# F-18 fluorodeoxyglucose imaging in myocardial ischemia: Beyond myocardial viability

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F-18 fluorodeoxyglucose (FDG) is now commonly used for metabolic imaging in nuclear medicine. In nuclear cardiology, its use has been limited primarily to the assessment of myocardial viability with positron emission tomography (PET), although its potential utility is expanding on the basis of new applications and instrumentation. In particular, recent data may stimulate a renewed interest in the use of FDG as a marker of myocardial ischemia. FDG is a glucose analog that is transported into the myocardium, phosphorylated, and trapped within the cytoplasm, thus indirectly reflecting regional glucose utilization. As such, it has the potential to track specific aspects of cardiac metabolism and therefore may be a useful marker of ischemia. In this issue of the Journal, Araujo et al report increases in regional FDG uptake colocalized in myocardial segments with dipyridamole-induced perfusion defects in patients with coronary artery disease and chronic stable angina. This increase in FDG uptake was consistent in all subjects, irrespective of symptomatic or electrocardiographic signs of ischemia during the dipyridamole infusion. This study highlights the potential utility of FDG as a sensitive noninvasive marker of ischemia and also raises interesting questions regarding the incidence and pathophysiology of ischemia during vasodilator stress in patients with coronary artery disease.

## METABOLIC RESPONSES TO ISCHEMIA

Relative glucose uptake and metabolism are affected by many factors, including substrate availability, insulin and catecholamine levels, and dietary state. In the fasting state at rest, the primary source of myocardial energy production is oxidation of fatty acids, with glucose accounting for less than 40% of energy production. It has been known for over 2 decades that acute myocardial ischemia is accompanied by increased exogenous glucose utilization in experimental models.[1,2] In general, the extent of this metabolic shift is proportional to both the degree of reduction in myocardial blood flow and the duration of ischemia.[3] Such initial observations formed the basis for evaluation of FDG as an ischemic marker. Schelbert et al[4] first demonstrated the feasibility of using FDG PET to detect ischemic myocardium in a canine model of partial coronary artery occlusion and rapid atrial pacing. More recently, experimental data have suggested that complex mechanisms are responsible for the alterations in myocardial glucose uptake during ischemia, with insulin playing a central role in the regulation of sarcolemmal glucose transport proteins and specific cellular enzymes.[5] Moreover, recent experimental data suggest that enhanced exogenous glucose uptake may persist for 24 hours or more after a relatively brief period of ischemia.[6] FDG uptake thus may represent a metabolic "signature" of recent ischemia, which has important implications for the potential clinical utility of FDG. Although the physiologic differences between FDG and glucose have not been fully elucidated, the weight of the experimental evidence suggests that FDG tracks myocardial glucose uptake and may be useful for the assessment of ischemia.

## CLINICAL STUDIES OF FDG IN ACUTE ISCHEMIA

The clinical utility of FDG as a scintigraphic marker of acute ischemia was a subject of considerable investigative effort in the 1980s. Early studies demonstrated increased FDG uptake, presumably from ischemia, in several groups of patients, including those with exercise-induced perfusion defects, unstable angina, and recent myocardial infarction. In a seminal investigation, Camici et al[7] examined the effects of acute, exercise-induced myocardial ischemia on FDG uptake in patients with chronic stable coronary artery disease and in healthy volunteers. FDG was injected 5 to 14 minutes post exercise, after regional myocardial rubidium uptake had returned to normal in the ischemic areas. In most patients, FDG uptake was increased in ischemic segments relative to

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nonischemic segments, whereas uptake in nonischemic segments was similar to that in healthy volunteers. Thus postexercise FDG imaging identified recently ischemic territories after the normalization of perfusion, heart rate, blood pressure, and electrocardiographic changes. A subsequent investigation reported that postexercise FDG uptake occurs in about 40% of patients with chronic coronary artery disease and left ventricular dysfunction and that this finding is predictive of functional recovery after revascularization.[8]

Similarly, FDG uptake may be increased regionally at rest in a subset of patients with coronary artery disease. In patients with prior anterior myocardial infarction, periinfarction ischemia has been demonstrated on FDG imaging in a similar distribution to the reversible perfusion defects seen on rest-stress perfusion imaging.[9] A similar study of patients with chronic stable coronary disease demonstrated increased resting FDG uptake in 75% of regions with previously demonstrated stress-induced ischemia.[10] The point of particular interest in both of these studies is that FDG was injected and imaged well after (up to 1 week) the stress perfusion study, suggesting that the enhanced FDG uptake may be a marker of repetitive stunning in jeopardized myocardial regions.

Increased FDG uptake also has been observed in patients with unstable angina, although the results are not conclusive. A study by Araujo et al[11] in 1987 demonstrated a 4-fold increase in FDG uptake in patients with unstable angina versus those with stable angina or healthy subjects. Furthermore, anti-ischemic therapy with nitrates partially normalized FDG uptake values. In contrast to the aforementioned studies, the increase in FDG uptake in these patients was diffuse and was not limited to the areas supplied by stenotic coronary arteries. This study thus highlights the potential role for FDG imaging in assessing efficacy of therapy, as well as the lack of a complete understanding of the pathophysiologic mechanisms involved in the process of FDG uptake, given that global, rather than regional, uptake of FDG was abnormal. More recently, the utility of FDG imaging in patients with unstable angina has been evaluated with resting sestamibi-FDG single photon emission computed tomography (SPECT).[12] In this study FDG uptake was increased in a portion of segments with or without resting perfusion defects, and overall sensitivity and specificity for the detection of significant coronary stenosis were very good (87% and 84%, respectively). These preliminary results suggest that FDG imaging may have a role in the assessment of patients with recent chest pain and/or unstable angina and may identify more patients at risk than perfusion imaging alone.

The current study by Araujo et al in the Journal extends the application of FDG imaging of ischemia to patients undergoing vasodilator stress. In this study FDG was injected approximately 20 minutes after dipyridamole stress, after the completion of perfusion imaging, and was compared with FDG study results obtained on a separate day without preceding stress. All 11 patients had angiographically confirmed coronary artery disease. In every patient the ratio of FDG uptake in ischemic compared with normal regions increased after dipyridamole stress, with FDG uptake an average of 3 times higher in ischemic regions than in normal regions. Although this finding seems to confirm previous studies that have indicated the potential utility of FDG imaging in acute ischemia, several aspects of the study deserve comment. First, the study cannot determine the approximate prevalence of dipyridamole-induced FDG uptake in an unselected patient population. All patients had increased FDG uptake after stress, and patients may have been selected on this basis. Second, the mechanism for enhanced FDG uptake after vasodilator stress cannot be defined on the basis of this study. Consideration of potential pathophysiologic mechanisms in this regard highlights the complexities of metabolic imaging and the limitations of current imaging techniques.

For example, the data in this study on first look suggest that mechanisms other than stress-induced ischemia may be operative because myocardial blood flow increased in ischemic regions, albeit modestly, in all but one patient during dipyridamole stress. If the increased FDG uptake was due to coronary steal, a common presumptive mechanism used to explain vasodilator-induced ischemia, one would expect a decrease in blood flow. One possibility is that dipyridamole itself, through changes in extracellular adenosine concentrations, alters myocardial substrate utilization independent of ischemia.[13,14] A second, and possibly more plausible, explanation relates to the susceptibility of the subendocardium to ischemia and the potential differences in blood flow and metabolism from endocardium to epicardium. It is well established that the subendocardial layer of myocardium is subjected to higher wall stress, leading to higher metabolic demands and perhaps diminished flow reserve. These factors contribute to a situation in which the subendocardium may become ischemic even while total transmural flow remains near normal.[15] In fact, vasodilator agents such as dipyridamole have been observed to cause subendocardial ischemia in the setting of severe coronary stenosis as a result of redistribution of flow across the myocardial layers.[16] Therefore it is possible that the increased FDG uptake observed in the current study reflects regional subendocardial ischemia induced by vasodilator stress. Even with the limitations of resolution of current imaging equipment, the hot-spot FDG signal from the ischemic subendocardium thus could be detected.

A related study by Abramson et al[17] was recently published in the Journal. This study examined the utility of using sestamibi SPECT and FDG PET for the diagnosis of coronary artery disease in women. The results suggest that hot-spot FDG imaging of ischemia may potentially overcome the problem of attenuation artifacts in cold-spot perfusion imaging. Nineteen women underwent exercise or dipyridamole stress testing with the simultaneous injection of sestamibi and FDG at peak stress, and the results suggested that FDG uptake was very accurate for the detection of coronary disease even in women with breast attenuation artifacts on perfusion images. Interestingly, all 5 patients with coronary disease who underwent stress testing with dipyridamole showed increased FDG uptake in an anatomic region that corresponded to the area of coronary stenosis. Although the mechanisms remain unclear, the study of Abramson et al, together with that of Araujo et al in this issue, strongly suggests a potential utility of FDG imaging after vasodilator stress to assess for coronary disease.

It is logical to assume that if FDG is a marker of acute ischemia, it may also be useful in the acute phase of myocardial infarction. Data regarding the utility of FDG imaging in this setting, however, are limited. The few clinical studies that have examined such patients indicate that FDG uptake in the infarction zone is variable, is not necessarily correlative to long-term viability, and may be affected by factors such as reperfusion and postinfarct inflammation.[18-21] Studies in this patient population are limited by the variability and rapidity of treatment (ie, reperfusion). If FDG is to have a role in the setting of acute myocardial infarction, it will most likely be in patients with equivocal presentations rather than in those with obvious infarction.

## PRACTICAL IMPLICATIONS FOR IMAGING AND FUTURE DIRECTIONS

The data on FDG imaging for acute ischemia suggest an exciting potential role for this radiotracer in clinical imaging. It should be recognized that its use in this regard is not new, given that the initial investigations that clearly demonstrated the potential utility of FDG were carried out over a decade ago. Recent interest in metabolic imaging with FDG among many nuclear cardiologists has been sparked perhaps by the increased availability of the radiotracer and instrumentation as a result of growing indications in oncology. Also, it is important to stress that in most studies in which FDG is used as a marker of acute ischemia, it is injected during a fasting state, in contradistinction to the preferred glucose-loaded state when FDG is used for viability assessment.

The studies reviewed here suggest several potential advantages of FDG imaging of ischemia over perfusion imaging alone. First, hot-spot imaging, although commonplace in general nuclear medicine, is not widely used in nuclear cardiology. Its advantages include increased specificity of the abnormal radiotracer signal, less need for high-resolution imaging systems, and a mitigation of the effects of attenuation, scatter, and partial volume. Second, FDG imaging may be unique in its ability as a memory marker to detect the metabolic signature of recent antecedent ischemia, possibly within a window of time that expands its diagnostic utility into the acute ischemia arena. Third, a metabolic tracer such as FDG may be ideally suited to detect global ischemia, or ischemia not caused by epicardial coronary artery stenosis, such as in patients with syndrome X[22] or cardiomyopathies. Thus FDG imaging may be an important adjunct to myocardial perfusion imaging.

However, a number of technical and physiologic questions remain. Some concerns have been raised in a previous editorial in the Journal,[5] and these include issues regarding the optimal timing of FDG injection and imaging, the conditions under which imaging is performed (fasting or after glucose loading), the utility of FDG imaging in patients with diabetes, and the optimal stressor. From a technical imaging standpoint, it is likely that questions regarding the metabolic conditions or timing of FDG injection are far more important than the type of imaging modality used (PET, coincidence detection systems, ultra-high-energy SPECT). The ability to use FDG SPECT, although less efficient than dedicated PET or coincidence systems for the detection of positron emitters, may foster the development of imaging protocols that allow simultaneous assessment of perfusion and metabolism if issues concerning spillover are settled. For purposes of detection of ischemia with FDG, it is likely that the low sensitivity and resolution of SPECT systems outfitted with ultra-high-energy collimators will not be major limitations to its use. Currently available software analysis packages are not designed to quantitate hot-spot images and need to be developed to reflect images in which the abnormal region has abnormally high uptake, a situation that does not occur with current perfusion agents. Modifications of such software may involve normalization to perfusion studies and new approaches to comparing studies with the use of 2 different isotopes.

FDG imaging may thus represent an important tool in our new armamentarium of radiotracers in the next decade. As a metabolic tracer, it remains a powerful tool with which to investigate cardiac pathophysiology noninvasively. Clinical studies should focus on the potential additive value of FDG imaging over perfusion imaging, in terms of both diagnosis and prognosis. It is quite pos-

sible that its use as a marker of ischemia will become at least as important, if not more important, than its use in the area of myocardial viability.

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