Internal Medicine Journal 2005; 35: 118–125

REVIEW

Clinical decision-making and myocardial viability: current perspectives

C. NELSON and T. H. MARWICK

Department of Medicine, University of Queensland, Brisbane, Queensland, Australia

Abstract

Not all myocardium involved in a myocardial infarction is dead or irreversibly damaged. The balance between the amount of scar and live tissue, and the nature of the live tissue, determine the likelihood that contractile function will improve after revascularisation. This improvement (which defines viability) may be predicted with about 80% accuracy using several techniques. This review examines the determinants of functional recovery and how they may be integrated in making decisions regarding revascularisation. (Intern Med J 2005; 35: 118–125)

Key words: myocardial infarction, viable myocardium, magnetic resonance imaging, single photon emission computed tomography, echocardiography.

WHAT IS VIABLE MYOCARDIUM AND WHY IS IT IMPORTANT?

Not all myocardium involved in an infarction is dead or irreversibly damaged. The process of infarction progresses as a wavefront, starting at an endocardial location and spreading towards the epicardium.[1] An infarct will cease spreading when the affected vessel is reperfused (spontaneously, pharmacologically or mechanically) or when the infarct encounters myocardium that is sufficiently collateralised to remain alive. Therefore, completed infarcts vary in their transmurality, with the epicardium being the most likely site of viable myocardium.

Although a dictionary definition of viability would refer to the presence of life, the most useful clinical definition would refer to dysfunctional myocardium that will recover contractile function, usually after being revascularised.[2] There are several problems with the conventional clinical definition of viable myocardium based on improvement of function after revascularisation. First, an element of selection bias is introduced by the decision to revascularise. Second, the time frame for hibernating segments to recover contractile function may be up to 14 months (most of the relevant studies do not reassess contractile function beyond 6 months) and this delay engenders potential confounding effects as a result of restenosis, graft closure, new plaque rupture and/or remodelling.[3] Third, revascularisation of viable myocardium has or may have benefits other than recovery of resting contractile function, including effects on mortality, left ventricular (LV) volumes and exercise tolerance.

Observational data indicate that revascularisation of patients with a significant burden of viable myocardium (about 25% of LV mass) results in improved LV function,[4] as well as reduced symptomatology[5] and improved survival.[6] The presence and extent of viability may be predicted preoperatively by several investigations, including thallium or technetium single photon emission computed tomography (SPECT (Tl SPECT, ^{99m}Tc SPECT)), positron emission tomography (PET), dobutamine echocardiography (DbE) and dobutamine stress cardiac magnetic resonance imaging (MRI). These have been extensively reviewed and compared,[7] the consensus being that as the sensitivity of these tests for predicting recovery of function is remarkably similar (Fig. 1), the best test to choose depends on local expertise. Another approach to the same problem is to assess the reduction of wall thickness or degree of replacement with scar (e.g. using delayed hyperenhancement by MRI), effectively defining the amount of non-recoverable tissue. This review will explore how to synthesise the variety of clinical information that might be used for clinical decision-making regarding revascularisation of viable myocardium.

PATHOPHYSIOLOGY OF VIABILITY AND ITS RESPONSE TO REVASCULARISATION

Much has been made in the past of the distinction between myocardial stunning and hibernation. Stunning (postischemic dysfunction) occurs when: 'an ischemic insult not of sufficient severity of duration to produce myocardial necrosis (causes) postischemic LV dysfunction'.[8] Hibernating myocardium is a chronic low-flow

Correspondence to: Thomas H. Marwick, University of Queensland, Department of Medicine, Princess Alexandra Hospital, Brisbane, Qld 4102, Australia. Email: tmarwick@soms.uq.edu.au

Received 10 November 2003; accepted 19 March 2004.

Funding: Supported in part by a grant from the National Health and Medical Research Council of Australia.

Potential conflicts of interest: None

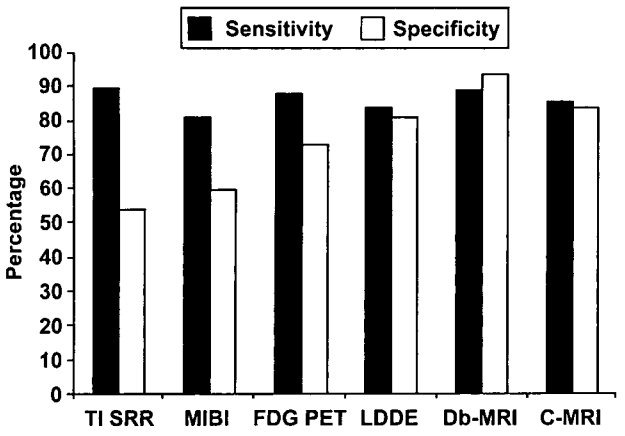

Figure 1 Sensitivity and specificity of single photon emission computed tomography (thallium stress-reinjection-redistribution (SRR) and ^{99m}Tc sestamibi), positron emission tomography (PET), fluorodeoxyglucose (FDG), low-dose dobutamine echo (LDDE), dobutamine magnetic resonance imaging (Db-MRI)) and contrast-enhanced MRI (C-MRI). Derived from Bax,[7] Baer[50] and Kim.[55]

state that induces 'resting LV dysfunction ... that can be partially or completely reversed by myocardial revascularisation and/or by reducing myocardial oxygen demand'.[2] The two entities are rarely as distinct clinically as suggested experimentally; although repeated stunning appears to be a more plausible explanation of the behaviour of several aspects of viable tissue, including the presence of normal coronary flow[9,10] with reduced flow reserve[11,12] and a dobutamine response.

Moreover, it appears that as the biochemical state of the tissue worsens, there are progressive ultrastructural changes and these are related to the likelihood and timing of functional recovery.[13,14] Indeed, severe ultrastructural changes are associated with a loss of dobutamine responsiveness, such that the tissue may only be identified using PET imaging with metabolic tracers (or in all probability, contrast enhanced MRI) and has a prolonged recovery time.[15]

Revascularisation of viable myocardium has been shown to significantly improve regional[16–19] and global contractile function.[19,20] Revascularisation of viable myocardium has also been shown to significantly improve symptoms: in one study, New York Heart Association functional class improved from 3.2 to 1.6.[20–22] The magnitude of improvement in heart failure symptoms after coronary artery bypass graft (CABG) is linearly related to the preoperative extent of myocardial viability;[5] viability of 18% of the LV having a sensitivity of 76% and a specificity of 78% for predicting a change in functional capacity after CABG.[5] Exercise capacity is also improved: in another study, the difference between preoperative and postoperative exercise capacity ranged from a reduction of 2.8 to an augmentation of 5.2 metabolic equivalents, with the degree of improvement of exercise capacity and the change in functional class correlating with the extent of viability.[18,23] A greater extent of viability preoperatively is associated with lower rates of hospitalisation for congestive heart failure and even death.[17] It is also unclear as to whether revascularisation significantly prevents or reverses remodelling. Yousef *et al.* found that percutaneous intervention to the left anterior descending artery resulted in significantly greater LV end systolic and end diastolic volumes than medical therapy alone.[24]

No randomised controlled trials have yet been completed that show a prognostic benefit of revascularisation based on assessment of viability in patients with CAD, although some are underway.[25,26] However, several observational studies point to a prognostic benefit of revascularisation based on assessment of viability compared to medical therapy alone.[6,27–29] Conversely, the absence of viability may preclude benefit from revascularisation.[28,30] In the meta-analysis reported by Allman *et al.*,[6] 3088 patients (mean ejection fraction 32%) studied with Tl SPECT, PET and DbE showed that revascularisation was associated with an 80% reduction in annual mortality (16% *vs* 3.2%; $P < 0.0001$). The cause of death in patients with ischemic LV dysfunction is probably both sudden cardiac death and progressive heart failure. However, the reduction of mortality with revascularisation in these patients is likely to be as a result of improvements in ejection fraction,[17] and there is conflicting evidence as to whether coronary bypass surgery decreases the risk of serious arrhythmia or arrhythmic death.[31–36] Some patients with chronic ischemic heart disease and ventricular tachyarrhythmias probably continue to be at risk of sudden death after revascularisation, especially if the rhythm remains inducible, and those with implanted cardioverter defibrillators have the same rate of device therapy and mortality as patients who are not revascularised.[34,36,37]

Nonetheless, enthusiasm for revascularisation needs to be tempered by the risks, particularly for operative intervention. From the Coronary Artery Surgery Study data, the operative mortality rate for patients with left ventricular ejection fraction (LVEF) ≤ 35% and angina as the predominant symptom was 6.9% compared with 1.55% for patients with LVEF > 35%.[38] More recently, Mitropoulos and Elefteriades identified 14 major studies between 1991 and 1999, of patients with LVEF < 35% undergoing CABG (a total of 1913 patients) and the reported operative mortalities ranged from 1.8 to 24%.[39] Additionally, perioperative mortality for isolated CABG with comorbidities and other high risk features has been estimated to be >28%.[25] Therefore, decision-making regarding revascularisation for viability includes not only the amount of viability, but the nature of the target vessels, and other determinants of risk including age and comorbidities. In summary, the recovery of contractile function appears to be the mechanism whereby revascularisation improves symptomatology and survival. Therefore, we believe that the current evidence base suggests that the only appropriate end-points of therapy should be recovery of contractile function, reduced symptomatology or improved survival.

CLINICAL FEATURES

Global and regional left ventricular function

Significance of left ventricular ejection fraction

The main situation where myocardial viability is of clinical relevance is in patients with moderate or severe LV dysfunction. These patients have increased perioperative and long-term mortality compared with patients with normal LV function[25] and also have the most to gain from revascularisation.[6] Therefore, the starting point of the subsequent decision process is the presence of significant LV dysfunction (ejection fraction < 35–40%), keeping in mind that the standard error for echocardiographically derived LVEF is 7.5%.[40]

Hypokinesia versus akinesia

It is often reported that any degree of wall thickening relates to the presence of contracting cells, *and is hence viable.*[41] While the first part of the statement is true, the second part does not necessarily follow, certainly in respect of the above definition incorporating functional recovery.[42] The reason is that a hypokinetic segment may contain various combinations of infarcted myocardium, normal live myocardium and stunned or hibernating myocardium; if the latter predominates, it may very well recover, while if the segment is made of dead and live tissue, it may remain hypokinetic after revascularisation (the probability of remaining hypokinetic increasing as the ratio of dead to live tissue in the segment increases). The lower specificity of functional testing in hypokinetic segments has been previously recognised with both scintigraphic and echocardiographic techniques.[19] The solution may be a more accurate appreciation of the transmural extent of scar (see below).

Angina

In patients with ischemic heart disease and LV dysfunction, Auerbach *et al.* reported angina to be present in 38% of patients with >4/19 segments being viable, compared with 18% of those with <4 segments being viable.[43] Therefore, angina is a marker of viability, albeit an insensitive one, presumably because ischemic segments are associated with viable segments. Moreover, revascularisation of ischemic myocardium leads to improvement in functional capacity even in the absence of significant viable myocardium.[20] Myocardium that is ischemic as well as viable is more likely to recover contractile function after revascularisation than myocardium that is viable but not ischemic.[27]

The presence of angina is an indication for revascularisation in a postinfarct patient, subject to the usual consideration of age, comorbidity and the details of coronary vasculature.[25,44] The decision is more difficult in patients with only mild angina and in whom the extent of disease lacks prognostic implications, in which case the identification of viability is necessary before revascularisation.[25]

Coronary anatomy

In patients with ischemic LV dysfunction, but without angina, the published angiographic literature has shown a survival benefit from revascularisation for certain coronary anatomical distributions of disease (hitherto referred to as prognostic disease). Patients with three-vessel disease and reduced ejection fractions (<50%) and patients with left main stenosis >50%, left main equivalent disease or proximal left anterior descending coronary artery stenosis >70% and an ejection fraction <50% undergoing surgical revascularisation have improved survival compared to those treated medically.[45–47] However, within these groups there are some subgroups for which a benefit from surgery has not been demonstrated,[48–50] and it should be recognised that these data may be less valid in the context of new developments in surgery and medical therapy, not to mention percutaneous intervention, since its collection.

For patients with prognostic disease, viability testing has been argued to further inform the risk versus benefit component of the revascularisation decision. Three studies (total 221 patients) showed that the number of significantly diseased vessels on coronary angiography did not add incremental prognostic information to viability assessment by thallium scanning.[30,51,52] However, in a prospective study of 137 consecutive patients by Pasquet *et al.*, patients with 3 vessel or left main disease always improved survival after revascularisation (albeit 3–4 times more in the presence of viable or ischemic myocardium), whereas among patients with 1 or 2 vessel disease, only those with ischemic or viable myocardium improved survival after revascularisation.[53] In these situations, viability assessment may be useful when the decision to revascularise is not clear-cut (e.g. in the presence of comorbidities).

The more difficult decision-making refers to two groups of patients without prognostic disease: those with extensive viability, and those with predominant symptoms of heart failure. In the first group, observational studies have shown more favourable outcome in those with viable myocardium who are revascularised rather than treated medically, and this seems to be especially true in those with worse LV function.[6] The extent of viability seems to be a determinant of the amount of prognostic benefit,[17] suggesting that the mechanism of prognostic benefit relates to the degree of improvement of ejection fraction. The same is likely to be true for improvement of heart failure symptoms, such that viability assessment is a prerequisite for coronary artery bypass grafting in patients whose main indication for surgery is heart failure.[23] At this stage, information gathered from coronary angiography and viability testing should be considered complementary. However, in the light of randomised controlled trials (e.g. Surgical Treatment for Ischemic Heart Failure Trial[26] and the Heart Failure Revascularisation Trial[54]), viability assessment may be proven superior to the current anatomical criteria for revascularisation.

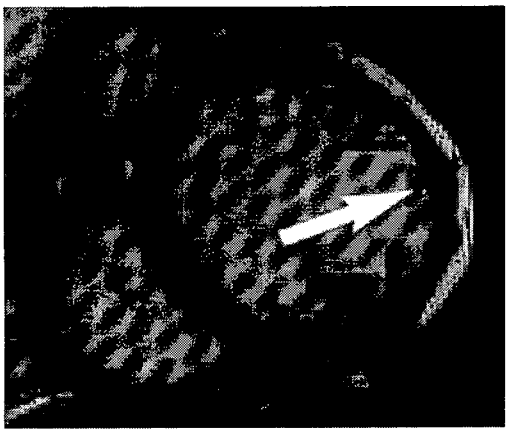

Figure 2 Left ventricular mid short axis view by cardiac magnetic resonance imaging demonstrating thinning of the lateral wall (arrow, measurements ranged from 2 to 4 mm).

Myocardial scar

Electrocardiographic Q waves

The presence of Q waves is not a reliable marker of myocyte necrosis; PET has revealed evidence of persistent tissue metabolism in 43–54% chronic electrocardiographic Q wave regions.[16,55] Conversely, residual R waves suggest that the tissue is still viable. Recent MRI studies have improved our understanding of these electrocardiographic features,[56] and they may be more reflective of the extent of damage than its transmurality. Electrocardiographic features would not be sufficient grounds to identify the presence of viable tissue.

Wall thinning on resting 2-D echo and magnetic resonance imaging

Chronic transmural infarction causes severe wall thinning, although it may require up to 4 months for thinning to occur.[41] Thinned segments are *unlikely* to recover. Faletra *et al.* predicted 87% of non-viable segments on 2-D echo (2DE) with a pattern of reduced end diastolic wall thickness (EDWT) (defined as EDWT <70% of adjacent normally contracting segments) and increased acoustic reflectance,[57] and Cwajg *et al.* found that an EDWT > 6 mm on 2DE had sensitivity of 94% and a specificity of 48% for recovery of function.[58] Therefore, thinned tissue *may* recover: this is to be especially considered in the presence of LV dilation. Moreover, the lack of thinning is not a good marker of viability, only 75% of viable segments were predicted with a pattern of normal EDWT and normal acoustic reflectance.[57]

Although measurements of LV wall thickening by MRI (Fig. 2) are probably more accurate than echocardiographic measurements,[59] this does not substantially alter the implications of these findings. Baer *et al.* found an EDWT of ≤5.5 mm by MRI to have a negative predictive accuracy of 90% to predict transmural scar, but a positive predictive accuracy of only 62%;[60] and Perrone-Filardi, using an MRI EDWT of 8 mm in akinetic regions, found a sensitivity of 74%, a specificity of 79% and a positive predictive value of only 55% for the prediction of metabolic activity by PET.[61]

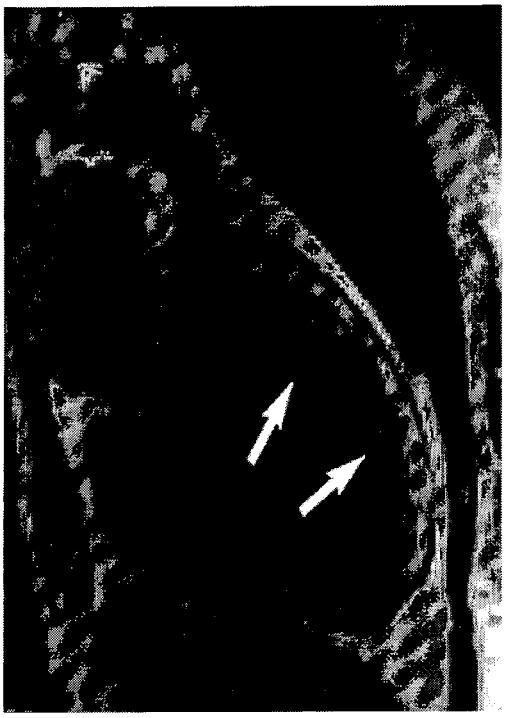

Figure 3 Contrast enhanced magnetic resonance imaging: vertical long axis view (equivalent to two-chamber echo view) demonstrating hyperenhancement of the inner 50–75% of the entire anterior wall (arrow). The scar is located on the endocardial surface (white), with live epicardium (black) seen as a thin rim outside the scar. Non-infarcted segments are black throughout the wall: outside the epicardium is a ring of white (pericardial fat).

Late contrast enhancement using gadolinium magnetic resonance imaging

Comparison of MRI with histopathology in dogs has shown that the spatial extent of hyperenhancement is the same as the spatial extent of infarction at every stage of healing (from 4 h through to 8 weeks).[62] Recently, it has been shown in humans that infarct size defined by MRI is correlated strongly and significantly with peak creatine kinase-MB values ($r = 0.90$, $P < 0.001$).[63] Moreover, the presence, location and transmural extent of the chronic (3 months) Q wave and non-Q wave myocardial infarction can be accurately determined by contrast enhanced MRI,[64] with the difference in image intensity between infarcted and non-infarcted regions being 500%.[64] Delayed hyperenhancement (Fig. 3) is thought to reflect passive diffusion of gadolinium throughout the extracellular space, resulting in higher gadolinium concentration in the expanded interstitial compartment of collagen-filled fibrous scar.[64] In a key study, Kim *et al.*

examined 804 dysfunctional segments and found that the likelihood of improvement in regional contractility post-revascularisation decreased progressively as the transmural extent of hyperenhancement increased ($P < 0.001$).[65] The percentage of the LV that was both dysfunctional and not hyperenhanced before revascularisation was strongly related to the degree of improvement in the global mean wall-motion score and ejection fraction (both $P < 0.001$). Nonetheless, although the likelihood of residual contractile function at rest decreases with increasing transmural extent of scar (TME), residual resting function is seen in many patients with 25–75% TME, although uncommonly in those with >75% TME.[60,66] Indeed, while the extremes of TME predict outcome, the less certain outcomes relate to intermediate levels of scar, in which situation the patients may benefit from combined functional assessment using wall motion techniques (Fig. 4).

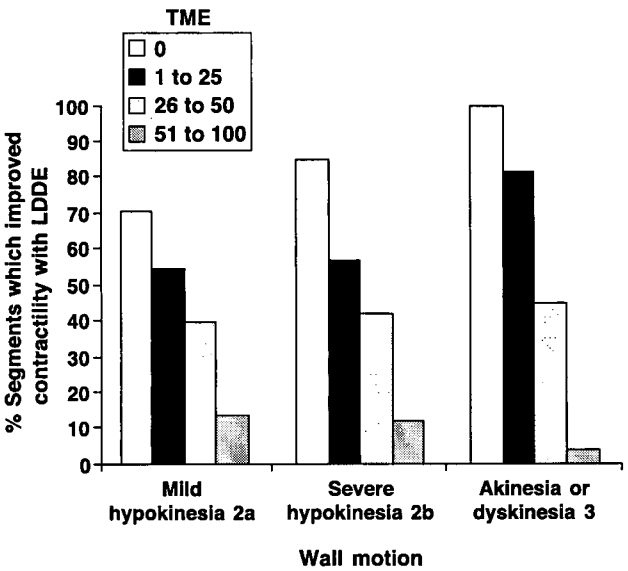

Figure 4 Impact of transmural extent of scar on the likelihood of recovery after revascularisation in hypokinetic and akinetic segments. Note that the extremes of transmural extent predict recovery well, but that intermediate degrees of scar thickness do not, signifying a need to evaluate the nonenhanced muscle by another technique. LDDE, low dose dobutamine echo.

Techniques for determination of viable myocardium

The available techniques for assessment of myocardial viability include Tl201 or ^{99m}Tc SPECT, ^{18}F deoxyglucose PET (usually in combination with a SPECT or PET flow tracer), DbE and cardiac MRI (delayed hyperenhancement usually with dobutamine stress or perfusion assessment). Although each identifies viable myocardium, they do so through the assessment of different parameters: DbE measures contractile reserve through augmentation of contractile function with low dose dobutamine, Tl SPECT measures myocardial myocyte cell membrane integrity through demonstration of intact Na/K-ATPase pump function, ^{99m}Tc SPECT identifies myocyte mitochondrial activity, PET quantifies flow/metabolism mismatch, and contrast enhanced MRI records the transmural extent of scar. Despite these differences, it is interesting that the tests indirectly identify the amount of scar, and the amount of scar determines the likelihood of recovery.[67–69] These investigations have been extensively compared;[7,70] techniques based on assessment of contractile reserve have greater specificity for predicting functional recovery than do techniques that identify perfused or metabolically active tissue. Nonetheless, the most important principle is to use the technique with the best local expertise.

CONCLUSION

Figure 5 summarises the approach that we use for assessment of myocardial viability. In practical terms, the issue is most important in the setting of moderate to severe LV dysfunction. An approach to revascularisation decisions based purely on traditional coronary anatomical indications is justified by the existing data, but in our opinion there is good evidence to include information from viability testing to better inform the risk/benefit assessment in revascularisation decisions. Defining extensive viability and limited scar may justify intervention to improve functional class or prognosis. Although this

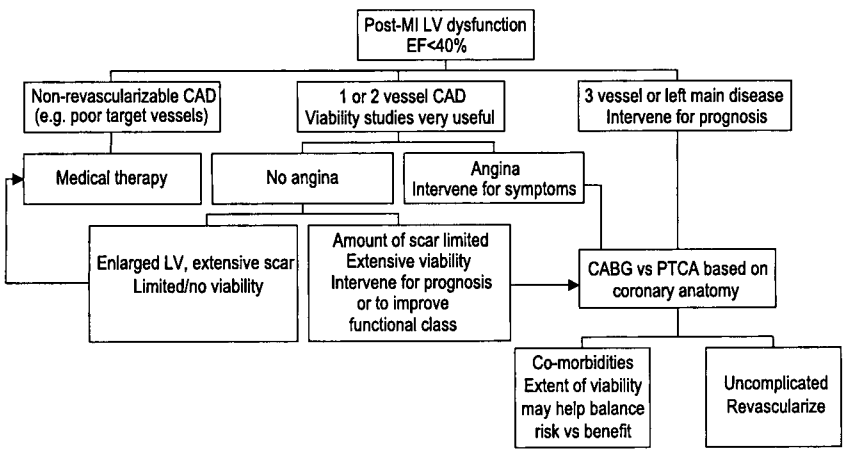

Figure 5 Suggested approach to decision-making regarding myocardial revascularisation based on symptom status, coronary anatomy, and extent of viable myocardium.

remains unproven in randomised trials, observational data indicate that revascularisation of viable myocardium (>25% of LV mass) results in reduced symptomatology, improved LV function and improved survival. Since the information from coronary angiography and viability testing is complementary, the order in which the tests are done is best dictated by pragmatism. In a referral centre with easy access to angiography, it is quite reasonable to perform viability testing after coronary angiography: therefore avoiding viability testing in patients with inadequate target vessels. However, an advantage of performing viability testing prior to angiography in these referral centres is that the option of ad hoc percutaneous coronary intervention is left open. In situations where angiography is less available, the lack of viability in an extensively impaired ventricle would suggest that intervention would be unlikely to alter outcome and may spare the patient unnecessary angiography.

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