EDITORIAL
Myocardial Viability—What Is the Definition?

The primary function of the heart is to pump. Although angina is a frequent consequence of coronary artery disease, the most serious manifestation of myocardial ischemia is contractile dysfunction. Indeed, left ventricular function is a major determinant of long-term survival (*1,2*). Numerous experimental and clinical studies have demonstrated that when regional contractile dysfunction is the result of either acute or multiple intermittent episodes of ischemia, restoration of nutritive perfusion with interventions such as thrombolytic therapy, angioplasty, or coronary artery bypass grafting will result in improvement in regional function. Jeopardized myocardium that manifests improved function after appropriate therapy is deemed *viable* in contrast to persistently dysfunctional, *nonviable* myocardium—typically the result of completed infarction. Accordingly, definitive evidence of myocardial viability is the temporal improvement in contractile function irrespective of the etiology of the dysfunction or the specific therapeutic intervention employed (*3,4*).

Clearly, the demonstration of temporal improvement in regional function is not a feasible approach for the prospective identification of jeopardized but viable myocardium for the purposes of guiding therapeutic interventions in individual patients. Unfortunately, it has proven exceedingly difficult to delineate viable from nonviable myocardium. Approaches proposed to identify viable myocardium such as improvement in regional function in response to inotropic stimulation or temporal changes in thallium-201 perfusion defects have proven problematic (*5,6*).

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For reprints contact: Steven R. Bergmann, MD, PhD, Cardiovascular Division, Washington University School of Medicine, Box 8086, 660 S. Euclid Ave., St. Louis, MO 63110.

METABOLIC IMAGING WITH POSITRON EMISSION TOMOGRAPHY

Prospective delineation of viable from nonviable myocardium based on patterns of myocardial perfusion and metabolism with positron emisson tomography (PET) is one of the most active areas of research with this modality. Myocardial ischemia induces characteristic changes in myocardial metabolism that accompany reductions in contractile function.

Under physiologic conditions, myocardial metabolism is virtually exclusively aerobic (*7*). The heart meets its energy demands largely by the oxidative metabolism of fatty acids and glucose. Even under fasting conditions, nonesterified fatty acids are the preferred energy source. With ischemia, oxidation of fatty acids is impaired and aerobic and anaerobic metabolism of glucose becomes proportionally more important. While it is felt that glucose metabolism can maintain cellular viability for a time after severe ischemia, it is unlikely that sufficient energy can be produced from anaerobic glucose metabolism to maintain viability indefinitely (*8*).

Nonetheless, since glucose metabolism (anaerobic and aerobic) predominates in ischemic myocardium, enhanced uptake of fluorine-18- (^{18}F) fluorodeoxyglucose (FDG) in relation to flow has been proposed as an accurate means to identify viable myocardium (*9–11*). FDG is a glucose analog that traces the initial components of the metabolic flux of glucose by the heart, including transmembranous transport and hexokinase-mediated phosphorylation. The phosphorylated FDG is trapped effectively within myocytes because the myocyte is relatively impermeable to it and because it is a poor substrate for further metabolism by either glycolytic or glycogen-synthetic pathways. Dephosphorylation of glucose-6-phosphate and presumably of FDG-6-phosphate appears to be quite slow although not negligible (*12,13*). The regional distribution of FDG, assessed 40–60 min after administration of tracer (an interval sufficient for a large proportion of uptake and phosphorylation), is thought to reflect overall glycolytic flux (*13*). The extent of myocardial uptake of FDG is dependent not only on the metabolic state of the tissue with respect to normoxia and ischemia, but also is sensitive to the pattern of myocardial substrate use (*9,14*).

Results from several studies of patients with coronary artery disease (presenting as either unstable or stable ischemic syndromes) have suggested that PET with FDG can identify viable myocardium in zones of contractile dysfunction. In patients with stable coronary artery disease, improvement in region function after revascularization was evident in 75%–85% of dysfunctional segments that exhibited FDG accumulation. In contrast, between 78%–92% of segments with diminished flow and concomitantly reduced FDG uptake failed to exhibit functional improvement aftery surgery (*10,11*). In contrast to these results, in patients studied within 72 hr of acute myocardial infarction, and treated conservatively (e.g., no pharmacologic or mechanical revascularization was performed), only 50% of segments demonstrating uptake of FDG improved functionally over time (*15*). These contrasting results can probably be explained by the inability of FDG to differentiate the metabolic fate of glucose in the myocardium (aerobic from anaero-

bic glucose metabolism or glycogen synthesis), the temporal pattern of glucose use (which varies with time after ischemia), as well as the natural fate of jeopardized myocardium (dependent on the amount of myocardium at risk, collateral flow and loading conditions among other factors).

To date, only ~75 patients have been studied prospectively to determine the accuracy of PET using FDG in identifying *viable* myocardium, that is, predicting the recovery of mechanical function. Despite the variable results depending upon the type of ischemic insult and the success of interventions, the finding of myocardial uptake of FDG is now being suggested as the sine qua non of viable myocardium. Consequently, studies designed to evaluate established as well as new diagnostic approaches for identifying viable myocardium are incorporating PET using FDG as the gold standard for myocardial viability in lieu of serial measurements of contractile function. This is premature.

The relatively poor spatial resolution of the current generation of tomographs operated in the ungated mode precludes delineation of transmural gradients of tracers within the myocardium. Accordingly, imaging with PET cannot distinguish FDG accumulation in metabolically active tissue within zones of infarction. These spared cells may accumulate FDG but may not be able to contribute to effective mechanical function. Further confounding the interpretation of enhanced uptake of FDG are recent experimental studies which suggest that even homogeneously infarcted myocardium can accumulate glucose (*16*). Moreover, preliminary studies suggest myocardial glucose utilization varies significantly during the time-course of reperfusion (*17*) and that the maintenance of oxidative metabolism during ischemia, and recovery of oxidative metabolism after recanalization, may be the critical determinant of ultimate functional recovery (*18,19*). Consequently, positron-emitting tracers that can measure oxidative metabolism or tissue hypoxia directly such as carbon-11-acetate or ^{18}F-fluoromisonidazole may prove to be more useful than FDG in identifying viable myocardium.

PRESENT STUDY

The study by Gould and colleagues, reported in this month's issue of the *Journal* (*20*), describes a new approach for identifying viable myocardium with PET using rubidium-82 (^{82}Rb). In 43 patients who had suffered myocardial infarction from 4 days to 72 mo prior to the PET study and who had undergone a spectrum of treatment ranging from no intervention to acute revascularization, estimates of sarcolemmal integrity based on ^{82}Rb tissue kinetics compared favorably with myocardial accumulation of FDG which, in this study, was the only criterion used to determine myocardial viability.

Clearly, this approach offers some strong logistical advantages over other PET approaches for identifying viable myocardium. Rubidium-82 is generator-produced, obviating the need for an on-site cyclotron. Obtaining all the necessary information regarding tissue viability from the administration of a single radiopharmaceutical decreases the complexity and duration of the study. Unfortunately, the lack of serial measurements of regional function and the lack of individual patient data severely limits the conclusions one can draw about the ability of PET using ^{82}Rb tissue kinetics to identify viable myocardium. As noted above, the use of FDG as the gold standard for identifying viable myocardium, particularly in the setting of myocardial infarction, is inadequate. Nonetheless, one conclusion that can be drawn from the study is that regional ^{82}Rb tissue kinetics do correlate with accumulation of FDG in the myocardium of patients with infarction.

The use of rubidium as an index of myocardial viability is predicated on the demonstrations by Goldstein that transiently ischemic myocardium (felt to be viable although functional assessments were not performed) retained extracted tracer whereas myocardium subjected to more prolonged periods of ischemia (and felt not to be viable) demonstrated increased back-diffusion of ^{82}Rb (*21,22*). In the present study, the ability to extract and retain rubidium was used to define viability.

Two static scans were employed to estimate retention, one 95-sec scan starting 95 sec after the beginning of tracer infusion and a late 4-min scan beginning 200 sec after the initiation of tracer administration. This "late" scan, which is now being proposed to evaluate loss of tracer from myocardium, is routinely used to delineate myocardial perfusion (assumed to be independent of metabolic status) (*23,24*). A final troubling assumption of the approach is that increased efflux of ^{82}Rb is an incontrovertible marker of irreversible injury. While rubidium behaves in many respects like potassium, skeletal, muscle, and myocardial kinetics of these two cations are not identical (*25,26*). In addition, although potassium efflux is thought to be a sensitive measure of tissue injury, early revascularization promptly restores cellular potassium homeostasis (*27*). Accordingly, the demonstration of efflux of these cations cannot be viewed as indicative of irreversible cell death. Regardless of these limitations, the approach described by the authors for assessing myocardial viability using ^{82}Rb is intriguing and certainly warrants further evaluation.

Therapeutic interventions designed to improve the balance of oxygen delivery and consumption in dysfunctional myocardium are implemented with the ultimate goal of improving regional contractile function. A primary goal of cardiac PET will likely continue to focus on the metabolic abnormalities that

underlie myocardial dysfunction. Nonetheless, from a clinical standpoint, the utility of any diagnostic approach purported to identify viable myocardium can only be accurately ascertained with a direct comparison with changes in regional function.

Robert J. Gropler
Mallinckrodt Institute of Radiology
St. Louis, Missouri
Steven R. Bergmann
Washington University School of Medicine
St. Louis, Missouri

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