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Stunning, Hibernation, and Assessment of Myocardial Viability

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The last 3 decades have witnessed an unprecedented improvement in the outcome of patients with acute coronary syndromes. The widespread use of thrombolytic therapy and percutaneous coronary interventions, in association with increasingly potent antithrombotic agents, has contributed to significant reductions in mortality and morbidity in these patients. Although overall survival has improved, a downside of this success has been the greater number of patients with residual left ventricular (LV) dysfunction undergoing progressive LV remodeling and congestive heart failure. This problem is compounded by the rising age of our population and the higher prevalence of comorbidities such as diabetes mellitus that confer an increased risk of coronary artery disease (CAD) and congestive heart failure. Patients with CAD represent by far the most numerous cohort among those with congestive heart failure, and their treatment remains a partial success.[1] Typically, these patients have multivessel disease, increased LV volumes, and variable degrees of regional and/or global systolic dysfunction, although more cases of isolated diastolic dysfunction have been reported recently.[2–4] In these patients, coronary revascularization may lead to symptomatic and prognostic improvement, and these clinical benefits are accompanied by evidence of reverse LV remodeling. In this context, the concept of myocardial viability was developed and a number of different techniques have been used to demonstrate the presence of viable tissue before coronary revascularization.

The aim of this review article is to summarize our current understanding of the concept of myocardial viability and its clinical implications in patients with CAD and chronic LV dysfunction. Throughout this review, we use the term viability to describe dysfunctional myocardium subtended by diseased coronary arteries with limited or absent scarring that therefore has the potential for functional recovery. Viability is a prospective definition, but it does not imply evidence of functional recovery after interventions. The term hibernation, which often is used synonymously for tissue viability, is a retrospective definition based on evidence of functional recovery after interventions.

Myocardial Stunning and Hibernation

Acute myocardial ischemia rapidly impairs contractile function.[5] This dysfunction can persist for several hours after transient nonlethal ischemia but eventually is followed by full functional recovery.[6] The latter phenomenon is known as myocardial stunning.[7–9] In patients with CAD, repeated episodes of demand ischemia may lead to cumulative stunning (Figure 1) that could be a substrate in the development of chronic postischemic LV dysfunction.[10]

The concept of myocardial hibernation was derived from clinical observations. More than 30 years ago, clinicians and surgeons started to notice that chronic myocardial dysfunction, present before coronary bypass, often improved after revascularization.[11–14]

In pathophysiological terms, a severe reduction in coronary flow reserve is common in both stunning and hibernation,[4] and recovery of function in hibernating myocardium after coronary revascularization is paralleled by restoration of an adequate coronary flow reserve (Figure 2).[15]

Clinically, in different patients, similar degrees of LV dysfunction may be associated with large differences in the amount of viable myocardium, and even extreme degrees of wall thinning do not necessarily indicate the absence of viability. The timing of coronary revascularization is very important because in some patients CAD progression may occur very rapidly, precluding later interventions.

An algorithm for identifying and treating patients with CAD and chronically dysfunctional but viable myocardium is presented in Figure 3.

Assessment of Viability

At present, we lack controlled prospective randomized studies, but indications exist from retrospective studies that patients who undergo a preoperative assessment of viability have better in-hospital and 1-year outcomes when a viability test is added to clinical and angiographic data.[16,17]

A detailed description of the technical characteristics of each imaging modality has been reviewed comprehensively in previous articles and American Heart Association/American College of Cardiology scientific statements.[18–20]

Dobutamine stress echocardiography (DSE) is used to assess myocardial contractile reserve. Low-dose dobutamine (5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) can lead to increased contractility in dysfunctional segments that are viable. At higher doses (up to 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ plus atropine to increase heart rate),

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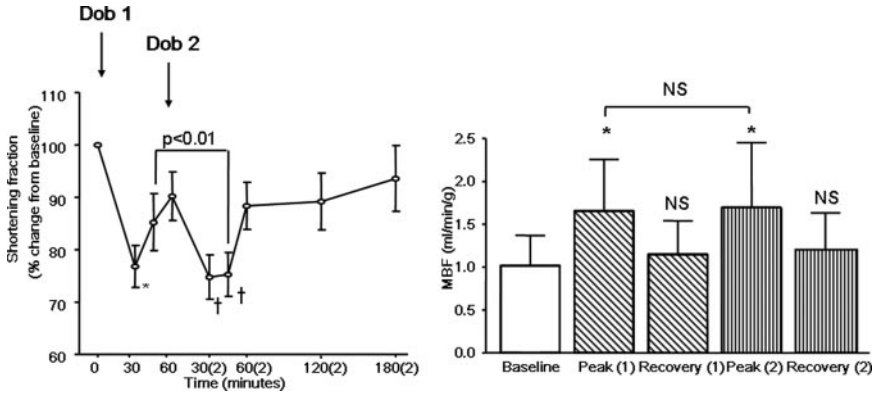

Figure 1. Repeated episodes of ischemia lead to cumulative stunning. Left, Regional LV function measured by echocardiography in a group of patients with single-vessel CAD (>70% diameter stenosis) and exercise-inducible ischemia. Cardiac function was assessed at baseline and after 2 episodes of dobutamine-induced ischemia separated by 60 minutes. Data are expressed as the percentage of change from baseline values (mean±SEM). Times (0, 30, 60 minutes) are the times after the first dobutamine infusion; those followed by (2) are the times after the second infusion of dobutamine. The dysfunction that develops during dobutamine stress persists during recovery, and its severity and duration after the second stress are greater than after the first. *$P<0.05$; †$P<0.001$ vs baseline before first infusion. Right, Regional myocardial blood flow (MBF) was measured during the same experiment using oxygen-15–labeled water and PET. MBF in the regions subtended by stenotic coronary arteries was measured at baseline, at the peak of the first dobutamine infusion [Peak (1)], in the recovery period after the first dobutamine infusion [Recovery (1)] (cross-hatched bars), and at the peak and in recovery after the second infusion [Peak (2) and Recovery (2), respectively] (hatched bars). The MBF data show that the myocardial dysfunction observed in the recovery phase is not due to abnormal MBF; therefore, the regions are stunned. *$P<0.05$. Adapted from Barnes et al.[10] Used with permission from the publisher. Copyright © 2002, the American Physiological Society.

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wall motion in these viable segments may further improve or diminish, reflecting inducible ischemia. This "biphasic response" is highly predictive of recovery of function after revascularization.[21] Predominantly scarred segments do not show incremental contractility with either dose. Dysfunctional segments with resting end-diastolic wall thickness <6 mm are thought to reflect areas with significant scar. They generally show little improvement in wall motion with DSE and do not improve after revascularization.[22–25] Dobutamine echocardiography evaluates contractile reserve as a predictor of improvement of ventricular function, and like radionuclide techniques, general agreement exists about its predictive accuracy (class I).[20]

Myocardial contrast echocardiography uses acoustically active gas-filled microbubbles as contrast agent that have a diameter smaller than red blood cells (<7 μm) and remain confined within the intravascular space. Myocardial contrast echocardiography produces myocardial opacification and facilitates the identification of LV borders compared with conventional echocardiography.[26,27] Tissue capillary blood flow determines myocardial perfusion and is the product of capillary blood volume and myocardial blood velocity, both of which can be assessed by myocardial contrast echocardiography. Once the contrast agent has reached a steady-state concentration in the bloodstream, during continuous intravenous infusion, a burst of high-intensity ultrasound is used to destroy the microbubbles within the myocardium. Subsequent microbubble replenishment is observed over the next 10 to 15 cardiac cycles and reflects myocardial blood velocity.[28,29] Segments are classified as viable if homogeneous contrast intensity is present, whereas the absence of contrast enhancement reflects nonviable myocardium in which necrosis of myocardial cells has resulted in obstruction and collapse of the microcirculation.[30] Myocardial contrast echocardiography has a high sensitivity for predicting functional recovery after revascularization but low specificity compared with DSE. The optimal strategy appears to be a combination of perfusion assessed by myocardial contrast echocardiography and contractile reserve by DSE.[28,31–36] The strengths of echocardiography-based techniques include safety, portability, low cost, and widespread availability of equipment. The main limitation is that the technique is highly operator dependent with high interobserver and intercenter variability. Furthermore, spatial resolution is relatively low and diagnostic accuracy is reduced in patients with poor acoustic window or significant LV impairment.

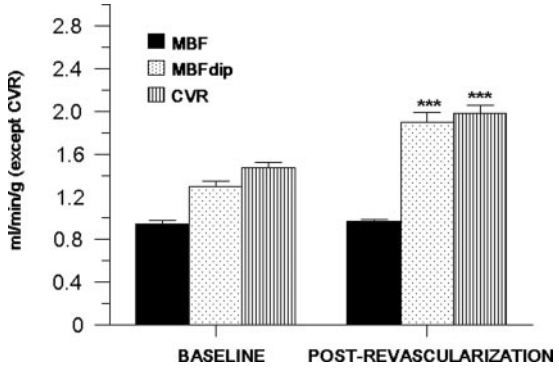

Figure 2. Revascularization of hibernating myocardium improves maximum myocardial blood flow (MBF) and flow reserve in parallel with wall motion. MBF measured by PET with oxygen-15–labeled water in 163 hibernating myocardial segments from 30 patients with CAD and chronic LV dysfunction before (baseline) and after coronary revascularization (post-revascularization). All segments had improved function after bypass surgery. The improvement in function was paralleled by a significant increase in dipyridamole-MBF (MBFdip) and coronary vasodilator reserve (CVR). ***$P<0.0001$. Adapted from Pagano et al.[15] Used with permission from the publisher. Copyright © 2001, BMJ Publishing Group.

Single-photon emission computed tomography (SPECT) is a widely available modality with well-established clinical and prognostic validation.[18] The tracers currently used include the potassium analog thallium-201 (^{201}Tl) and technetium-99m (^{99m}Tc) –labeled compounds.

Myocardial uptake of ^{201}Tl is dependent on regional flow and sarcolemmal membrane integrity. Several protocols can be used with ^{201}Tl that require injection of a tracer either after stress or at rest with subsequent late imaging following the

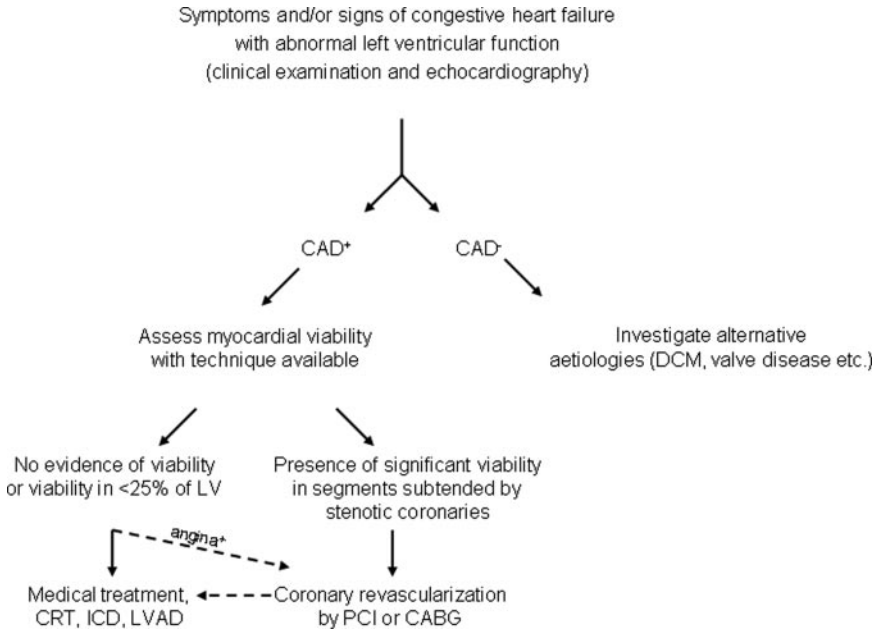

Figure 3. Algorithm for the identification of patients with chronically dysfunctional but viable myocardium. This flowchart is based on the observation that information on both LV function and coronary anatomy is generally already established in most patients. The watershed examination to decide on best treatment strategy is the assessment of myocardial viability. CAD^+ indicates the presence of significant coronary artery disease; CAD^-, absence of significant coronary artery disease; DCM, idiopathic dilated cardiomyopathy; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVAD, LV assist devices; PCI, percutaneous coronary interventions; and CABG, coronary artery bypass graft.

redistribution of the tracer. The initial acquisition soon after ^{201}Tl injection primarily reflects delivery of the tracer through blood flow. The images acquired 4 to 24 hours after tracer injection are a marker of sarcolemmal integrity, which in turn reflects tissue viability.[37,38]

^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are the 2 most commonly used ^{99m}Tc-labeled tracers. Both are lipophilic molecules, and their intracellular retention requires intact mitochondrial function with preserved membrane potential. Similar to ^{201}Tl, uptake of these agents provides information on both myocardial perfusion and viability.[39] However, compared with ^{201}Tl, the ^{99m}Tc-labeled tracers undergo much less redistribution with time. They emit higher-energy photons than ^{201}Tl, which are ideal for SPECT and are subjected to a reduced amount of soft-tissue attenuation. These features result in higher-quality images and fewer artifacts compared with ^{201}Tl. Relative to ^{201}Tl protocols, less radiation exposure is present as a result of the shorter half-life of ^{99m}Tc. The use of gated SPECT provides information on regional and global LV function and viability simultaneously.[40]

SPECT has higher sensitivity and lower specificity than techniques based on the assessment of residual contractile recovery, although specificity improves with gated SPECT.[41] The main limitations of this technique include exposure to significant amounts of ionizing radiation, rather low spatial resolution, and attenuation artifacts. The combined use of SPECT and multislice computed tomography may improve diagnostic performance of SPECT by removing attenuation artifacts.

Positron Emission Tomography

Early studies demonstrated that myocardial ischemia and infarction could be distinguished by analysis of positron emission tomography (PET) images of the perfusion tracer ^{13}N-labeled ammonia ($^{13}NH_3$) and the glucose analog ^{18}F-fluorodeoxyglucose (FDG) acquired after an oral glucose load.[42] Regions that showed a concordant reduction in both myocardial blood flow and FDG uptake ("flow-metabolism match") were considered to be irreversibly injured, whereas regions in which FDG uptake was relatively preserved or increased despite having a perfusion defect ("flow-metabolism mismatch") were considered ischemic but still viable.[43] However, this approach has inherent limitations, particularly related to FDG and the way in which it is currently used.

The uptake of FDG by the myocardium and scan quality depend on many factors such as dietary state, cardiac workload, sympathetic drive, and the presence and severity of ischemia.[44] Many patients with heart failure are insulin resistant, and the amount of endogenous insulin released after oral glucose loading will not induce maximal stimulation of myocardial glucose/FDG uptake.[45]

To minimize these problems and to avoid the need of a simultaneous $^{13}NH_3$ scan, which requires a cyclotron on site, an alternative protocol, the main feature of which is the use of the hyperinsulinemic euglycemic clamp, has been developed.[46] During the clamp, plasma free fatty acid levels are dramatically reduced, and metabolism in insulin-sensitive tissues switches to glucose use (Figure 4).[47,48] FDG is injected during the steady-state phase of the clamp, resulting in high and rapid myocardial FDG uptake and low tracer concentration in the blood pool, leading to improved image quality even in patients with insulin resistance. The scan acquisition time is reduced to 15 to 20 minutes, starting 20 to 30 minutes after FDG injection. This approach has been tested in a European multicenter study.[49]

PET-FDG data also can be analyzed using a quantitative approach that, however, requires longer dynamic acquisitions. A threshold value for the metabolic rate of glucose of $\geq 0.25\ \mu mol \cdot g^{-1} \cdot min^{-1}$ allowed the best prediction of improvement in functional class of at least 1 grade after revascularization.[50]

The main strengths of PET compared with SPECT are its superior spatial resolution and attenuation correction. PET is generally regarded as the gold standard for viability assess-

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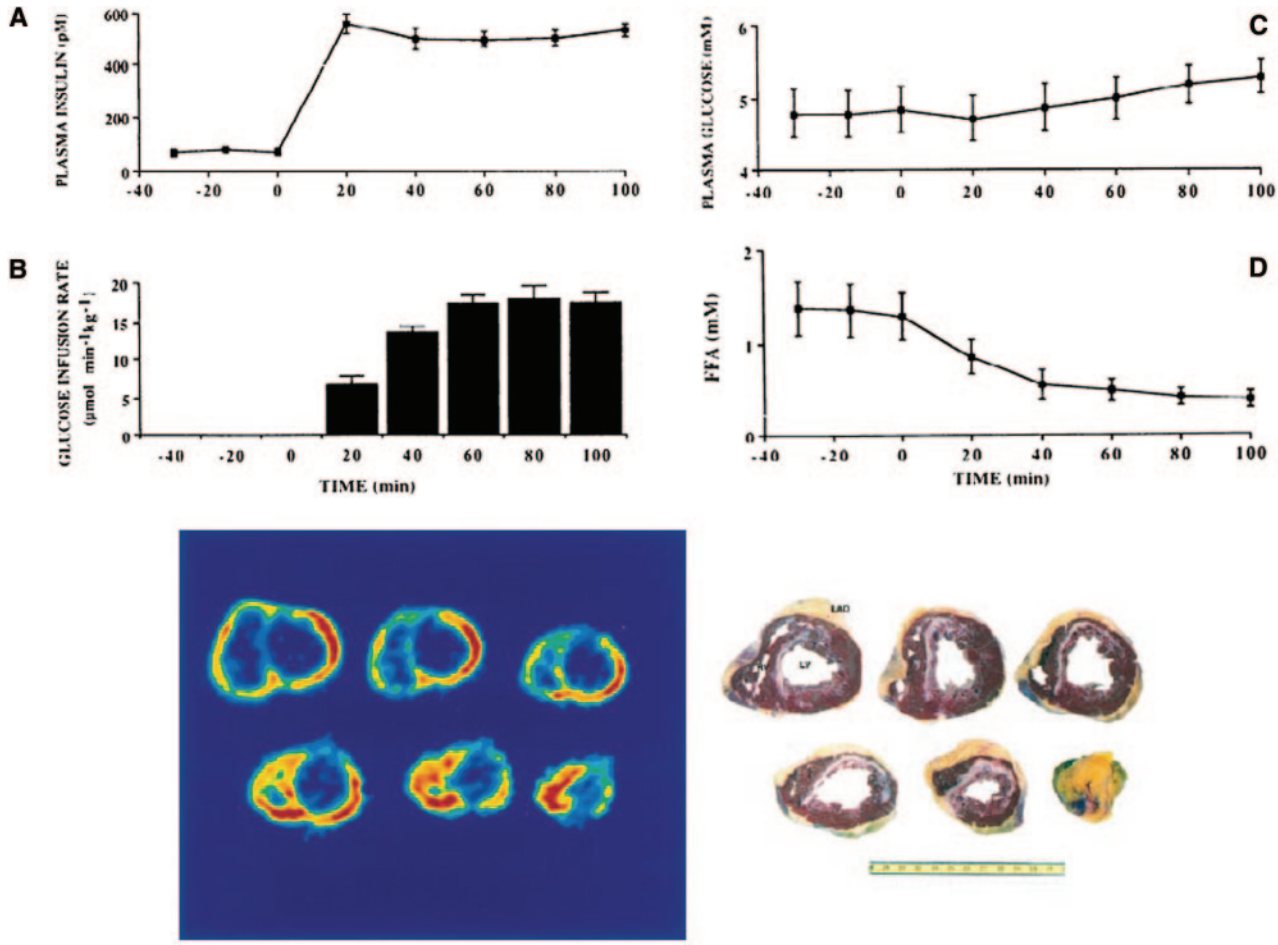

Figure 4. Euglycemic, hyperinsulinemic clamp and FDG-PET scanning. A, Plasma insulin concentration; B, exogenous glucose infusion rate; C, plasma glucose; D, free fatty acid (FFA) concentrations. Adapted from Ferrannini et al.[47] Used with permission from the publisher. Copyright © 2002, the American Physiological Society. Bottom, Corresponding apical views of in vivo short-axis images (left, both rows: right to left=apex to base) and ex vivo digital photograph of the six 1-cm–thick short-axis slices of the same patient's heart (explanted during the transplantation procedure) after TTC staining (right, both rows: right to left=apex to base). On the heart specimen (right), remote nonischemic myocardium is stained in red; infarcted nonviable tissue remains unstained. Note the patchy nature and mosaic pattern of infarction in the patient's heart specimen and the good agreement between FDG uptake and scar distribution. LAD indicates left anterior descending artery; RV, right ventricle. Adapted from Chareonthaitawee et al.[48] Used with permission from the publisher. Copyright © 2002, Springer Verlag.

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ment. Reduced availability of PET scanners and the need for a cyclotron on site have been the main limitations to wider clinical applications. Recently, however, the number of scanners available has increased to ≈1200 in the United States and 400 in Europe. In the United States, the annual procedure volume for cardiology was estimated to be 154 000, of which ≈68 000 were viability and ≈86 000 were rubidium-82 perfusion scans (information from scanner manufacturers).

Stress/redistribution/reinjection or rest/redistribution with ^{201}Tl, resting sestamibi SPECT, and perfusion $^{13}NH_3$/FDG PET is classified as class I level of evidence B for the prediction of the improvement in regional and global LV function. The ability to predict improvement in heart failure symptoms after revascularization is less well established and is classified as IIa level of evidence B for PET.[19]

Cardiovascular Magnetic Resonance

Cine imaging with gradient echo sequences provides information on global LV function, regional wall motion, and thickening. It has been used in conjunction with dobutamine stress similarly to DSE.[51,52] An important advance has been the application of gadolinium-chelated contrast agents to detect perfusion defects, microvascular obstruction, and areas of scarred tissue/fibrosis.[53–58] Gadolinium-chelated contrast agents have paramagnetic properties that yield a bright signal in areas where they accumulate, are metabolically inert, and are safe to administer via a peripheral line as a single bolus with a negligible risk of nephrotoxicity, except in patients with end-stage renal failure. Gadolinium-chelated contrast agents do not penetrate myocytes with intact membranes. However, they diffuse and accumulate within the extracellular space when its volume of distribution is increased (eg, replacement fibrosis) or into myocytes with ruptured cell membrane (eg, acute infarction). Depending on the dose, 10 to 15 minutes after injection, a "late" steady-state phase is reached when gadolinium-chelated contrast agents have washed out of normal myocardium but remain in scarred or acutely infarcted tissue. The latter are characterized by a

Table 1. Results of Different Imaging Modalities to Predict Recovery of Global LV Function After Revascularization

	Patients, n	Sensitivity, Mean (95% CI)	Specificity, Mean (95% CI)	PPV, Mean (95% CI)	NPV, Mean (95% CI)
Conventional nuclear					
^{99m}Tc-sestamibi [60]	19	71 (51–91)	40 (18–62)	...	...
SPECT FDG[63,70]	94	86 (79–93)	93 (88–98)	...	...
^{201}Tl rest, reinjection[22,62,63,65]	211	84 (79–89)	70 (64–76)	97 (92–100)	93 (86–100)
^{201}Tl rest redistribution+FDG[64]	47	86 (76–96)	92 (84–100)	90 (81–99)	89 (80–98)
Total	371	84 (80–88)	77 (73–81)	94 (89–98)	91 (85–97)
Echocardiography					
DSE[22,60,62,63,65,66,72]	408	76 (71–80)	81 (77–85)	84 (77–91)	91 (85–96)
DSE+strain rate[66]	55	67 (55–79)	89 (81–97)	...	...
End-diastolic wall thickness[22]	43	63 (49–77)	68 (54–82)	...	...
Total	506	74 (70–77)	81 (77–84)	84 (77–91)	91 (85–96)
PET					
FDG[49,70]	205	81 (75–86)	65 (59–72)	...	...
Total	205	81 (75–86)	65 (59–72)	...	...

PPV indicates positive predictive value; NPV, negative predictive accuracy.

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bright, hyperenhanced signal on specialized T1-weighted inversion recovery scans, whereas the signal from normal myocardium has been "nulled" and appears black.[56] This has led to the aphorism that "bright is dead."

This technique allows assessment of the transmurality of necrosis, and the minimum amount of myocardium that can be imaged is ≈1 g with a spatial resolution of ≈2 mm.[56] The transmural extent of infarction correlates with the likelihood of functional recovery of dysfunctional myocardium after revascularization.[54,55,59] These findings are resulting in a paradigm shift. The absence of significant late gadolinium enhancement in thinned (<5 mm) hypokinetic myocardium, previously assumed to represent scarred tissue, often is associated with restoration in wall thickening and function after revascularization.

Main current limitations of this technique are the relative cost, limited availability, comparatively long study times, and the difficulty of performing scans in patients with implanted devices, although new cardiovascular magnetic resonance–compatible materials are being developed. Higher-field (ie, 3-T) clinical scanners may potentially offer better signal-to-noise ratio, reduced scan imaging times, and increased spatial resolution.

Impact of Revascularization on LV Function and Long-Term Survival

Revascularization and Improvement of LV Function

From the clinical perspective, recovery of global function is more important than regional improvement. Several studies have shown that LV ejection fraction (EF) improved significantly (ie, ≥5%) after revascularization in ≈60% of patients (range, 38%[60] to 88%[61]).[15,22,49,60–71] The meta-analysis published by Underwood et al[18] demonstrated an increase in LVEF in patients with evidence of hibernating myocardium but no improvement in those without hibernation.

We have examined 20 studies carried out with established techniques to assess viability in patients with LV dysfunction (LVEF ≤45%) caused by CAD that were published between 1998 and 2006. The pooled data are presented in Tables 1[22,49,60,62–66,70,72] and 2.[22,66,67,70,72–81] The estimates of the sensitivity, specificity, positive predictive value, negative predictive value, and 95% confidence intervals (CIs) of the diagnostic tests were calculated using a weighted sum of the values, with weighting determined by the number of patients in the study.

The pooled data reported in Table 1 summarize the ability of different imaging modalities to predict the recovery of global LV function (sensitivity and specificity values) after revascularization in a population, with a prevalence of viability assessed by the optimal cutoff (ie, number of viable segments) identified by the receiver-operating curve analysis.[22,49,60,62–66,70,72] The generally accepted opinion[18,82] that SPECT and PET demonstrate higher sensitivity is confirmed. On the other hand, in this population, DSE has superior specificity and lower positive predictive value.[64] Negative predictive value is similar for both DSE and SPECT. The importance of the definition of the cutoff value has to be highlighted. In fact, shifting the optimal cutoff value to a higher number of viable segments can improve specificity but at the expense of a decline in sensitivity.[62] A higher prevalence of viability also will result in a higher positive predictive value and a lower negative predictive value. The predictive value of each technique could be maximized by a multimodal approach, as proposed by Bax and coworkers,[62,63] who observed an enhanced accuracy of predicting outcome with sequential testing using ^{201}Tl SPECT and DSE.

The time course of recovery of viable myocardium can protract up to 14 months.[83] This prolonged recovery time can be due, at least in part, to the fact that dysfunctional segments can present different stages of structural abnormality, spanning from normal (stunning) to the characteristic features of

Table 2. Results of Studies That Evaluated the Improvement in Function on a Segmental Basis

	Patients, n	Sensitivity, Mean (95% CI)	Specificity, Mean (95% CI)	PPV, Mean (95% CI)	NPV, Mean (95% CI)
CMR					
Contrast enhanced[67]	29	97 (91–100)	68 (51–85)	73 (57–89)	93 (84–100)
Dobutamine stress[73–75]	193	94 (90–97)	90 (86–94)	86 (81–91)	92 (88–96)
Total		94 (91–97)	87 (83–91)	84 (79–89)	87 (89–96)
Conventional nuclear					
^{99m}Tc-sestamibi[76]	30	96 (89–100)	55 (37–73)	87 (75–99)	80 (66–94)
SPECT FDG[70]	47	89 (80–98)	86 (76–96)	...	...
^{201}Tl rest, reinjection[22,76,77]	104	86 (80–93)	63 (54–73)	69 (60–8)	85 (78–92)
Total	181	89 (84–93)	68 (61–75)	73 (66–81)	84 (78–90)
Echocardiography					
DSE[22,66,72,73,77–80]	424	76 (72–80)	81 (77–84)	66 (61–71)	89 (86–93)
DSE SRI[66]	55	82 (72–92)	80 (69–91)	...	...
End-diastolic wall thickness[22]	43	94 (87–100)	48 (33–63)	53 (38–68)	93 (85–100)
Total	522	78 (74–81)	78 (74–81)	64 (59–70)	90 (86–93)
PET					
PET-FDG[67,70,75,79–81]	280	89 (85–93)	57 (51–63)	73 (66–80)	90 (86–95)
Total	280	89 (85–93)	57 (51–63)	73 (66–80)	90 (86–95)

PPV indicates positive predictive accuracy; NPV, negative predictive accuracy; CMR, cardiovascular magnetic resonance; and SRI, strain rate index.

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hibernating tissue (ie, sarcomere loss, glycogen accumulation, disarray of mitochondria, and fibrosis).[84] A long follow-up (ie, ≥12 months), however, has been achieved in only a limited number of studies.[83,85,86] In the vast majority of studies, the time interval between revascularization and assessment of LV function at follow-up ranged from 2 to 6 months. This variable time of recovery and follow-up is likely to represent a significant confounding factor in view of the longer recovery period required by hibernating myocardium with more severe structural abnormalities. Furthermore, we lack consistent information on the role of reverse remodeling and reduction of wall stress initiated by the segments that recover function at an earlier stage.

In the planning of treatment strategies, a current challenge is the question of how much viable myocardium is required to achieve a significant improvement in LV function after coronary revascularization. General consensus exists that the changes in LVEF after revascularization are linearly correlated with the number of viable segments,[15,64,67,70,73,74,77] although resting LVEF correlates weakly with exercise capacity in heart failure patients.[87,88] Although the relationship between symptoms and severity of underlying disease is elusive, the magnitude of improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy seems to be related to the quantitative extent of myocardial viability.[89] The lack of a standardized procedure for the segmentation and nomenclature of the LV, which has evolved independently within each technique, has made comparisons very difficult. Assuming that the segmental division encompasses the totality of the LV (ie, 100%), the majority of studies agree that to yield the best sensitivity and specificity to predict a ≥5% improvement in LVEF, at least 25% of the LV should be viable using DSE[22,62,63,66] and ≈38% using conventional nuclear medicine and PET.[49,62,63] In a comprehensive patient stratification, the presence and extent of myocardial scarring are important predictive factors.[83,85,90] In dyskinetic and akinetic segments, the absence of scar or a transmural extension of scar of <25% have been considered predictive of functional recovery, with a positive predictive value of 88% and a negative predictive value of 89%.[54]

In studies that evaluated the improvement of function on a segmental basis (Table 2), SPECT and PET demonstrate excellent sensitivity, whereas echocardiography and cardiovascular magnetic resonance with dobutamine stress have superior specificity and positive predictive value.[22,66,67,70,72–81] In a preliminary study in a small group of patients, late-enhancement cardiovascular magnetic resonance in direct comparison with ^{99m}Tc-sestamibi and FDG-PET showed better negative predictive value for segments classified as nonviable 6 months after revascularization.[67]

In interpreting these results, we must consider several potential confounding factors. Small-cohort, retrospective studies are limited by patient selection and posttest referral bias, which tend to raise the measured sensitivity and lower the specificity of the diagnostic test.[91] Younger symptomatic patients with a higher likelihood of viable myocardium and no extensive comorbidity are more likely to be referred for viability assessment to evaluate feasibility of revascularization.

Technical limitations are also inherent to the revascularization technique. In the case of bypass surgery, these include suboptimal insertion of the distal end of the graft with poor runoff. In the case of percutaneous coronary interventions, incomplete revascularization, restenosis, and late in-stent thrombosis may impair adequate tissue perfusion. Further-

Table 3. Mortality Rates by Patient Subgroups

	Total Patients, n	Weighted Average Annual Mortality	95% CI
Medical therapy viability present			
DSE[99–105]	362	11.23	7.98–14.48
PET[106]	50	6.25	0.00–12.96
^{99m}Tc-sestamibi[39,107]	110	11.17	5.29–17.06
^{99m}Tc-sestamibi+PET-FDG[108]	30	10.33	0.00–21.23
^{201}Tl rest, reinjection; DSE[109]	43	9.67	0.83–18.50
Total	595	10.64	8.17–13.12
Medical therapy viability absent			
DSE[99,101–105]	447	12.05	9.03–15.06
^{99m}Tc-sestamibi[107]	27	13.85	0.82–26.87
^{99m}Tc-sestamibi+PET-FDG[108]	26	3.33	0.00–10.23
Total	500	11.69	8.87–14.51
Revascularization viability present			
DSE[68,99–105]	338	3.09	1.24–4.93
PET[106]	43	7.5	0.00–15.37
^{99m}Tc-sestamibi[39,107]	171	3.16	0.54–5.78
^{99m}Tc-sestamibi+PET-FDG[108]	42	0	0.00–0.00
^{201}Tl rest, reinjection; DSE[109]	94	1.67	0.00–4.25
Total	699	3.71	2.31–5.12
Revascularization viability absent			
DSE[68,99,101–105]	348	8.78	5.80–11.75
^{99m}Tc-sestamibi[107]	50	8.77	0.93–16.61
^{99m}Tc-sestamibi+PET-FDG[108]	25	3.33	0.00–10.37
Total	423	8.45	5.80–11.10

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more, both bypass and percutaneous coronary interventions can lead to new areas of necrosis with scar formation.[55,92] Finally, extreme degrees of adverse LV remodeling can hamper the improvement in function independently of the total number of viable segments.[93,94]

Treatment and Survival Rates

The prognostic value of viability testing and the impact of therapeutic choice on survival have been tested in a meta-analysis of 24 nonrandomized studies carried out between 1992 and 1999 which included 3088 patients with an LVEF <40%. The meta-analysis demonstrated a significant association between revascularization and improved survival rate in patients with LV dysfunction and evidence of myocardial viability independently of the imaging technique used.[95,96] This meta-analysis failed to show any benefit of revascularization in the absence of significant viability and reported a higher annual mortality in patients with viable myocardium who were treated medically. An important corollary was the incremental survival benefit after revascularization in those patients with the worst LV function.

Medical therapy was not standardized in the studies analyzed by Allman et al,[95] and the adherence to optimal therapy was not adequately described. In the last decade, the medical treatment of heart failure has continued to improve,[97,98] and significant advances have been made in the techniques for coronary revascularization.

To explore potential changes in the outcome of patients with postischemic heart failure with and without viable myocardium that may have occurred from the publication of the results of Allman et al,[95] we pooled the data from 14 nonrandomized studies published between 1998 and 2006 that reported long-term Kaplan-Meier survival curves. Patients were subdivided into 4 groups based on treatment (medical or revascularization by bypass surgery or percutaneous coronary intervention) and the presence or absence of viable myocardium. Of the 14 studies selected, 8 had patients in all 4 groups. The mortality rates were weighted for the number of patients and calculated per year by dividing the mortality by the number of follow-up years to account for different final time points among the studies.

The pooled data are summarized in Table 3.[39,99–109] In agreement with the results of Allman et al,[95] a trend for a survival benefit in patients with ischemic cardiomyopathy, with even modest amounts of viable tissue, was present in patients who underwent revascularization compared with patients with viable myocardium treated medically. In the absence of viable myocardium, no clearcut difference can still be observed between treatments despite the fact that refinement of surgical and percutaneous revascularization procedures such as widespread use of arterial grafts and more persistent patency of the vessels after PCI[110] have reduced intraprocedural and periprocedural risks.

Reviewing the most recent literature, we observed that the annual mortality rate in patients treated medically appears to be similar regardless of the presence of viability (Table 3). This is different from what was reported by Allman and coworkers,[95] and it could be a reflection of the optimization, by 21st century standards, of patient management.[106,108] In a prospective study cohort of 167 patients studied with PET using N-13 ammonia and FDG, Desideri et al[111] reported that the risk of cardiac death is not significantly increased if the extent of viability is ≤20% of the LV. The risk of death is increased only when the extent of viable tissue exceeds 20% of the LV, and together with the presence of left bundle-branch block, it is an independent predictor of mortality.

Observational studies in small cohorts of patients have highlighted that a long waiting time between assessment of viability and revascularization affected both the postoperative recovery of function[112] and survival by increasing preoperative mortality.[113] A comparison of the outcome after early (within 30 days) or late (>30 days) revascularization in 2 parallel groups of patients showed a significant improvement in function and lower mortality in the group with shorter waiting times.[114]

The impact of the time of revascularization on prognosis has recently been highlighted by Tarakji et al,[17] who assessed viability with PET using FDG and rubidium-82 in the largest prospective cohort of 765 consecutive patients. They applied a propensity analysis matching 153 patients who underwent early revascularization within 6 months and 153 who did not. Their conclusion was that early intervention might be associated with reduced mortality from all causes independently of the amount of viable myocardium detected preoperatively. Several issues were not addressed in this study: Only a minority of patients underwent revascularization without evidence of viability; the impact of arrhythmias and implantable cardioverter-defibrillator implantation is uncertain during the progression of the study; and the same applies to medical therapy that was suboptimal by present standards at the beginning of the observation period in 1997.

The impact of the amount of viability on subsequent survival after revascularization remains unclear because contrasting data are reported in a number of other studies that, using the Cox proportional-hazards model, demonstrated a positive prognostic effect on survival.[68,99–101,106,107] The presence of scar[106] or extensive myocardial remodeling[115,116] as independent predictors of survival can add incremental prognostic value to the amount of viable myocardium. These 2 parameters are likely to bear more weight in future studies using late-contrast-enhancement cardiovascular magnetic resonance to assess viability and to add prognostic power to LVEF, which is a baseline predictor of mortality independent of the cause of LV dysfunction.[117] It has already been demonstrated that in patients without a history of previous myocardial infarction, late enhancement involving a small amount of myocardium carries a higher risk of adverse cardiac events.[118]

Long-awaited large, prospective, multicenter, randomized trials testing the prognosis of patients on optimal medical therapy by year 2000 standards plus revascularization against optimal medical therapy alone are ongoing. We hope that they will provide a clearer picture as to whether long-term prognosis is improved by early revascularization in this patient population (Surgical Treatment for Ischemic Heart Failure [STICH]).[119] Positron Emission Tomography and Recovery Following Revascularization-2 (PARR-2), the follow-up of PARR-1,[90] has recently been completed. This randomized, multicenter trial that enrolled 430 patients seems to show a trend toward better 1-year outcome when PET-FDG–guided therapy is used instead of standard care.

Conclusions

Although different large, randomized trials have demonstrated a significant reduction in mortality for heart failure patients treated medically, symptomatic heart failure continues to have a high mortality rate.[120,121] In more than two thirds of cases, heart failure is secondary to CAD.

In the last 3 decades, 2 new causes of LV dysfunction, ie, myocardial stunning and hibernation, have been recognized in addition to tissue necrosis. Both conditions are reversible and imply the presence of viable myocardium. Furthermore, evidence has accrued that they may contribute to LV dyssynchrony and heart failure in patients with CAD.

Several powerful imaging techniques can be used clinically to identify viable tissue (and to distinguish it from scar) within dysfunctional LV segments subtended by diseased coronary arteries. This information can be used to stratify patients more effectively and to guide their subsequent treatment. Although we still lack data from ad hoc randomized trials to prove this point unequivocally, a great number of studies in thousands of cases have provided compelling evidence that revascularization of dysfunctional but viable myocardium may lead to reverse LV remodeling and confer prognostic benefits in patients with postischemic heart failure.

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Disclosures

None.

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