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Viable but Dysfunctional Myocardium: Pathophysiology, Detection, and Treatment

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One of the greatest determinants of survival in patients with coronary artery disease (CAD) is left ventricular (LV) function. Since improvement in ventricular function improves prognosis, the detection of LV dysfunction that has potential for improvement is a clinically important issue, especially in patients immediately after MI (myocardial infarction), and in those who have chronic CAD with LV dysfunction.[1,2]

We define dysfunctional myocardium as *viable* if there is recovery of regional or global LV function upon restoration of blood flow, either spontaneously, or with coronary revascularization through PTCA (percutaneous transluminal coronary angiography) or CABG (coronary artery bypass grafting).[3] Two processes are thought to result in dysfunctional but viable myocardium: stunning and hibernation.

Pathophysiology

Myocardial stunning is a result of acute ischemic injury and subsequent coronary reperfusion with prolonged but reversible LV dysfunction. The most common clinical example is the patient post-MI who has successful early reperfusion with thrombolytic agents but has significant LV dysfunction that returns to normal in 7–10 days. Stunning can also result from other less severe episodes of ischemia such as unstable angina pectoris or variant angina.[5]

In its purest form, stunning represents blood-flow–contraction mismatch. Despite restoration of blood flow, contractile dysfunction is present and can persist from days to weeks before function returns spontaneously to normal. The mechanism of myocardial stunning is thought to be a combination of ischemic and reperfusion injury. The precise pathophysiologic basis remains a subject of debate. Some possible mechanisms include altered calcium transients, production of cytotoxic oxygen-derived free radicals, and abnormal energy use by contractile proteins with reduced myofilament responsiveness to calcium ions.[6]

At pathology, non-viable myocardium shows extensive fibrosis. In regions with reduced flow and preserved metabolic activity the myocardial cells have reduced contractile material and increased glycogen content. There is cellular swelling, reduction of sarcoplasmic reticulum, and the appearance of numerous small mitochondria. With these cellular alterations, it is not surprising that ventricular function improves only slowly after the restoration of normal flow and prevention of ischemia.[4]

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Myocardial hibernation was originally defined as chronic LV dysfunction secondary to sustained severe reduction in coronary blood flow that improves with revascularization. The most common clinical example is the patient with congestive heart failure (CHF) and significant CAD being considered for CABG surgery. In its purest form, it represents a blood-flow–contraction match. The mechanism is thought to be a down-regulation of contractile elements to decrease energy requirements in the face of reduced oxygen delivery.[5]

More recent data suggest that hibernation is, in fact, due to repetitive episodes of stunning. Several studies have suggested either no or only a modest reduction of resting blood flow in patients with reversible LV dysfunction. These patients have severely abnormal coronary flow reserve, which suggests that impaired function likely results from repetitive episodes of ischemia with a persistent stunning effect. Thus hibernation and stunning likely co-exist. One could argue that, with this much overlap, the clinical distinction between hibernation and stunning might not be relevant. This is, however, not the case since management differs widely, with no specific intervention required for the case of stunning on one hand, and the need for revascularization in the case of hibernation on the other hand.[6]

Detection

Non-invasive assessment of myocardial viability has proved clinically useful to distinguish hibernating or stunned myocardium from irreversibly injured myocardium. These techniques include metabolic imaging with PET (positron emission tomography), SPECT (single-photon emission computed tomography), perfusion imaging with thallium-201 or one of the new technetium-99m labeled agents, and dobutamine stress echocardiography.[5,6,7]

Positron imaging

PET imaging uses positron-emitting radionuclides to label physiologic substrates or their analogues. Myocardial flow tracers (e.g., ammonia-13n or 15O-water) are used to assess and to quantify regional myocardial blood flow. The most commonly used metabolic tracer is fluorodeoxyglucose-18 (FDG-18), a glucose analogue. FDG-18 delineates the initial uptake and phosphorylation of glucose, but it is not further metabolized. The hallmark of viable myocardium is normal or reduced blood flow and preserved or increased glucose metabolism (blood-flow–metabolism mismatch).[9,10,12] In numerous studies of PET imaging to identify viable myocardium, overall positive predictive value (PPV) was 75–85%, and negative predictive value (NPV) was 80–90%.[6,8]

Thallium-201

Thallium-201 is an analogue of potassium that is actively taken up by myocardial cells. This uptake is dependent on myocardial blood flow, sarcolemmal integrity, and intact metabolic function. Once it is in the myocyte, redistribution occurs via the NaK-ATPase pump. Thallium-201 decays, releasing gamma rays that are picked up by a gamma camera and are converted to images. Images obtained immediately after injection reflect flow-dependent initial distribution (regional myocardial blood flow). Delayed images reflect redistribution of the potassium pool (myocardial viability).[11,12]

Indicators of viability are normal thallium uptake with exercise or stress, and thallium defects that are partially or totally reversible on the redistribution or reinjection images. The addition of delayed, reinjection, or rest imaging has been proposed to overcome the limitations of the original protocol. Previous studies have shown that many non-reversible defects are due to severely ischemic but viable myocardium or a mixture of scar and viable myocardium.[13] The following protocols exist:

1) stress, 4-hour redistribution
2) stress, 4-hour and 24-hour redistribution
3) stress, 4-hour redistribution and reinjection
4) rest, 4-hour redistribution

The newer imaging strategies (items 2 and 3) improve the identification of viable myocardium. The stress-rest-late redistribution protocol (item 2) permits a longer period of thallium redistribution (8–24 hours). Regions supplied by critically stenosed coronary arteries are allowed greater time for thallium delivery and uptake.[14] The stress-rest-reinjection protocol (item 3) uses a reinjection of a small dose of thallium (1–2 mCi) immediately after a conventional 3–4 hour redistribution image. This results in elevated serum thallium

levels that, during later imaging, usually show increased redistribution. Up to 50% of fixed defects on 4–hour redistribution imaging revealed increased tracer uptake with reinjection.[15] The overall positive predictive value (PPV) in such studies is 80–87%; the negative predictive value (NPV) is 82–100%.[6,8]

An important addition to viability assessment is thallium quantification. There is a near linear relation between regional thallium activity and likelihood of recovery of regional LV dysfunction after revascularization. The majority of fixed-thallium defects shown to be mild to moderately severe (defined as thallium uptake of >50% of normal thallium activity in the heart) on stress-redistribution images will be proven viable on PET imaging.

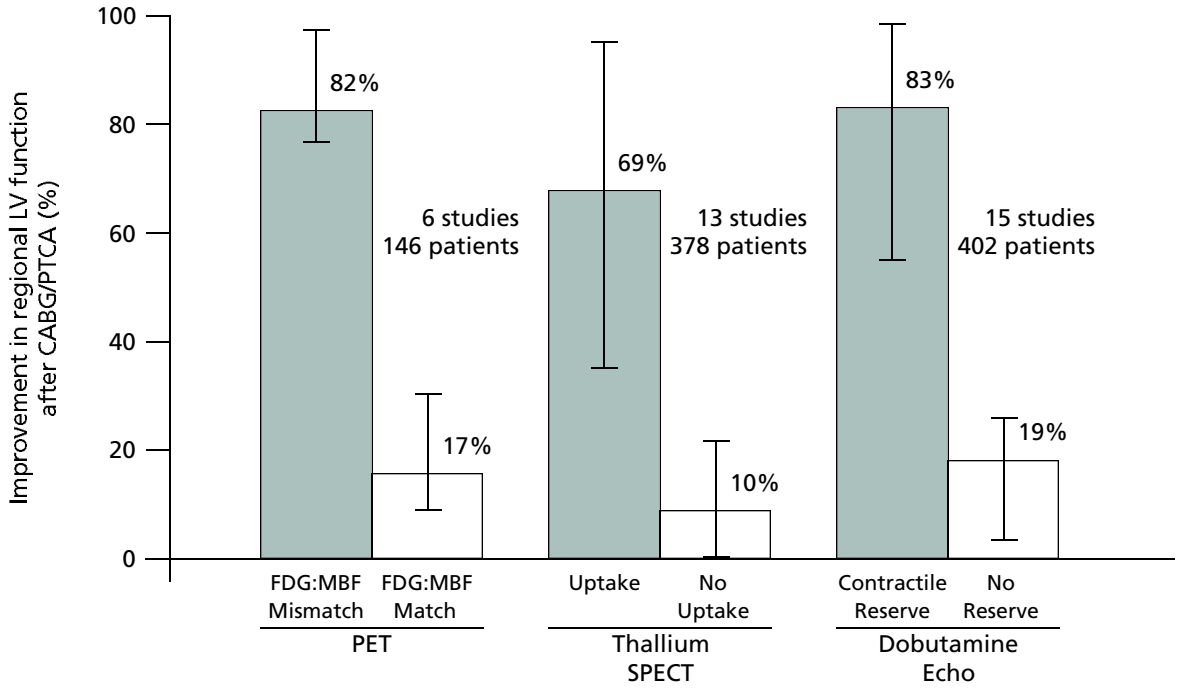
Sestamibi

Technetium-99m sestamibi is a flow-dependent myocardial perfusion agent with minimal redistribution. High photon flux enables first-pass acquisition during tracer injection, giving ventricular function data as well as perfusion images. Gated tomographic perfusion images are used to identify wall motion and myocardial thickening. Readings that are normal or mildly reduced (≥50–60% of normal regions) reflect viable myocardium. Although recent studies suggest comparable uptake of sestamibi and thallium at rest, others have suggested that rest sestamibi imaging underestimates the presence of viable myocardium.[16] Lack of significant redistribution leads to an underestimation of myocardial viability in the setting of resting hypoperfusion. The predictive value might improve with use of ventricular function data or if nitroglycerin is administered prior to the rest injection.

2-dimensional echocardiography

The hallmark of viable myocardium is the presence of myocardial thickening, either at rest or with provocation. Dobutamine stress echocardiography is the most widely used

Figure 1: Likelihood of improved regional LV function after revascularization, based on non-invasive methods to detect viable myocardium. The range of values reported from individual studies is indicated by the horizontal bars connected by vertical lines. The shaded bars represent PPV, and the open bars represent the inverse of the NPV.



Adapted from R.O. Bonow, *Circulation*, 1996.

echocardiographic technique to assess myocardial thickening and viability. The underlying hypothesis is that myocardium dysfunctional at rest is viable if there is augmented thickening or contraction with low-dose inotropic stimulation. This reversible wall motion or thickening abnormality is thought to indicate a need for reperfusion or revascularization. Wall motion and thickening are assessed at rest and during infusion of incremental doses of intravenous dobutamine. Typical doses for viability studies are 2.5–5.0 µg/kg/min (low dose) and 5–10 µg/kg/min (high dose). Some protocols use peak doses up to 20–40 µg/kg/min.[17]

Patients with dobutamine-revealed myocardial thickening soon after an MI have "stunned" myocardium that will demonstrate improved ventricular function with time. A biphasic response (improvement at low doses and deterioration at high doses) best predicts recovery of LV function post-revascularization. Other responses are much less predictive.[18] Overall sensitivities and specificities range from 69–97% and 73–100%, respectively.[6,8]

Myocardial contrast echocardiography utilizes an intra-coronary injection of sonicated myocardial contrast agents performed in conjunction with coronary angiography along with simultaneous acquisition of 2D-echocardiographic images. Newer contrast agents have been developed that can cross the pulmonary circulation, thus enabling intravenous administration. The presence of contrast effect in the myocardium signifies an intact intravascular bed, microvascular perfusion, and collateral flow in these segments – hence, viable myocardium.[19]

In a recent editorial[8] Bonow compared data from numerous studies of these various techniques. Figure 1 illustrates the comparative predictive values:[8]

- PET imaging—PPV 82%, NPV 83%
- thallium SPECT imaging—PPV 69%, NPV 90%
- dobutamine echocardiography—PPV 83%, NPV 87%

Overall uncertainty still exists regarding the relative accuracies of each method in predicting recovery of LV function and whether some patient subsets are better evaluated with a particular test. The main reason is the lack of definitive trials comparing all three methods in a large series of patients undergoing revascularization.

Table 1: Factors affecting improvement in left ventricular function after coronary revascularization

- Presence and degree of preoperative myocardial hibernation or stunning
- Coronary anatomy
- Completeness of revascularization
- Presence and degree of perioperative infarction and necrosis
- Graft patency
- Reliability of method to detect improvement
- Left ventricular size
- Presence of concomitant primary cardiomyopathy
- Abnormal microvasculature

Treatment

The assessment of viability remains highly clinically relevant. Patients with recovery of LV function either post-MI or post-revascularization have a significantly enhanced prognosis. The presence of viable myocardium predicts improved symptoms and prognosis in patients who undergo revascularization.[20,21] The converse also applies: Patients with no demonstrably viable myocardium might not benefit from interventions, and they are best treated with aggressive medical therapy. It is particularly relevant to assess the presence of viable myocardium in the following situations:

- ischemic cardiomyopathy and CHF
- post-MI
- post-thrombolytic therapy
- high-risk interventions (CABG, PTCA)
- potential cardiac transplantation.

Other factors besides viability affect the improvement in LV function post-revascularization (table 1), and they should be considered also.

The benefit of revascularizing viable but dysfunctional myocardium is likely more than just improvement in LV function. There is the clinical benefit of attenuation of LV dilatation and remodelling, the reduction in ventricular arrhythmias, and the possible reduced risk of subsequent fatal ischemic events (even without significant improvement in LV function). Future studies in the assessment of myocardial viability should focus on trying to predict which patients will benefit symptomatically and prognostically from coronary revascularization.

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Upcoming Scientific Meetings

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23-26 Feb 98
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Abstracts of Interest

Relation Between the Severity of Reduction in Thallium Activity Within Irreversible Defects and Percent Collagen Replacement in Chronic Ischemic Cardiomyopathy.

JAMSHID SHIRANI, JAETAE LEE, GOPAL SRINIVASAN, ET AL.

Prior studies have shown that the severity of reduction in thallium (TI) activity within irreversible TI defects correlates with the degree of metabolic activity as assessed by PET. To determine the histomorphologic correlate of irreversible TI defects, we studied 13 chronic ischemic cardiomyopathy pts waiting for cardiac transplantation with stress (S)-redistribution (RD)-reinjection (RI) TI SPECT. The explanted hearts were sliced in short-axis sections (mean thickness 8 mm) and the volume fraction of collagen from midventricular slices were studied quantitatively using computerized videodensitometry after staining with picrosirius red. The corresponding tomograms for TI-S, TI-RD, TI-RI were divided into 8 segments and the myocardial segment with maximum counts on the TI stress tomogram was used as the normal reference segment for that tomogram. A total of 49 segments were identified to have irreversible TI defects; 18 mild (60-84%), 9 moderate (50-59%), and 22 with severe (<50% of peak) reduction in TI activity. Overall, there was an inverse correlation between TI uptake on RI (mean 59±18%) and percent collagen replacement (mean 31±16, r=-.58, p<0.01). The mean volume fraction of collagen replacement was significantly lower in mild (21±11%) compared to moderate (38±14%) and severe (36±16%) TI segments (p<0.001). Of the 18 mild irreversible TI segments, only 1 (6%) exhibited transmural infarction compared to 6 of 9 (67%, p<0.001) with moderate and 16 of 22 (73%, p<0.001) with severe TI defects. These data provide a histomorphologic confirmation that the severity of reduction in TI activity is useful in estimating the extent of collagen replacement in pts with chronic ischemic cardiomyopathy.

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Improvement of Left Ventricular Function After Positron Emission Tomography Based Revascularization Strategies in Patients With Hibernating Myocardium. A Prospective Randomized Comparison With Single Photon Emission Computed Tomography

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For clinical assessment of myocardial viability 13-N ammonia/18F-FDG PET and stress/rest 99m-Tc-Sestamibi SPECT have been reported to have similar sensitivity and specificity. However, both techniques have not been compared in a prospective randomized study. We included consecutive patients who underwent coronary angiography for stable angina. All had wall motion abnormalities with questionable viability and revascularization decision depended on presence or absence of viability. Echo LV wall motion score index (WMSI) was assessed. All patients underwent both PET and SPECT. Outcome of PET or SPECT was used in a blinded randomized fashion for treatment strategy. Six months after revascularization (CABG or PTCA) or the decision to treat medically echo was repeated, and cardiac events were monitored for 2 years. Analysis of 40 patients (mean age 57 years, 36 men, 26 patients multivessel disease, mean WMSI: 1.58 and mean LVEF: 0.41) was performed. Twenty patients were randomized to SPECT and 20 patients were randomized to PET. Revascularization or medical treatment was equally distributed in both groups. The 20 patients in the PET group showed an improvement in WMSI from 1.66±0.45 to 1.43±0.38 (p<0.004). In the SPECT group (n=20) WMSI did not change significantly (1.54±0.36 to 1.49±0.31 [p=NS]). The improvement in WMSI in the PET group was significantly different from the SPECT group (p=0.04).
Therefore, in patients with chronic CAD and wall motion abnormalities assessment of myocardial viability by PET rather than SPECT enhances revascularization decisions as evidenced by a better recovery of LV function. Follow up will show if these findings result in a different clinical outcome.

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