^{18}F-FDG Uptake as a Surrogate Marker for Antecedent Ischemia

Patients often present to the physician's office or in the emergency department complaining of chest pain that occurred several hours earlier. Determining whether chest pain that resolved long before the patient presents for medical attention was a consequence of myocardial ischemia can be diagnostically challenging. Clinical history has low specificity, and the findings on physical examination are often normal. A resting electrocardiogram may be positive half the time, if acquired during chest pain, and frequently is normal when acquired several hours after the resolution

See page 1986

of the chest pain. Although myocardial enzymes and markers are extremely useful in detecting myocardial infarction, they are not positive in patients with myocardial ischemia, and they may remain undetectable until several hours after the onset of myocardial infarction.

A metabolic switch from fatty acids to glucose seems pivotal in preserving myocardial viability and likely represents the earliest adaptive response to myocardial ischemia (*1*). Applying a dual-isotope ^{99m}Tc-sestambi and ^{18}F-FDG simultaneous-injection-and-acquisition protocol, He et al. (*2*) have previously shown that a metabolic switch from fatty acid to glucose use occurs promptly when myocardial ischemia is induced during exercise. In the current issue of *The Journal of Nuclear Medicine*, investigators from the group of He et al. expand on their prior observation by demonstrating that the exercise-induced metabolic switch to glucose may persist for 24 h, despite restoration of blood flow at rest (*3*).

CARDIAC METABOLISM IN NORMAL AND POSTISCHEMIC MYOCARDIUM

Increased glucose metabolism has long been identified as a hallmark of reversible ischemic myocardium (*1*). The application of a metabolic radiotracer for imaging, as opposed to a perfusion tracer, potentially extends the scope for noninvasive imaging of an ischemic event beyond the resolution of symptoms. This concept applies to tracers or tracer analogs of both long-chain fatty acids and glucose. The uptake of tracers or tracer analogs by previously ischemic heart muscle is either decreased (in the case of fatty acids) or increased (in the case of glucose). Delayed recovery of regional fatty acid metabolism, as an imprint of a prior ischemic event, has been shown with β-methyl-*p*-^{123}I-iodophenyl-pentadecanoic acid (BMIPP) and termed ischemic memory (*4,5*). The corollary finding by Dou et al. (*3*) in this issue, using ^{18}F-FDG, provides further credence to the concept of metabolic stunning and accentuates the role of ^{18}F-FDG as a marker of antecedent ischemia.

Cardiac metabolism involves the conversion of fuels into cellular energy in the form of adenosine triphosphate. For a given physiologic state, the heart consumes the most efficient metabolic fuel to meet its energy demands. Under normal conditions of blood flow and oxygen delivery, fatty acids are the preferred metabolic source of fuel for the heart, because their breakdown by β-oxidation in the mitochondria yields an abundance of energy-rich phosphates. During an acute increase in work load, for example, inotropic stimulation, the heart immediately mobilizes its metabolic reserve contained in glycogen (transient increase in glycogen oxidation) and meets the needs for additional energy from the oxidation of carbohydrate substrates (glucose and lactate) (*6,7*). When the oxygen supply is decreased, the heart helps protect itself from an oxygen-lacking fate of infarction by switching its energy source to glycolysis, which can supply adenosine triphosphate in the cytoplasm under anaerobic conditions.

Although the metabolic switch in postischemic or stunned myocardium reflects an adaptive response to acute myocardial ischemia with recovery of regional function, this may differ from chronic states of hypoperfusion and regional dysfunction (hibernating myocardium). In hibernating myocardium, improvement in regional wall motion after revascularization (*1*) or in response to low-dose dobutamine stimulation (*8*) may depend on the presence and extent of degenerated myocytes and loss of myofibrils in the region as a consequence of a chronically hypoperfused state (*9*). Increased regional glucose use during dobutamine infusion, even at low doses, might represent acute ischemia rather than metabolic adaptation to chronic hypoperfusion that was presumably present before the infusion of dobutamine. Nonetheless, when glucose use is relatively increased in hypoperfused myocardial regions (termed mismatch defect), the likelihood of improvement in regional wall motion after revascu-

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larization is high. On the other hand, when glucose use is absent in hypoperfused regions (termed matched defect, reflecting excessive scar tissue formation), the likelihood of improvement in regional wall motion after revascularization is rather low (*1*).

PERSISTENT ^{18}F-FDG UPTAKE 24 H AFTER EXERCISE

In this issue of *The Journal of Nuclear Medicine*, Dou et al. (*3*) studied patients with a strong clinical suggestion of coronary artery disease using a simultaneous dual-isotope injection of sestambi and ^{18}F-FDG at peak exercise and a reinjection of both radiotracers 24 h later, at rest, thereby ensuring perfect coregistration of the regional perfusion and metabolic signal. Among the 24 patients who completed the exercise and in whom 24-h delayed images were acquired, 31 vascular territories had greater than or equal to 70% coronary artery narrowing, of which 19 (61%) demonstrated increased ^{18}F-FDG uptake and only 12 (39%) had reversible sestamibi perfusion defects. Thus, the metabolic signal with ^{18}F-FDG was more sensitive than that with sestamibi for detecting myocardial ischemia. Among patients with abnormal ^{18}F-FDG uptake at peak exercise, 47% exhibited residual abnormal ^{18}F-FDG uptake at rest 24 h after the exercise-induced ischemia, which translates to 57% of vascular territories and is consistent with the concept of ischemic memory. Patients with residual ^{18}F-FDG uptake at 24 h had higher ^{18}F-FDG uptake and a lower rate–pressure product at peak exercise than did those patients with no ^{18}F-FDG uptake at 24 h.

It remains untested, however, whether the findings in the current study apply to patients with diabetes mellitus or others with an altered metabolic milieu and substrate availability. Nonetheless, these findings are supported by prior data in experimental animals and in human subjects, in which upregulation of glucose uptake by the ischemic myocardium was shown to persist for hours to days, even after a brief episode of ischemia (*10,11*).

EXPERIMENTAL EVIDENCE OF METABOLIC DERANGEMENTS AFTER A TRANSIENT EPISODE OF MYOCARDIAL ISCHEMIA

The feasibility of using ^{18}F-FDG PET to detect ischemic myocardium was first demonstrated by Schelbert et al. in a canine model of partial coronary artery occlusion and rapid atrial pacing (*12*). In the ischemic segment, the authors observed a fall in fatty acid use (assessed by ^{11}C-palmitate) and an increase in glycolytic flux (assessed by ^{18}F-FDG PET). Subsequent studies have demonstrated that enhanced exogenous glucose uptake may persist for 24 h or longer after a period of transient ischemia (*10*). In experimental studies, brief periods (3–5 min) of myocardial ischemia were shown to induce glucose transporter 4 sarcolemma translocation (*13,14*) and activate glycogen synthase. More prolonged ischemia, lasting 20 min, was shown to accelerate regional glycolytic flux, which persisted for 24 h or longer into the recovery phase (*10*). In intact rats, a 20-min coronary artery occlusion followed by 24 h of open-artery reperfusion resulted in a 25% reduction in regional ^{13}N-ammonia myocardial blood flow and a 50% increase in ^{18}F-FDG glucose use, despite restoration of regional function. Reperfused myocardial regions exhibited preferential shunting of imported glucose away from glycogen synthesis and into glycolysis. Others have suggested that stimulation of α-adrenoreceptors during myocardial ischemia may result in an increase in glucose transporter, leading to an increase in ^{18}F-FDG uptake (*15*). These experimental data provide support to the clinical observations of persistent metabolic derangements after a transient episode of myocardial ischemia, for example, on the treadmill (*2,5*). Hence, increased regional ^{18}F-FDG uptake likely represents an adaptive response to myocardial ischemia, which may constitute a clinically accessible late metabolic signature of antecedent ischemia.

CLINICAL EVIDENCE OF METABOLIC DERANGEMENTS AFTER A TRANSIENT EPISODE OF MYOCARDIAL ISCHEMIA

The earliest clinical observation of increased exogenous glucose use in previously ischemic myocardium was in 1986 (*11*). Among patients recovering from exercise-induced ischemia assessed by ^{82}Rb PET, ^{18}F-FDG was injected 8 min after the termination of exercise. The ^{18}F-FDG PET images recorded 60 min after tracer injection showed enhanced glucose use in the previously ischemic regions. These early observations in human subjects were expanded to study patients undergoing coronary artery revascularization (*16*). Among patients who had undergone preoperative ^{82}Rb PET and postexercise ^{18}F-FDG PET before revascularization, 73% of hypoperfused, dysfunctional regions exhibiting ^{18}F-FDG–avid signal showed improvement in regional function after revascularization. In contrast, 74% of hypoperfused, dysfunctional myocardial regions without ^{18}F-FDG–avid signal showed no improvement in regional function after revascularization (*16*).

Increase in regional ^{18}F-FDG uptake has also been shown among patients with angiographically documented single-vessel coronary artery narrowing (≥75%) and abnormal vasodilator reserve by ^{15}O water (*17*). Two ^{18}F-FDG PET studies were performed: one at rest, without preceding stress, and the other after vasodilator stress, 20 min after the beginning of dipyridamole infusion. Increased poststress myocardial ^{18}F-FDG uptake was consistently observed in the areas of vasodilator-induced alterations in perfusion, which was not present at rest. Stress-induced myocardial ischemia with ^{18}F-FDG has also been shown in women undergoing simultaneous injections of sestamibi and ^{18}F-FDG at peak stress under fasting conditions (*18*).

GLUCOSE (HOT-SPOT) VERSUS FATTY ACID (COLD-SPOT) METABOLIC IMAGING

Hot-spot imaging is commonly preferred in nuclear medicine procedures, where a malignant lesion, for example,

appears significantly more intense than does the surrounding soft-tissue or skeletal structures. However, when it comes to cardiac application of ^{18}F-FDG to detect myocardial ischemia under fasting conditions, it may be difficult to resolve and conclusively localize the hot-spot ^{18}F-FDG signal in the ischemic myocardium when the rest of the myocardial regions have no discernable signal to serve as a reference standard. Thus, visual assessment of regional myocardial ^{18}F-FDG uptake 24 h after transient ischemia is rather difficult, and assessment of regional function on simultaneously acquired gated ^{18}F-FDG images is unattainable in most cases. Furthermore, fasting myocardial cardiac ^{18}F-FDG PET studies have been shown to have a heterogeneous myocardial distribution even in healthy subjects (*19*). Thus, whereas large myocardial regions may be easily identified on hot-spot ^{18}F-FDG imaging, smaller regions of myocardial ischemia or nontransmural ischemia may go unnoticed or simply be dismissed as background activity. The latter may explain the relatively smaller percentage of ischemic myocardium detected on delayed 24-h images in the current study than what has been previously published on earlier experimental studies with ^{18}F-FDG and on clinical studies with the fatty acid analog BMIPP (*5*). Moreover, Dou et al. (*3*) used a modified SPECT camera to detect both ^{99m}Tc and ^{18}F signals simultaneously. It is possible that a dedicated PET camera, or hybrid PET/CT with anatomic coregistration of the heart, may have further improved the sensitivity of detecting persistent ^{18}F-FDG uptake at 24 h.

Concomitant myocardial perfusion imaging is not a prerequisite for cold-spot fatty acid metabolic imaging, unless, of course, the patient has had a prior myocardial infarction. Mild-to-moderate cold defects, indicating nontransmural ischemia, are more easily detected with fatty acid than with ^{18}F-FDG metabolic imaging. The interpretation of cold fatty acid metabolic signals is also more congruous with the current practice for interpreting myocardial perfusion images, making the transition from perfusion to metabolic imaging more efficient. Currently available cardiac software programs for quantification or grading the severity of a myocardial signal are designed for cold-spot and not for hot-spot myocardial imaging, and modifications of such software may be challenging. On the other hand, hot-spot ^{18}F-FDG imaging may potentially overcome the problem of differentiating attenuation artifacts from true metabolic abnormalities in fatty acid imaging. Future studies will likely address questions regarding the metabolic conditions (fasting vs. glucose loading) and the need for simultaneous myocardial perfusion or CT to better resolve the location and size of the ^{18}F-FDG signal in the myocardium.

CONCLUSION

^{18}F-FDG has been shown to be a sensitive noninvasive marker of myocardial ischemia. The finding of a persistent metabolic switch from fatty acid to glucose, 24 h after the resolution of transient myocardial ischemia on a treadmill, provides the potential for diagnosing myocardial ischemia in the acute-care setting. Thus, metabolism plays a critical role in sustaining myocellular viability by adapting quickly to the ischemic injury response, albeit with a prolonged recovery phase, with recovery of metabolism lagging behind perfusion for 24–30 h or more.

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