

# How can stunning be detected clinically?

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*Noninvasive imaging is well-suited to the assessment of myocardial viability. In PET, preserved metabolic activity in regions with reduced blood flow is an accurate clinical marker, with  $\approx 85\%$  accuracy for predicting the efficacy of revascularization. Nevertheless, early after reperfusion therapy, this method may overestimate the presence and extent of viable myocardium. Regions of severely ischemic or hibernating myocardium may also be identified by Tl 201 imaging, using late redistribution imaging, thallium reinjection imaging, or rest-redistribution protocols. Tc 99m sestamibi has theoretic weaknesses for viability assessment, but recent data suggest that this agent is very satisfactory for clinical viability assessment. Low-dose dobutamine echocardiography is also useful for detection of viable myocardium. Although these methods appear to have similar diagnostic accuracy, large-scale studies comparing PET, Tl 201, and dobutamine echocardiography are required early after reperfusion therapy or revascularization to determine their relative efficacies.*

In a large subset of patients recovering from acute myocardial infarction, left ventricular (LV) performance is reduced on the basis of regionally stunned or hibernating myocardium (or a combination of stunned and hibernating myocardium) rather than irreversibly infarcted myocardium. The detection of reversibly dysfunctional myocardium is clinically relevant, as regional and global LV function in such patients may improve substantially after revascularization. Noninvasive imaging methods to assess myocardial metabolic activity, membrane integrity, and inotropic reserve are ideally suited for this assessment.

## Positron emission tomography

Positron emission tomography (PET) has emerged as a promising method for demonstrating viable myocardium in patients with coronary artery disease and chronic LV dysfunction. Myocardial viability by PET is identified on the basis of intact metabolic activity in regions of severely underperfused and dysfunctional myocardium. The most extensive experience thus far has been achieved using  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) as a marker of regional exogenous glucose utilization in such hypoperfused regions. In particular, a pattern of enhanced FDG uptake

in regions with reduced perfusion (termed the FDG/blood flow "mismatch") indicates viable tissue that has preferentially shifted its metabolic substrate toward glucose rather than fatty acids or lactate. The finding of preserved metabolic activity in myocardial regions with reduced blood flow has been demonstrated in several studies to be an accurate clinical marker with which to distinguish viable myocardium from myocardial fibrosis, with positive and negative predictive accuracies in the range of 85% for identifying regions that will manifest improved function after revascularization. Thus, PET appears to yield excellent viability information in patients with chronic coronary artery disease.

However, the use of metabolic imaging with FDG may be limited early after reperfusion therapy for acute myocardial infarction. Although the kinetics of glycolysis after myocardial reperfusion is incompletely understood, the available data suggest that recovery of glucose metabolism is rapid and returns to either aerobic levels or is only slightly increased in stunned myocardium after restoration of blood flow.

PET is more promising in regions with persistent hypoperfusion, as there is a high predictive accuracy that a region with reduced FDG uptake represents irreversibly damaged myocardium. In contrast, the predictive accuracy that a region with FDG/blood flow



mismatch represents viable tissue that will improve in function is only 50%. Thus, metabolic imaging with FDG early after reperfusion therapy identifies necrotic myocardium accurately but may substantially overestimate the presence and extent of viable myocardium. PET imaging with  $^{11}\text{C}$ -acetate has also emerged as a means to evaluate myocardial viability as a marker of blood flow and oxidative metabolism. In one study, preservation of myocardial oxidative metabolism was predictive of restoration of mechanical function after revascularization in patients with recent myocardial infarction. However, in another study, $^{11}\text{C}$ -acetate did not provide additional independent information in terms of myocardial viability beyond that provided by regional blood flow and glucose metabolism.

### **Thallium 201 imaging**

The requirements for cellular viability include intact sarcolemmal function to maintain electrochemical gradients across the cell membrane, as well as preserved metabolic activity to generate high-energy phosphates. These processes also require adequate myocardial blood flow to deliver substrates and wash out the metabolites of the metabolic processes. As the retention of thallium 201 is an active process that is a function of cell viability and cell membrane activity, as well as blood flow, thallium 201 should in theory be taken up and retained by viable myocardial regions that also retain FDG and other metabolic tracers. However, initial thallium uptake appears to overestimate myocardial viability early after reperfusion therapy (up to several hours after reperfusion). Hence, early thallium uptake after reperfusion cannot differentiate viable from necrotic myocardium. On the other hand, necrotic

myocardium cannot retain thallium and, despite its initial uptake, thallium washout is accelerated in necrotic tissue. Consequently, rapid early thallium washout might be used to indicate nonviability. This concept underscores the importance of redistribution imaging several hours after thallium administration, to allow for washout from necrotic myocardium and "wash-in" of viable regions served by a coronary artery with a residual flow-limiting stenosis.

In patients studied several days to weeks after myocardial infarction, testing for myocardial viability follows the same algorithms as in patients with chronic LV dysfunction. As many regions of severely ischemic or hibernating myocardium appear to have irreversible thallium defects on standard exercise-redistribution imaging, standard thallium scintigraphy may not provide satisfactory precision in identifying viable myocardium. These relatively poor results with exercise-redistribution imaging may be overcome using other imaging protocols. These include: (i) late (24-72-hour) redistribution imaging; (ii) thallium reinjection imaging, in which imaging is repeated after a small additional dose of thallium is injected at rest after a period of redistribution following stress imaging; or (iii) thallium imaging without exercise using a rest-redistribution protocol. In each of these protocols, both defect reversibility and severity of the thallium defect are important markers of viable myocardium.

### **Technetium Tc 99m sestamibi imaging**

Technetium 99m sestamibi, like thallium 201, requires intact sarcolemmal and mitochondrial processes for retention, and this

agent has been shown to be an excellent marker of cellular viability. In both experimental and clinical settings in which sestamibi delivery is adequate to dysfunctional myocardium, such as after reperfusion to previously ischemic or damaged myocardium, the uptake and retention of sestamibi tracks with markers of myocardial viability rather than pure markers of perfusion. However, sestamibi does not redistribute as readily as thallium after its initial uptake either during exercise or at rest. Thus, compared to thallium, sestamibi has inherent weaknesses for viability assessment in clinical situations in which blood flow is severely impaired and tracer delivery is reduced. Several studies comparing rest-exercise sestamibi imaging to thallium imaging indicate that sestamibi underestimates viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction. In addition, a large percentage of sestamibi defects in patients with left ventricular dysfunction demonstrate FDG activity by PET imaging, indicating viability. However, three recent studies indicate that a quantitative analysis of regional sestamibi activity after administration at rest substantially increases the accuracy for identifying viable myocardium compared to thallium imaging and PET imaging. These recent findings with sestamibi should be considered preliminary in nature until confirmed by larger, more definitive studies.

### **Dobutamine echocardiography**

Previously ischemic, stunned myocardium can be identified following administration of inotropic agents such as dopamine, isoproterenol, and dobutamine, as well as by postextrasystolic

potentiation. Experimental studies in dogs have demonstrated that postischemic dysfunctional myocardium bears considerable contractile reserve that may be recruited after moderate inotropic stimulation without causing detrimental effects.

Recently, low-dose dobutamine infusion to enhance regional systolic wall thickening during echocardiography has been proposed and applied successfully to patients after thrombolytic therapy for acute myocardial infarction and in patients with chronic LV dysfunction.

The results of these studies, thus far in small numbers of patients, suggest that this method provides data at least as accurate as that achieved using scintigraphic methods.

### Clinical implications

The identification of viable myocardium has become an area of intense interest for several reasons. Among these is the rather unique potential of nuclear cardiology techniques to distinguish viable regions on the basis of perfusion, cell membrane integrity, and metabolic activity, and the ability of dobutamine echocardiography to assess regional inotropic reserve. Although the available data imply that each of these methods has similar diagnostic accuracy, larger-scale studies comparing PET, thallium 201, Tc 99m sestamibi and dobutamine echocardiography are required in patients studied early after reperfusion therapy for acute myocardial infarction and those undergoing revascularization to determine the relative efficacies of these methods in identifying viable myocardium.

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