are evident from these results. The sensitivity of myocardial ischemia imaging is higher compared to stress-rest MPI for diagnosing CAD. Furthermore, its sensitivity for detecting individual coronary vascular territories with significant luminal obstruction is substantially greater compared to stress-rest MPI. This is particularly useful in the presence of multivessel CAD, where increased ^{18}FDG may be observed in all diseased vascular territories (Figure 3). It is relatively uncommon to observe reversible perfusion abnormalities in all 3 vascular territories in the presence of severe 3-vessel CAD. Inferior wall perfusion abnormalities are often difficult to differentiate from artifacts due to diaphragmatic attenuation. Ischemia-induced increased ^{18}FDG uptake in the inferior wall is not affected by diaphragmatic attenuation artifacts. Exercise ^{18}FDG imaging can also reduce the imaging time and radiation dose to the patients by eliminating the need for rest MPI. These early promising results warrant further large multicenter clinical studies to evaluate the role of stress ^{18}FDG imaging in routine clinical practice.

Fatty Acid Metabolic Imaging for Myocardial Ischemia

The free fatty acid metabolism and its uptake by the heart decrease with the onset of myocardial ischemia. This decreased free fatty acid uptake persists for many hours. Therefore, radiolabeled analogues of free fatty acid can also be used for imaging myocardial ischemia. These agents have also been used for detecting an episode of myocardial ischemia in patients who present several hours after experiencing an episode of chest pain.[40–44] Because this is a cold-spot imaging agent, where myocardial segments with ischemia show reduced radiotracer uptake, its advantages over MPI are unclear. This technique may be useful for confirming an episode of myocardial ischemia that occurred hours earlier. Several radiolabeled free fatty acid derivatives have been evaluated for imaging cardiac fatty acid metabolism. Of these, ^{123}I-labeled β-methyl iodophenyl pentadecanoic acid (^{123}I-BMIPP) is the most widely studied

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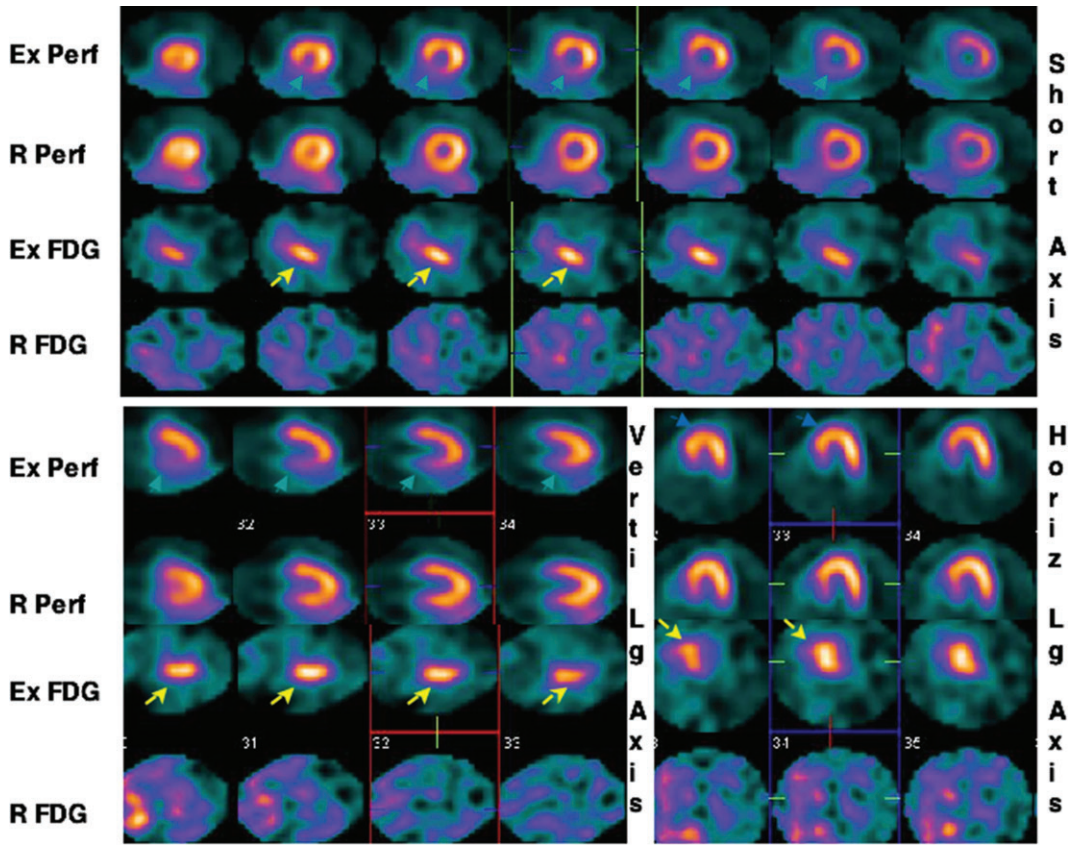

Figure 4. This 49-year-old male with exertional angina underwent exercise (Ex) and rest ^{99m}Tc-sestamibi (Perf) and ^{18} F-fluorodeoxyglucose (FDG) imaging 24 hours apart. Representative short axis, and vertical (Verti) and horizontal (Horiz) long (Lg) axes slices of the heart are shown. Reversible perfusion abnormality in the posterior septum and inferior walls is observed on this study. Intense FDG uptake on the exercise images (yellow arrows) is seen in the corresponding segments. No FDG uptake is seen in the heart on rest images. This patient was found to have 85% narrowing of the right coronary artery. Reproduced with permission from Dou et al.[40]

agent. After its myocardial uptake, it has prolonged myocardial retention. This agent has been in wide use in Japan for the last 20 years. However, in the United States, this is still an investigational agent. Dilsizian and colleagues injected ^{123}I-BMIPP within a 30-hour window of exercise-induced myocardial ischemia in 32 CAD patients.[41] They observed decreased regional ^{123}I-BMIPP uptake in 94% of the myocardial segments with ischemia on stress-rest MPI. In a meta-analysis by Inaba and Bergman involving 7 studies and 528 patients, the sensitivity and specificity of resting ^{123}I-BMIPP imaging for the identifying significant CAD were 78% and 84%, respectively.[43] These results support the potential utility of ^{123}I-BMIPP for imaging metabolic signature of myocardial ischemia or ischemic memory hours following an episode of myocardial ischemia.

Conclusion

Cardiovascular imaging has advanced significantly in the recent years. Recent advances permit ultrafast noninvasive imaging of coronary arterial lumen, atheromatous plaques, and calcium contents of coronary arteries. Nuclear imaging, though lacking the ultrafast speed and high resolution of these techniques, has an unparalleled ability to non-invasively image molecular, biochemical, and metabolic phenomena, and cell membrane receptor and transporter functions under a multitude of physiological and metabolic milieu. Nuclear molecular imaging techniques can be used as clinical imaging tools. Molecular imaging can also provide experimental tools for studying cardiac pathophysiology under various disease conditions and their modulation with therapeutic interventions. Myocardial metabolic imaging using ^{18}FDG and ^{123}I-BMIPP provides novel diagnostic tools for CAD with different but somewhat complimentary strengths. ^{18}FDG is more suitable for imaging of exercise-induced myocardial ischemia and diagnosing CAD, whereas ^{123}I-BMIPP is more suitable for identifying patients presenting with a recent episode of chest pain that resolved spontaneously, leaving no obvious abnormality at presentation, and who warrant closer observation and coronary angiography. Further studies are warranted to establish their role in routine clinical practice.

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