Myocardial Ischemia, Fluorodeoxyglucose, and Severity of Coronary Artery Stenosis: The Complexities of Metabolic Remodeling in Hibernating Myocardium

To the Editor:

Myocardial imaging of perfusion (with either $^{13}$N-ammonia or $^{82}$Rb) and of metabolism with fluorodeoxyglucose (FDG) is a validated method for differentiating viable myocardium from necrosis or scar. Early in its clinical application, FDG was injected during exercise stress to intensify the difference between normal and ischemic myocardium. This approach was based on the following general principles of myocardial metabolism. (1) Normally perfused, nonischemic myocardium metabolizes primarily fatty acids. (2) Underperfused, ischemic myocardium metabolizes glucose. (3) Fasting suppresses glucose metabolism in normally perfused myocardium (but has no effect on anaerobic glucose metabolism in ischemic myocardium). (4) Catecholamines released during exercise stress further suppress exogenous glucose metabolism in normal myocardium but do not alter anaerobic glucose metabolism in ischemic myocardium. In principle, “hot-spot” imaging of myocardial ischemia would therefore identify “significant stenosis” of a coronary artery independently and separately from myocardial perfusion or anatomic stenosis severity.

However, those of us who enthusiastically supported FDG imaging quickly abandoned this approach 17 years ago. Hot-spot imaging during exercise was deemed not reliable because heart metabolism was, in fact, more complex than the generalized concepts outlined above. The switching of metabolic substrates in the heart is a complex process and cannot be reliably assessed by FDG under fasting and exercise conditions. Consequently, FDG uptake in the heart under these conditions does not reliably differentiate between ischemic and nonischemic myocardium.

Although FDG imaging did not prove diagnostically useful under exercise conditions, at rest it was able to differentiate between ischemic, viable myocardium and necrotic, scarred myocardium. Not surprisingly, this approach is used widely for deciding on revascularization procedures. The understanding of myocardial metabolism has now evolved with a better molecular and genetic understanding of these early and perhaps erroneous concepts.

There is no question that imaging with the glucose tracer analog FDG by positron emission tomography (PET) has opened a window to assessing regional metabolic activity of the heart in vivo. When combined with a tracer of myocardial blood flow, valuable new insights have been obtained into the pathophysiology of myocardial ischemia. More importantly, the concept of “perfusion-metabolism mismatch” (perfusion down, glucose metabolism up) has proven to be an accurate way of assessing myocardial viability in hibernating myocardium. Experiments in isolated, perfused hearts support this concept; the acute reduction in coronary flow causes an acute switch from aerobic to anaerobic glucose metabolism, as shown by a decrease in oxygen consumption and glucose oxidation on the one hand and a pronounced increase in lactate production on the other hand. The situation is more complex in chronically ischemic, “viable” myocardium. Irrespective of the inciting stimulus (reduced coronary flow at rest, reduced coronary flow with exercise, or repetitive bouts of ischemia followed by reperfusion), the myocardium remodels and activates a program of cell survival. This programmed cell survival includes metabolic, structural, and functional remodeling of the myocardium in response to myocardial ischemia. In many aspects, hibernating myocardium resembles the fetal heart as evidenced by its preferential metabolism of glucose and the presence of large amounts of glycogen in the cardiomyocytes.

The vast literature on programmed cell death, or apoptosis, and our own observations on programmed cell survival support the idea of a direct link between metabolic pathways and the pathways of cellular adaptation or maladaptation. Striking evidence in support of this hypothesis is provided by cancer cells. Cancer cells not only possess an increased rate of glucose metabolism, they are also less likely to “commit suicide” when damaged. Recent observations suggest that the downregulation of function and oxygen consumption in hibernating myocardium is an adaptive response that prevents supply-demand imbalance during submaximal increases in cardiac workload when coronary flow reserve is limited. Furthermore, persistent stunning, even without evidence for chronic ischemia, recapitulates the phenotype of myocardial hibernation. In other words, metabolic reprogramming of the ischemic myocardium probably initiates and sustains the functional and structural features of hibernating myocardium. If the investigators of the current study had included a group of patients imaged at rest, their findings would likely have been the same.

The unanswered questions in the paper by He et al are not single-photon emission CT (SPECT) versus PET imaging. Our concerns arise from several well-documented basic concepts in the literature, including the concepts of myocardial metabolism, assessment of the severity of coronary artery stenosis, dynamics of myocardial perfusion, and standards of statistical power to draw valid conclusions.

In addition to oversimplified concepts of myocardial metabolism, the visual estimates of stenosis severity on coronary arteriograms as a reference standard have been repeatedly proven inadequate by comparison to quantitative coronary arteriography, coronary flow reserve, and pressure-derived fractional flow reserve. For moderate stenosis from 50% to 75% diameter narrowing, visual estimates have little relation to either coronary flow reserve or pressure-derived fractional flow reserve and short-term clinical outcomes.

Figure 3 of the paper by He et al is a case in point. It illustrates the combined problems of myocardial FDG uptake and visual estimates of stenosis severity. This case has uniform normal perfusion scans, uniform normal uptake of FDG, and reportedly 60% diameter stenoses of left circumflex and right coronary arteries, with 70% stenosis of the left anterior descending by visual estimation on the coronary arteriogram. The authors show the case as a purported example of myocardial ischemia identified by FDG uptake with no perfusion abnormalities due to “balanced” coronary artery stenoses.

There are several problems with this example that raise general questions about the methodology and the authors’ conclusions. This example most likely demonstrates normal FDG uptake in normally perfused nonischemic myocardium for the following reasons. (1) Myocardial FDG uptake after fasting and during exercise is common in the absence of
ischemia since the above, oversimplified concepts are not diagnostically reliable. (2) According to the authors’ own visual estimates, the stenoses were not balanced; one was reported as 70% and the other two as 60% diameter narrowing. This difference causes significantly different fluid dynamic effects due to flow being proportional to the radius raised to the fourth power. (3) Numerous reports document 30% to 60% overestimation of stenosis severity on coronary arteriograms by experienced cardiologists. The stenoses in this example were more likely 50% or less that did not limit coronary flow reserve enough to cause ischemia. (4) There was no indication that the stenoses were proximal to branches, which would have to be the case for uniform perfusion images because even small proximal branches would demonstrate relative differences in coronary flow reserve instead of perfectly uniform perfusion. (5) K.L.G. first reported the conceptual possibility of “balanced” stenoses created experimentally with great difficulty using 2 flowmeter-monitored, precisely controlled experimental stenoses that ignored other arterial branches.19 However, in his 35-year career of searching thousands of PET or SPECT images and arteriograms, he has yet to find 1 single case of proven, perfectly balanced, moderate 60% to 75% diameter stenoses of the left main and right coronary arteries or balanced, 3-vessel stenoses proximal to all branches that caused perfectly uniform low perfusion with ischemia.

There are many causes of normal myocardial perfusion images despite disease, including severe diffuse 3-vessel or small-vessel disease, left ventricular hypertrophy, inadequate stress, diffuse coronary spasm, inadequate imaging, or even severe stenosis of all 3 coronary arteries proximal to any branches. Visual overestimation and relatively normal perfusion would be a more likely scenario than uniform myocardial ischemia caused by perfectly balanced 60% stenoses proximal to any arterial branches. To make a long story short, Figure 3 most likely demonstrates normal FDG uptake in normally perfused myocardium, which is common during exercise.

Lastly, the small number of patients in this study precludes valid conclusions, particularly with the great variability of myocardial FDG uptake in the fasting state. The absence of adequate normal controls precludes determination of specificity that would likely demonstrate significant numbers of subjects with good myocardial FDG uptake during exercise in the absence of coronary artery stenosis or ischemia. The down scatter from FDG into the technetium window degrades the perfusion images, resulting in such a low sensitivity of perfusion imaging as to make the conclusions moot. Accurate perfusion imaging identifies coronary artery stenosis well before the stenosis causes stress-induced ischemia.19 The base-to-apex, longitudinal myocardial perfusion gradient after dipyridamole even identifies diffuse coronary atherosclerosis before stenosis becomes severe enough to cause stress-induced segmental perfusion defects.22

Although generally considered as a decline, age and maturity provide a perspective for avoiding the pitfalls of rediscovering the wheel, recycling old ideas, or history repeating itself, at least for 1 generation. With due respect for the authors and their reviewers, we consider this paper an example of history repeating itself.

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Response

We feel honored to be noticed by the authorities in PET and myocardial metabolism. We thank them for agreeing with our reasoning and logic for exploring 18fluorodeoxyglucose (18FDG) for ischemia imaging.1 We agree that myocardial metabolism during exercise is inadequately understood, but we disagree with this argument being used to dismiss any effort to explore its use for ischemia imaging. If a lack of complete understanding of the physiology and mechanism were to be used as a basis for outright rejection, a large number of commonly used diagnostic/therapeu-
tic modalities including currently used myocardial perfusion imaging would never have gained clinical acceptance. Better understanding of the physiology often grows with the potential clinical use and applications of a technology. We hope our study stimulates more research into cardiac metabolism during exercise.

Gould and Taegtmeyer abandoned the use of 18FDG use for ischemia imaging 17 years ago. However, their insistence on this position 17 years later is not justified. Several technical developments and a better understanding of the dynamics of image acquisition, processing, and interpretation in the interim warrant a reevaluation of 18FDG for ischemia imaging. An important consideration in this regard is the realization of a need for a roadmap for proper localization with hot-spot imaging agents. In its absence, abnormal radiotracer uptake can easily be mislocalized within the myocardium or to an extracardiac structure, and noncardiac activity can be mistakenly localized to the myocardium. This is exemplified by Figure 1 illustrates this point. This patient has a small but very intense and localized uptake in the anteroapical segments, corresponding to the site of reversible perfusion abnormality. In the absence of myocardial perfusion images, it would not have been possible to process and orient the images so as to allow its localization to the apex. Similarly, in patients with no myocardial uptake, the very faint residual blood pool activity could inappropriately be localized to the myocardium. This is exemplified by Figure 4 of our article. No consideration was given to some of these technical, but nevertheless critical, issues in previous studies. A number of approaches can be used for obtaining a myocardial roadmap. We used simultaneous perfusion-18FDG imaging, made possible by the use of a thicker crystal gamma camera with ultra-high-energy collimators for a pixel-by-pixel match between 18FDG uptake and perfusion.

We do not dispute the use of resting 18FDG imaging for myocardial viability. Indeed, it would be interesting to see resting 18FDG images in patients with abnormal exercise 18FDG uptake. This could not be carried out in our study because of logistical, dosimetric, and regulatory considerations. Studies are under way to address this. But we disagree with the authors' speculation of similar 18FDG uptake patterns on exercise and resting studies. We are including another figure (Figure 2) to illustrate the difference between abnormal and normal 18FDG uptake in the same patient with coronary artery disease (CAD) before and after revascularization.

We respectfully disagree with their interpretation of Figure 3 of our article. The intense global 18FDG uptake has no resemblance to normal exercise 18FDG studies. This is an intriguing case with a number of interesting but unanswered questions. However, this list of questions does not include a mistaken interpretation. This patient developed chest pain and ST-segment depression on exercise. Anecdotally, all nuclear cardiologists have observed rare cases with no or only minimal perfusion abnormality despite severe multivessel CAD. Angina and electrocardiographic changes at a relatively low workload and sometimes hypotension point to the presence of more severe CAD than what one would infer from the perfusion studies.

We agree with the limitations of angiography. Like myocardial metabolism, the coronary vasoreactivity and relationship between the severity of CAD on resting coronary angiogram and exercise flow limitations are also inadequately understood. We share the authors' dislike for the term "balanced ischemia." We did not use this term in our article. However, it is reasonable to speculate the presence of global ischemia, which does not have to be "balanced." A variable degree of flow heterogeneity may still occur in such cases, which may be below the resolution of single-photon emission computed tomography imaging. Direct ischemia imaging may be quite useful in such cases.

Scientific concepts and principles never grow old. With the availability of newer tools and better understanding of previously unknown scientific variables, some of the age-old principles continue to inspire new developments and research. Radon described the mathematical principles of tomographic imaging in 1917, decades before tomographic imaging became possible clinically. 15N- Ammonia has only recently been approved for myocardial perfusion imaging; however, the first report of its use for perfusion imaging was published in 1972, well before any radionuclide perfusion imaging was used in clinical practice.

Although it is based on a relatively small sample size, our study does provide a fair proof of the viability of 18FDG for ischemia imaging. Studies are currently under way to address the issues raised by our own study as well by our esteemed colleagues.

Figure 1. Exercise (Ex) and resting (R) Tc-sestamibi and exercise 18FDG ischemia (Is) images of a 60-year-old man with angina and no prior myocardial infarction. There is a small area of reversible perfusion abnormality involving the anteroapical segments. Intense localized and matching 18FDG uptake is present in the same segments. In the absence of simultaneously acquired perfusion, it would not have been possible to properly process, orient, and align the ischemia images.


Drs Jain and He hold a patent pending for the technique of myocardial ischemia imaging with FDG.


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