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

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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 history\(^1\text{–}^5\) 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.\(^7\text{–}^8\)

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,\(^10\text{–}^11\) allowing the potential for the more widely available SPECT imaging technique to assess metabolic activity with \(^18\)FDG. 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 \(^201\)Tl or \(^99m\)Tc-based agents such as sestamibi or tetrofosmin.

The availability of \(^18\)FDG 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 \(^18\)FDG metabolic imaging is done with SPECT techniques compared with PET techniques? (2) Is the combined use of SPECT \(^18\)FDG 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 \(^18\)FDG 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 \(^18\)FDG 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 colleagues\(^12\) have studied a group of 28 patients with chronic CAD and significant resting LV dysfunction (average ejection fraction, 33±15%). All patients underwent \(^18\)FDG 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 \(^201\)TI SPECT data from the same patients. Using various thresholds of \(^18\)FDG PET activity as the reference standard for myocardial viability, the authors found an excellent correlation between regional activities of \(^18\)FDG with both SPECT and PET technologies. The use of ROC curves demonstrated that the SPECT \(^18\)FDG data have excellent ability to discriminate viable from nonviable myocardial segments (as defined by the \(^18\)FDG 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 \(^18\)FDG PET used as the reference standard. Thus, to the extent that \(^18\)FDG PET is an adequate reference standard for regional viability, it may be concluded from these data that...
quantified regional activities of both 18FDG 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 underestimation of myocardial viability (as defined by a 60% 18FDG PET threshold) by thallium SPECT imaging compared with 18FDG 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 18FDG PET imaging, the majority of which were also found to have preserved metabolic activity by 18FDG SPECT imaging. Thus, for patients in whom issues regarding myocardial viability are most relevant, that is, those with severe LV dysfunction, 18FDG 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 not 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 18FDG 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 discordancces involving PET 18FDG 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 18FDG and also very good correlation between SPECT thallium imaging and 18FDG imaging by both SPECT and PET techniques. 18FDG data from SPECT or PET appeared to identify preserved metabolic activity in a small subgroup of territories considered scarred by thallium. However, 18FDG SPECT also identified apparently preserved metabolic activity in a small subpopulation of segments that were identified as predominantly scarred by both SPECT thallium and 18FDG PET. The clinical relevance of the latter finding remains undetermined.

These important and comprehensive data build on several previous studies examining the use of 18FDG SPECT imaging (Table).

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

Hence, the data from Srinivasan and colleagues12 confirm and extend the previous observations regarding the use of 18FDG SPECT imaging to identify myocardial viability. The generally higher concordance of the 18FDG SPECT data with both 18FDG 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-
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 201Tl with metabolic 18FDG 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 18FDG SPECT imaging.

**Is there loss of data integrity as 18FDG 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 18FDG 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 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 201TI demonstrated apparent metabolic activity by 18FDG 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 18FDG 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, 18FDG SPECT imaging may provide incremental information optimizing sensitivity to detect residual viable myocardium. Previous studies combining rest thallium or sestamibi perfusion imaging with 18FDG metabolic imaging suggests another clinical scenario in which incremental data may be provided by 18FDG 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. Vom Dahl and colleagues demonstrated that the addition of 18FDG 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, 18FDG 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 201TI (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. Sciagra and coworkers, using a stepwise multivariate discriminative function analysis, demonstrated that quantitative regional activity of 201TI 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 18FDG SPECT imaging is needed to confirm this point and to define the relationship between the continuous spectrum of 18FDG-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 $^{201}$Tl 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 such as those of Sciagra and colleagues do indeed suggest that traditional thinking regarding the need for multiple image sets in all patients may be obsolete. The present study by Srinivasan and coworkers also suggests that evaluation of metabolic activity by SPECT imaging alone may be sufficient for such purposes in selected circumstances. A very important question, however, involves when resting viability information alone is sufficient and when more comprehensive information regarding stress-induced regional ischemia may also be necessary. In this regard, Kitiou and colleagues, in a preliminary study, reported that dysfunctional myocardium in which stress-induced ischemia can be demonstrated is more likely to recover function compared with dysfunctional segments with mild to moderate irreversible thallium defects, that is, preserved viability but no apparent inducible ischemia. A single SPECT rest or redistribution thallium or sestamibi study alone would be insufficient to make such a distinction. How best to choose patients in whom a more comprehensive protocol is necessary requires further study.

There are many unresolved issues of great interest in the field of assessment of myocardial viability in patients with CAD and LV dysfunction. One such issue regards the appropriate end point in imaging studies of myocardial viability. The present study, like many others, uses metabolic activity by PET as the reference standard. Metabolism studied by PET, however, has only 80% to 85% accuracy in predicting functional recovery after revascularization in asynergic segments. Regional functional recovery after revascularization, an end point itself in many studies, may be a sufficient but not necessary condition for improvement in clinical and prognostic outcomes in a patient after revascularization. As discussed by Bonow, many favorable outcomes associated with revascularization may not require regional functional recovery at rest after revascularization. These include stabilization of the electrical milieu, prevention of subsequent myocardial infarction, improved symptoms and functional capacity, and improved overall outcome in terms of natural history. Preliminary data from our laboratory working in collaboration with investigators in the United Kingdom have demonstrated that even only moderately preserved viability within an infarct zone after anterior myocardial infarction is associated with an attenuation of subsequent remodeling over time. Lombardo and colleagues recently reported that after revascularization of dys-synergic but viable myocardium, contractile reserve was recovered even in segments in which resting function did not itself improve. Pagley and coworkers observed that among patients with severe CAD and LV dysfunction undergoing revascularization, those patients with more preserved viability by thallium imaging had a significantly more favorable event-free survival compared with patients with less evidence of preserved viability. Follow-up LV function was not uniformly reported among patients in this study. An important concept to be tested in large databases now being assembled is whether natural history outcomes in patients with LV dysfunction are improved by revascularization of a significant territory of viable myocardium independent of functional recovery. In this regard, Samady and colleagues, in a recent preliminary report, found that in patients with LV ejection fraction of $<$30%, survival at almost 3 years after revascularization was similar among patients with no postoperative increase in ejection fraction compared with those with significantly improved LV function. If these data are confirmed, techniques that optimize sensitivity of detection of viable myocardium (even of a magnitude not sufficient for contractile recovery) will be favored over those that optimize specificity of functional recovery.

The evolution of perfusion, metabolic, and functional imaging techniques has broadened our understanding of the pathophysiology of states of hibernation and stunned myocardium, at the same time contributing importantly to the clinical care of patients with CAD and LV dysfunction. Even traditionally held concepts, such as the relatively stable adaptation of
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. 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 FDG 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 and ACE inhibitors in heart failure. In these latter syndromes, however, these effective strategies are thought to be significantly underutilized in the populations of interest. 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


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