The compelling pathophysiology of the states of reversible LV dysfunction, myocardial hibernation, and myocardial stunning have spawned a voluminous literature as clinical investigators attempt to optimize the noninvasive identification of patients with these conditions before consideration of revascularization. Such techniques have direct relevance in patients with clinical syndromes associated with LV dysfunction. This is perhaps most important and most relevant in patients with a clinical syndrome of heart failure and a significant degree of global LV dysfunction, a subset of whom will derive considerable benefit in terms of outcome and recovery of LV function after revascularization. Several studies have now suggested that revascularization in the setting of LV dysfunction and significantly retained myocardial viability is associated with an improved natural history1–5 as well as improvement in heart failure symptoms and functional capacity.6 Besides providing clinically relevant data, noninvasive scintigraphic and echocardiographic techniques have also helped to illuminate the complex perfusion, metabolic, and functional correlates of these states of reversible LV dysfunction, which remain subjects for debate.7,8

Steps Forward in the Assessment of Myocardial Viability in Left Ventricular Dysfunction

James E. Udelson, MD

Traditionally, the scintigraphic techniques for evaluation of myocardial viability could be broadly categorized into the SPECT method and agents assessing both perfusion and cell membrane integrity, and PET with tracers assessing perfusion and metabolic activity, including features of both cellular fatty acid and glucose metabolism.9 More recently, however, these distinctions have blurred with the advent of high-energy collimators for SPECT imaging of positrons,10,11 allowing the potential for the more widely available SPECT imaging technique to assess metabolic activity with 18FDG. Because PET technology is not widely available, and because on the basis of its expense and nonuniform reimbursement in this era of cost containment it is unlikely to be as available as SPECT in the future, the ability of SPECT imaging to assess regional metabolic activity in states of LV dysfunction is potentially of great interest. This would be particularly true to the extent that imaging of preserved or enhanced metabolic activity in patients with LV dysfunction is more fundamentally sound or accurate for detecting myocardial viability than imaging cell membrane integrity with available SPECT agents such as 201Tl or 99mTc-based agents such as sestamibi or tetrofosmin.

The availability of 18FDG imaging with SPECT methodology thus brings up a host of interesting questions as one considers the relative merits of the various techniques and agents: (1) Is there loss of data integrity as 18FDG metabolic imaging is done with SPECT techniques compared with PET techniques? (2) Is the combined use of SPECT 18FDG imaging in addition to SPECT perfusion imaging advantageous over SPECT perfusion imaging alone? (3) Is the assessment of metabolic activity by itself sufficient for clinical decision making regarding revascularization in the setting of LV dysfunction? (4) How does 18FDG imaging with PET or SPECT compare with optimal iterations of SPECT thallium or sestamibi imaging? If indeed metabolic tracers identified with SPECT imaging compare favorably to the more widely validated SPECT agents and protocols, then one must ask whether SPECT imaging of 18FDG can (or should) replace SPECT perfusion imaging for the routine assessment of myocardial viability in relevant clinical scenarios.

Several of these questions are addressed by a report in the current issue of Circulation. In a comprehensive investigation, Srinivasan and colleagues12 have studied a group of 28 patients with chronic CAD and significant resting LV dysfunction (average ejection fraction, 33±15%). All patients underwent 18FDG imaging studies with SPECT as well as PET, and the scintigraphic data from the two techniques were compared and then were also compared with stress-redistribution-reinjection 201TI SPECT data from the same patients. Using various thresholds of 18FDG PET activity as the reference standard for myocardial viability, the authors found an excellent correlation between regional activities of 18FDG with both SPECT and PET technologies. The use of ROC curves demonstrated that the SPECT 18FDG data have excellent ability to discriminate viable from nonviable myocardial segments (as defined by the 18FDG PET data), with areas under the ROC curve ranging from 0.92 to 0.95. The ROC curve analysis also demonstrated an excellent discriminative ability for the SPECT thallium redistribution/reinjection data to define myocardial viability, with areas under the ROC curve ranging from 0.90 to 0.95, again with 18FDG PET used as the reference standard. Thus, to the extent that 18FDG PET is an adequate reference standard for regional viability, it may be concluded from these data that...
quantified regional activities of both $^{18}$FDG SPECT and SPECT thallium redistribution/reinjection images provide generally similar and accurate data regarding regional myocardial viability in LV dysfunction.

As subsets of the patients and segments were examined, however, small differences between the tracers and the techniques were discerned: among patients with a more severe degree of LV dysfunction (LV ejection fraction $\leq 25\%$), there appeared to be a slight underestimate of myocardial viability (as defined by a 60% $^{18}$FDG PET threshold) by thallium SPECT imaging compared with $^{18}$FDG SPECT imaging, and among segments with severe irreversible SPECT thallium defects (which would generally be considered as scarred myocardium), 43% of such segments were found to be viable by $^{18}$FDG PET imaging, the majority of which were also found to have preserved metabolic activity by $^{18}$FDG SPECT imaging. Thus, for patients in whom issues regarding myocardial viability are most relevant, that is, those with severe LV dysfunction, $^{18}$FDG SPECT imaging may have an advantage compared with SPECT thallium imaging.

The discordant segments, however, represent just over 5% of the entire population of segments examined in these 28 patients, and $\approx 8\%$ of segments with abnormal stress thallium findings. Moreover, the majority of the discordant segments appeared to be located in the inferior wall, and as the authors discuss, the discordance is likely due at least in part to a physiological limitation of thallium delivery or uptake but rather to the physical property of attenuation of photons in SPECT thallium imaging from the inferior region compared with the higher-energy photons of $^{18}$FDG and the correction for such attenuation when PET technology is used. These modest differences between tracers and techniques may indeed be obviated with the use of attenuation correction algorithms for SPECT, as the authors acknowledge. Previous studies have also demonstrated discordances involving PET $^{18}$FDG imaging and SPECT sestamibi imaging predominating in the inferior wall.14,15

The authors conclude from their data that there is generally excellent correlation between the SPECT and PET evaluations of regional activities of $^{18}$FDG and also very good correlation between SPECT thallium imaging and $^{18}$FDG imaging by both SPECT and PET techniques. $^{18}$FDG data from SPECT or PET appeared to identify preserved metabolic activity in a small subgroup of territories considered scarred by thallium. However, $^{18}$FDG SPECT also identified apparently preserved metabolic activity in a small subpopulation of segments that were identified as predominantly scarred by both SPECT thallium and $^{18}$FDG PET. The clinical relevance of the latter finding remains undetermined.

These important and comprehensive data build on several previous studies examining the use of $^{18}$FDG PET imaging (Table).

Burt and coworkers,16 using semiquantitative visual analysis, found 91% concordance between $^{18}$FDG PET and SPECT techniques in 20 patients with CAD. Bax and colleagues,17 with extensive experience in developing the techniques of planar and SPECT $^{18}$FDG imaging, reported a 77% concordance in quantitative uptake of $^{18}$FDG PET compared with SPECT in 20 patients with coronary disease and LV dysfunction. A similar degree of concordance was seen when combined perfusion/metabolism studies were performed with $^{201}$TI/$^{18}$FDG SPECT compared with $[^{13}$N$]ammonia/$^{18}$FDG PET. In a subsequent analysis,18 these investigators reported that $^{201}$TI/$^{18}$FDG perfusion/metabolic SPECT data had more powerful predictive value for functional recovery in dysynergic myocardium than dobutamine $^{201}$TI-reinjection data (without redistribution) or low-dose dobutamine echocardiography. Other authors have reported qualitatively similar information between $^{18}$FDG PET and SPECT studies.19,20

Hence, the data from Srinivasan and colleagues12 confirm and extend the previous observations regarding the use of $^{18}$FDG SPECT imaging to identify myocardial viability. The generally higher concordance of the $^{18}$FDG SPECT data with both $^{18}$FDG PET and SPECT thallium in the present study compared with several of the previous reports may be due in part to methodological differences of the studies. The use of both redistribution and reinjection thallium images will opti-

### Studies of $^{18}$FDG SPECT Imaging

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*EF indicates ejection fraction; PPV, positive predictive value; and NPV, negative predictive value.

*Ten of these patients overlap with Reference 18.
mize the detection of stress defect reversibility, and thus myocardial viability, compared with the use of redistribution or reinjection images alone; this would tend to favor the higher concordance for $^{201}$TI with metabolic $^{18}$FDG data seen in the study of Srinivasan and coworkers.

The entirety of the data at hand allows us to begin to address some of the questions raised by the availability and feasibility of $^{18}$FDG SPECT imaging.

Is there loss of data integrity as $^{18}$FDG metabolic imaging is performed with SPECT techniques compared with PET techniques?

Despite the inherently more limited spatial resolution of SPECT compared with PET and the lack of attenuation correction in these SPECT studies, the weight of the data would suggest that there is generally a very good correlation between regional activity data of $^{18}$FDG obtained with SPECT methodology compared with those obtained with PET and that data integrity is not greatly compromised. The degree of concordance in these studies is similar to that previously reported for thallium stress-redistribution-reinjection data and concordance in these studies is similar to that previously reported for thallium stress-redistribution-reinjection data and rest-redistribution thallium data.

The more limited spatial resolution of SPECT compared with PET would suggest, however, that in some instances, a truly infarcted segment may not be adequately resolved with SPECT. Indeed, Srinivasan and colleagues found that 27% of segments concordantly considered infarct by both PET and $^{201}$TI demonstrated apparent metabolic activity by $^{18}$FDG--SPECT, raising questions as to possible loss of specificity by the metabolic SPECT approach (though this discordance represented only 3% of all abnormal thallium segments). This apparent small loss of specificity will be examined in future studies with the use of coincidence detection techniques applied to SPECT. After collision of a high-energy positron with an electron, two high-energy gamma rays are emitted in exactly opposite directions. This annihilation event can be captured in coincidence by two detectors placed on opposite sides of the body. Only when a coincidence event is detected simultaneously by these opposed cameras is a count recorded. This technique allows more precise localization of annihilation events (and tracer source) than single photon emission detection alone, contributing to improved spatial resolution. Coincidence detection for SPECT systems is now a reality, and this principle derived from PET imaging may allow improved resolution of SPECT metabolic imaging, addressing issues of specificity.

Is the combined use of SPECT $^{18}$FDG imaging in addition to SPECT perfusion imaging advantageous over SPECT perfusion imaging alone?

The present study would suggest that in specific clinical circumstances, such as in a patient with severe LV dysfunction and segments with severe irreversible thallium defects, $^{18}$FDG SPECT imaging may provide incremental information optimizing sensitivity to detect residual viable myocardium. Previous studies combining rest thallium or sestamibi perfusion imaging with $^{18}$FDG metabolic imaging suggests another clinical scenario in which incremental data may be provided by $^{18}$FDG imaging. In dysfunctional segments with moderately severe reduction of thallium or sestamibi uptake (in the range of 40% to 60% of peak uptake), our laboratory and others have demonstrated that there is only an intermediate probability of functional recovery after revascularization, consistent with the general concept that scintigraphic data provide a continuous spectrum of values, relating to a continuous spectrum of probability of functional recovery. von Dahl and colleagues demonstrated that the addition of $^{18}$FDG imaging information using PET in such segments with an intermediate sestamibi uptake can help differentiate those segments which are far more likely to show functional recovery from those which are far less likely to recover function after revascularization. Similar data are suggested by the PET perfusion/metabolism studies by Tamaki and coworkers. Thus, the serial application of perfusion followed by metabolic imaging techniques may be advantageous when the initial perfusion studies suggest only an intermediate probability of functional recovery in a dysynergic territory and when the clinical decision regarding revascularization requires more precise definition of the likelihood of functional recovery in such a territory. In selected clinical scenarios, then, $^{18}$FDG SPECT imaging may indeed provide incremental value beyond perfusion imaging data alone. It is important to recognize, however, that in the majority of patients with chronic CAD and LV dysfunction, clinical decisions regarding revascularization can often be made on the basis of the standard perfusion imaging techniques and protocols already widely used, a concept supported by the excellent discriminative ability of $^{201}$TI (high area under the ROC curve) to discern metabolic evidence of viability by PET in the present study.

Is the assessment of metabolic activity alone sufficient for clinical decision making regarding revascularization in the setting of LV dysfunction?

Certain studies now suggest that a “snapshot” of SPECT tracer uptake reflecting cell membrane integrity may provide sufficient data regarding the probability of functional recovery in asynergic myocardium in selected circumstances. Scigra and coworkers, using a stepwise multivariate discriminative function analysis, demonstrated that quantitative regional activity of $^{201}$TI using the redistribution images alone (3 to 4 hours after rest injection) provided the most powerful data predicting functional recovery after revascularization compared with rest thallium data or the reversibility between the rest and the redistribution images. Similar findings were also suggested in a study from our laboratory, as well as that of Ragosta and colleagues. Thus, although no data are available regarding functional recovery in the patient population studied by Srinivasan et al., it is likely that the demonstration of preserved metabolic activity in dysfunctional myocardium may alone provide sufficient data in selected patients for clinical decision making in the setting of known severe CAD and significant LV dysfunction. Further information regarding functional recovery on follow-up in patients studied with $^{18}$FDG SPECT imaging is needed to confirm this point and to define the relationship between the continuous spectrum of $^{18}$FDG-SPECT uptake and probability of functional recovery.
How does $^{18}$FDG imaging with PET or SPECT compare with optimal iterations of SPECT thallium or sestamibi imaging?

The data from the present investigation, as well as previous studies, would suggest that indeed, $^{18}$FDG imaging with SPECT or PET techniques provides generally concordant information with an optimized SPECT thallium protocol and as noted above, may provide incremental information in certain clinical scenarios, specifically in patients with a more severe degree of LV dysfunction. Studies in larger numbers of patients comparing $^{18}$FDG-SPECT data to optimized $^{201}$TI or sestamibi protocols will assist in defining more precisely the incremental yield of this newer technique beyond the standard techniques and form the basis for comparisons of relative costs and effectiveness.

The ideal agent for assessing regional myocardial viability in asynergic myocardium would preferentially target hibernating or repetitively stunned myocardium compared with predominantly scarred or relatively normal myocardium. Although there is controversy regarding whether the enhancement of $^{18}$FDG uptake in reversibly dysfunctional myocardium is predominantly due to chronic stimulation of anaerobic metabolism or to a distinct metabolic alteration involving activation of glycogen synthase resulting in the observed increase in glycogen stores seen in biopsy studies, the use of this agent for metabolic imaging is conceptually quite attractive. More than 10 years ago, Camici and colleagues reported prolonged enhancement of regional $^{18}$FDG uptake after stress-induced ischemia. It may be that in patients with chronic CAD and LV dysfunction, exercise or postexercise injections of $^{18}$FDG may lead to further preferential uptake in areas of reversible ischemic dysfunction. Whether the underlying pathophysiology represents the classic model of hibernation or the proposed mechanism of repetitive stunning, superimposition of a demand-ischemic stress may serve to preferentially enhance $^{18}$FDG uptake relative to flow in reversibly dysfunctional myocardium and optimize scintigraphic detection, an interesting area for further research in this field.

In a time in which it is appropriate to evaluate the extent of testing truly necessary to make an informed clinical decision, another important area of future investigation will involve how much, or perhaps more importantly how little, information is needed from scintigraphic or echocardiographic techniques to optimize decision making for revascularization in the setting of CAD and LV dysfunction. Studies in larger numbers of patients comparing $^{18}$FDG-SPECT data to optimized $^{201}$TI or sestamibi protocols will assist in defining more precisely the incremental yield of this newer technique beyond the standard techniques and form the basis for comparisons of relative costs and effectiveness.
chronic but reversible LV dysfunction, are evolving; new data suggest a more dynamic process with steady ischemic degeneration of myocardial structural and cellular elements and suboptimal outcomes in the absence of relatively prompt revascularization.44

The study of Srinivasan and coworkers represents another step forward in this evolution. Metabolic imaging is now accessible well beyond specialized PET centers, given the availability of 18FDG through regional cyclotrons as well as the advent of high-energy collimation for SPECT systems. The precise role for metabolic SPECT imaging and its specific advantages and cost-effectiveness comparisons to more standard techniques remain to be determined. Perhaps more important is that such studies underscore the general concept that in patients with severe, chronic CAD and LV dysfunction, noninvasive imaging techniques provide information regarding potential benefit of revascularization to balance against the higher-risk nature of surgery in this population. Research in this area often focuses on the nuances and differences in tracers and methodologies, perhaps analogous to the studies of various thrombolytic agents for myocardial infarction to balance against the higher-risk nature of surgery in this population. In these latter syndromes, however, these effective strategies are thought to be significantly underutilized in the populations of interest.45,46 Although tracers and techniques for assessment of myocardial viability will continue to evolve, it is the broader application of these imaging techniques in relevant populations, particularly those with heart failure and significant LV dysfunction, that will likely have significant impact in reducing the morbidity and mortality associated with the clinical syndromes of chronic ischemic LV dysfunction.

References


Assessment of Myocardial Viability


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James E. Udelson

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