Review Article:

MYOCARDIAL VIABILITY- ASSESSMENT AND CLINICAL RELEVANCE

*BASHIR HANIF *, ATIF BASHIR*

Summary:

The assessment of myocardial viability is an important indication for noninvasive imaging in patients with coronary artery disease and chronic ischemic left ventricular dysfunction. Left ventricular function is a major determinant of survival in coronary artery disease. The goal of myocardial viability assessment is to differentiate patients with potentially reversible from irreversible left ventricular dysfunction[9]. In patients with chronic coronary artery disease and left ventricular dysfunction, there exists an important subpopulation in which revascularization may significantly improve regional or global left ventricular function, as well as symptoms and hence therapeutic and prognostic benefits in selected patients. The underlying pathophysiology involves reversible myocardial dysfunction (hibernation or stunning) which may exist independently or may coexist within the same patient.

Stunned myocardium refers to the state of persistent regional dysfunction after a transient period of ischemia followed by reperfusion, most commonly present in acute coronary syndromes. Hibernating myocardium refers to a condition of chronic sustained abnormal contraction due to chronic underperfusion in patients with coronary artery disease in whom revascularization causes recovery of function. These states of potentially reversible left ventricular dysfunction commonly have preserved cell membrane integrity and metabolic activity to maintain cellular functions in the absence of normal myocyte contractility secondary to resting ischemia. Stunned myocardium improves its function early post revascularization, whereas hibernating myocardium may need longer time to fully recover in function. Furthermore, exercise capacity improved in patients with viable myocardium, and long term prognosis appeared favorable if patients with viable myocardium underwent revascularization.

Viable myocardium has unique characteristics and these form the basis for the different imaging modalities that are currently available for the assessment of myocardial viability. A number of diagnostic techniques have emerged for differentiating viable from non viable myocardium in dysfunctional regions. These include evaluation of regional perfusion, cell membrane integrity, and metabolism using nuclear techniques with various radionuclide tracers; contractile reserve using dobutamine echocardiography or magnetic resonance imaging. More conventional approaches of identifying scarred and necrotic myocardium including presence of occluded coronary artery, regional contractile dysfunction, Q waves on electrocardiogram have been shown to be less accurate. New modalities include use of metabolic tracers with single photon emission tomography (SPECT), precise quantitative metabolic evaluation with positron emission tomography (PET), assessment of microvascular integrity with contrast echocardiography and use of magnetic resonance imaging (MRI). Most of these techniques are reasonably accurate in predicting myocardial viability.

INTRODUCTION

Myocardial Viability Assessment in Clinical Practice

A number of important points concerning the application of viability assessment in clinical practice, need to be clarified as they are often source of confusion for practicing physicians. First, the patients who are being considered for myocardial viability assessment should have documented coronary artery disease, with myocardial dysfunction, and these patients should be candidates for myocardial revascularization. Second, the methods utilized for viability assessment and for diagnostic or

* *Medical Director, Chief of Cardiology and Director Interventional Cardiology Tabba Heart Institute, Karachi.*

prognostic evaluation for patients with coronary artery disease overlap considerably, such as stress-redistribution thallium study. A reasonable assessment of myocardial viability can be obtained with relatively minor modifications of existing protocols, such as reinjection of thallium in patient with fixed thallium defects on conventional stress-redistribution images. If myocardial viability is the primary question in a patient, it is important to decide on the tracer, and the technique that would most accurately address the clinical question. Third, the presence of myocardial viability is not an all or none phenomenon. In dysfunctional myocardial regions there may be combination of scarred, necrotic and viable myocytes. Preservation of myocardial viability exists as a spectrum in a territory with regional dysfunction, from the possibility of no preserved viability (i.e. complete transmural infarction) to completely preserved viability (i.e. transmural hibernation or stunning with the potential for full recovery of function). The utility of viability assessment rests on the assumption that revascularization will not have therapeutic benefit in the absence of viable myocytes.

Myocardial Viability assessment with Single Photon Computed Tomography (SPECT)

Radionuclide tracers commonly utilized for assessment of myocardial viability with single photon emission computed tomography (SPECT) include Thallium 201 and Technetium-99m labeled perfusion tracers. Although these tracers have different cellular kinetics, their myocardial uptake reflect both perfusion and cell membrane integrity and therefore, myocardial viability. Thallium-201 for the last two decades is the most widely studied and used radiotracer for viability assessment[1]. Many studies in the literature evaluate the techniques for assessing viability by assigning a specific threshold or cut off point, often 50 or 60% of maximum tracer uptake [1,4,7].

Techniques and Protocols for assessing myocardial viability

Thallium -201

Thallium -201 is a clinically important tracer for assessing both regional blood flow and myocardial viability. Myocardial uptake early after intravenous injection of Tl-201 is proportional to regional blood flow with a high first pass extraction fraction of approximately 85%, the later distribution (redistribution) of thallium over a 3-4 hour period is a function of regional blood volume and is unrelated to flow. The uptake of Tl-201 is an energy-dependant process requiring intact cell membrane integrity and the presence of Tl-201 implies preserved myocyte cellular viability. Redistribution of thallium begins within 10-15 minutes after injection and is prolonged in regions of hypoperfusion and is related to rate of thallium clearance from the blood. The rate of thallium clearance from myocardial regions is linked to the concentration gradient across the myocytes and the blood.

The redistribution properties of Tl-201 have been used as an important marker of myocardial viability in stress imaging followed by a 3-4 hour redistribution image[1]. The presence of a reversible perfusion defect and /or preserved Tl-201 uptake on

Table 1
Viability Features, Techniques and Their Viability Criteria

Features	Technique	Viability Criteria
Glucose metabolism	FDG PET/SPECT	Normal perfusion/FDG uptake Perfusion-FDG mismatch
Intact cell membrane	Thallium-201	Redistribution Activity > 50%
Intact mitochondria	Technitium-99m-sestamibi	Activity > 50% Improved tracer uptake postnitrates
Contractile reserve	Dobutamine echo (MRI)	Improved contraction during infusion of low dose dobutamine

FDG, fluorodeoxyglucose; PET, positron emission tomography; SPECT, single photon emission computed tomography; MRI, magnetic resonance imaging

the 3-4 hour redistribution images is an important sign of regional viability. The absence of an important degree of redistribution or Tl-201 uptake on the redistribution images is not sufficient to suggest absence of myocardial viability.

Tl -201 Reinjection

Tl-201 reinjection is one of the most widely studied protocol for assessing viability in the presence of inconclusive result on initial stress/redistribution imaging. A second dose of Tl-201 (usually 50% of the initial dose) is reinjected after the redistribution images are complete, and a third set of images is obtained 15-20 minutes later. Approximately 50% of regions with fixed defects on stress/redistribution imaging will show significant enhancement of Tl-201 uptake after reinjection, which is predictive of future improvement in regional left ventricular function after revascularization[4]. The presence of a severe Tl-201 defect after reinjection identifies areas with very low probability of improvement in function[7].

Late Redistribution imaging

Late redistribution imaging involves obtaining a third set of images 24 to 48 hours after the initial stress Tl-201 injection, essentially allowing more time for redistribution to occur[2]. Although improvement in uptake on late redistribution images has good positive predictive value for potential improvement in regional function, the negative predictive value is suboptimal in some patients. This is likely due to low to very low Tl-201 blood levels, such that redistribution does not take place even after a prolonged time period. The late redistribution images may also be limited by suboptimal image quality due to continued washout and decay of the tracer.

Rest-Redistribution

The stress-redistribution-reinjection of Tl-201 protocol provides important diagnostic and prognostic information regarding both inducible ischemia and viable myocardium[18]. However, if only the presence and extent of myocardial viability within dysfunctional region and not the inducible ischemia is desired, or in patients who cannot or should not undergo exercise testing, it is reasonable to perform only rest-redistribution Tl-201 imaging[11]. After injecting 3 mCi of Tl-201 at rest, images are obtained 15-20 minutes later, which reflect regional blood flow at rest, and images obtained 3-4 hours later after redistribution will generally reflect preserved viability. Additional delayed imaging at 24 hours after injection may be helpful to establish more completely redistribution in myocardial regions, which appear to have significant tracer uptake but no redistribution by 4 hours.

Technetium-99m labeled perfusion tracers

The Tc-99m based tracers- sestamibi, teboroxime and tetrofosmine has negligible redistribution properties as compared to Tl-201. Therefore the ability of these tracers to assess myocardial viability was questioned initially. However, now there is substantial body of literature especially with sestamibi suggesting similar performance characteristics to Tl-201 for predicting improvement in regional function after revascularization[12,19,20]. Sestamibi is a lipophylic cationic complex that is taken up across the sarcolemal and mitochondrial membranes of myocytes by passive distribution. At equilibrium, it is retained within the mitochondria due to a large negative transmembrane potential and thus reflect cellular viability. Sestamibi performed at rest, using quantitative analysis, resulted in favorable positive (80%) and negative (96%) predictive accuracies for functional recovery after revascularization. There are number of other studies in the literature that suggest that sestamibi may underestimate myocardial viability, particularly in patients with severe left ventricular systolic dysfunction[19,20,24].

Tetrofosmine (Myoview) or Teboroxime uptake in assessing myocardial viability, although less extensively studied and limited experience appears to have similar characteristics as those of sestamibi[22,23].

Whether the factors contributing to impaired Tc-99m labeled tracer uptake and defect reversibility when compared to thallium relate to differences in extraction fraction, blood clearance, redistribution or response to altered metabolic states remains unknown. The following protocols modifications to overcome this limitation, has been proposed:

1. Dual isotope imaging that combines rest-redistribution thallium with stress sestamibi/ myoview.
2. Nitrate administration before rest sestamibi/ myoview injection[21].

3. Acquisition of delayed redistribution images.
4. Combined sestamibi perfusion and functional imaging.

Some studies have demonstrated that by incorporating information about resting function in addition to the perfusion viability data, improves the sensitivity and/or specificity for predicting functional recovery after revascularization.

Metabolic imaging with Positron Emission Tomography (PET)

The use of metabolic radiotracers with PET is generally considered the non invasive gold standard for viability assessment. The principle for using metabolic tracer for PET imaging is based on the concept that viable myocytes are metabolically active and scarred tissue is metabolically inactive.

A number of alterations in myocardial metabolism occur in myocardial ischemia[15]. The ability to label physiologic compounds such as nitrogen, carbon, and fluorine; the high energy emissions; and the generally short half life of the tracers allows examination of numerous physiologic processes.

In clinical practice, knowledge of both regional perfusion and metabolism yields the most comprehensive assessment of viability. The most commonly used PET protocol involves evaluation of myocardial glucose metabolism with 18F-FDG (fluorodeoxyglucose) in conjunction with PET or SPECT examination of myocardial blood flow with 13N-ammonia or Tc-99m sestamibi/tetrofosmine, respectively[13,14]. In general, the pattern of perfusion-metabolism mismatch is the most predictive of functional recovery after revascularization. The overall accuracy of FDG PET for predicting recovery of function after revascularization is in the 80-90% range.

In recent years, advances in SPECT have made it possible to acquire the images of the heart using high-energy PET tracers, such as FDG[10]. The widespread availability of SPECT technology as compared to PET (only one available in Pakistan at present that has been recently installed in Lahore) could enable the application of FDG in daily practice of nuclear cardiology. It is now possible to image FDG with SPECT by using high-energy collimators (true single photon imaging) or with coincidence detection capability (hybrid PET-SPECT systems). Fatty acid imaging with Tc-99m labeled tracers is another area of considerable interest and is the subject of ongoing investigations.

Table 2
Radionuclide Imaging Agents Commonly Used to Assess Myocardial Viability

Agent	Mechanism	Validated Protocols
Single- Photon Tl-201	Requires myocyte cell membrane integrity for uptake (energy-department)	Stress/redistribution plus or minus re-injection Stress/late redistribution Rest/ redistribution
Tc-99m- sestamibi	Requires myocyte cell membrane integrity For uptake (electrochemical gradient)	QA or SQVA scoring of resting uptake uptake after nitrates
Positron F18- FDG	Preserved myocyte glucose uptake and phosphorylation	"Mismatch" pattern in conjunction with perfusion imaging QA of resting uptake
N-13- ammonia	Correlates with MBF	Resting MBF image in conjunction with FDG
Rubidium -82	Requires myocyte cell membrane integrity For uptake (energy -dependent)	Early wash out image

FDG; fluorodeoxyglucose, MBF; myocardial blood flow: QA; quantitative analysis, SQVA; semiquantitative visual analysis, Tl-201; thallium-201

Magnetic Imaging Resonance

Magnetic resonance imaging has emerged as an alternative noninvasive imaging approach for discrimination of fixed scar vs. viable but dysfunctional myocardium. MRI has an excellent resolution, making differentiation between the epi- and endocardium possible. It has been recently demonstrated that contrast -enhanced MRI allows highly accurate identification of viable myocardium. Infarct avid imaging analogues to that formerly performed with Tc-99m-pyrophosphate can be performed by using MRI and a conventional gadolinium based contrast agent[25]. Potential advantages include improved resolution now available with MRI and an ability to image chronic and acute infarctions.

Dobutamine Stress Echocardiography

Infusion of low dose dobutamine (5 -10 mcg/kg/min) have been demonstrated to increase contractility (with out a substantial increase in heart rate) in dysfunctional but viable myocardium; this phenomenon has been referred to as "contractile reserve". This contractile reserve is not observed in segments without viable myocardium[27]. A low-high dose protocol has been used for evaluation of viability. With this protocol, (infusion of upto 40 mcg/kg/min with addition of atropine if needed), both viability and ischemia could be detected[26,28]. Four response patterns are possible with this protocol:

1. Biphasic response (initial improvement followed by worsening of wall motion);
2. Worsening (direct deterioration of wall motion with out improvement);
3. Sustained improvement (improvement of wall motion without subsequent deterioration);
4. No change (no change in wall motion during the entire study);

All patterns except pattern 4 (which represents scar tissue) are related to the presence of viable myocardium. However, not all patterns are related to jeopardized myocardium: pattern 1 represents viability with superimposed ischemia, pattern 2 represents ischemia (probably myocardium perfused by a critical stenosed vessel) and pattern 3 is probably related to subendocardial necrosis. Hence not all patterns are predictive of improvement of function post revascularization[29].

Comparison of Techniques for myocardial viability

All the radionuclide techniques (and dobutamine echocardiography) perform in a relatively similar

Table 3
Recommendations for Radionuclide Techniques to Assess Myocardial Viability

	Indication	Test	Class	Level of Evidence
1.	Prediticting improvement in regional and global LV function after revascularization.	Stress/redistribution/reinjection TI-201	I	B
		Rest-redistribution imaging	I	B
		Perfusion plus PET FDG imaging	I	B
		Resting sestamibi imaging	I	B
		Gated-SPECT sestamibi imaging	IIa	B
		Late TI-201 redistribution imaging (after stress)	IIb	B
		Dobutamine RNA	IIb	C
		Postexercise RNA	IIb	C
		Postnitroglycerin	IIb	C
2.	Predicting improvement in heart failure symptoms after revascularization	Perfusion plus PET FDG imaging	IIa	B
3.	Predicting improvement in heart in Natural history after revascularization	TI-201 imaging (rest-redistribution and stress/redistribution/reinjection)	I	B
		Perfusion plus PET FDG imaging	I	B

FDG; fluorodeoxyglucose, PET; Positron emission tomography; RNA; radionuclide angiography;
SPECT; single photon emission computed tomography; Tl-201; thallium-201, ACC/AHA/ASNC Practice Guidelines, 2003.

manner regarding positive and negative predictive values for predicting improvement in regional function[31]. Single photon techniques (Tl-201 and Tc-99m labeled tracers) appeared to be slightly more sensitive, whereas PET and dobutamine echocardiography appeared to be more specific. Overall the PET techniques appeared to have slightly better accuracy. This improvement in overall accuracy however is accompanied by less accessibility and a higher level of technical complexity and higher cost. A meta -analysis of outcome studies related to myocardial viability has demonstrated no difference between the techniques commonly used to assess viability (PET versus single photon radionuclide versus dobutamine echocardiography) with regard to reduction of mortality or unfavorable cardiac events after revascularization[32].

Conclusion:

Prognostically, the patients with perfusion-metabolism mismatch have very high mortality if medically managed and much lower mortality if revascularized. Patients with matched defects i.e. no viable myocardium, indicating scar, resulted in no such difference in outcomes in terms of mortality between medical and surgical management. Recent studies using Thallium imaging likewise suggested the potential prognostic significance of viability assessment using standard SPECT techniques.

The most important elements for identifying patients suitable for viability assessment include the identification of LV dysfunction, documentation of coronary artery disease and selection of the method of assessment. In most cases, SPECT imaging with either thallium or Tc-99m labeled tracers, with semi quantitative analysis is appropriate, although thallium imaging appears to have higher sensitivity. PET if available, yields optimal sensitivity and is particularly indicated in patients with severe left ventricular systolic dysfunction. In some centers, dobutamine echocardiography may be performed for viability assessment. Functional MRI, microvascular integrity assessment with contrast echocardiography and new Tc-99m radiotracers are few of the promising techniques in the future. Larger studies that address the role of viability assessment in clinical practice, its affect on outcomes and its cost are needed.

Thus, for the clinician faced with a patient with coronary artery disease and left ventricular dysfunction, the key decision is whether or not to proceed with revascularization with an expectation of clinical benefit to the patient. The presence of active angina in the setting of left ventricular dysfunction would itself suggest a clinical benefit from revascularization. Otherwise, radionuclide assessment of the extent of myocardial ischemia and viability can contribute importantly to a revascularization decision. If substantial ischemia or viability of dysfunctional territories is found in the setting of stenotic coronary arteries technically amenable to revascularization, the literature would suggest a clinical benefit from revascularization. In the absence of substantial ischemia or viability, such benefit is significantly less likely. For these reasons, prerevascularization testing is an important part of the diagnostic workup of patients with ischemic cardiomyopathy and may help to guide optimal treatment.

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