Assessment of Myocardial Viability in Chronic Left Ventricular Dysfunction

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Abstract

Differentiation of infarcted from viable myocardium is of critical clinical importance in patients with severely impaired left ventricular function. While positron emission tomography is considered the "gold-standard" modality for detection of viable myocardium, expense has limited its more widespread use. Therefore, many centers employ surrogate tests for metabolic viability. Various imaging protocols involving thallium-201 are currently used to establish myocardial viability. In several recent studies, low-dose dobutamine echocardiography has been useful in predicting recovery of poorly contractile myocardium. Myocardial contrast echocardiography is a promising new technique which may predict viability by defining areas of preserved microvascular integrity. The clinical role of these diagnostic modalities in the setting of depressed ventricular function is as yet uncertain. Clarification of the utility of these tests should allow more judicious selection of patients who would derive the greatest survival benefit from revascularization procedures.

Key Words

myocardium (viability), diagnostic techniques, stress echocardiography (dobutamine), magnetic resonance imaging, radionuclide imaging, echocardiography (contrast), chronic left ventricular dysfunction

INTRODUCTION

Because the distinction between reversible and irreversible ventricular dysfunction has important clinical implications, much interest currently centers on the determination of myocardial viability. Asynergic but viable myocardium may either be "hibernating" or "stunned". Myocardial hibernation as initially propounded by Rahimtoola[1,2] and later by Braunwald & Rutherford[3] is a condition where myocardial perfusion is chronically reduced but still sufficient to maintain tissue metabolism. The decreased contractile function may represent an adaptive response of the myocardium to prolonged underperfusion, with decreased aerobic and increased anerobic metabolism to preserve cellular viability[4]. Consistent with this concept is the demonstration that abnormally contracting, underperfused myocardium appears macroscopically normal when examined at autopsy[5]. Restoration of blood flow to hibernating myocardium should improve cardiac contractile function as evidenced by numerous angioplasty and surgical series[2,6-11]. The diagnosis of hibernating myocardium was therefore in the past established only retrospectively.

Stunned myocardium on the other hand refers to persistent post-ischemic dysfunction despite restoration of normal or adequate coronary flow[12]. The reversible myocardial dysfunction thus produced generally lasts days to weeks[13,14]. Generation of noxious oxygen-derived free radicals[15] and/or impaired calcium homeostasis causing transient cal-

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cium overload[16] are postulated mechanisms of myocardial stunning. Studies purporting to demonstrate functional improvement with revascularization soon after myocardial infarction or unstable angina must therefore consider the confounding influence of myocardial stunning[17,18]. Even so, the absence of a recent unstable coronary syndrome in a patient with long-standing left ventricular (LV) dysfunction does not exclude the presence of stunned myocardium as silent repetitive ischemia, either spontaneous or related to exercise, and may lead to prolonged stunning and theoretically produce chronically dysfunctional myocardium[12]. In the clinical setting, therefore, it is often difficult to be certain if depressed regional contractility is related to hibernation, stunning, or a combination of both[12].

Regardless of the exact pathophysiologic mechanism of chronic LV dysfunction, the ability to prospectively determine if myocardium is viable may be clinically relevant. While trials comparing the outcome of surgical and medical therapy indicate that survival benefit is greatest in the surgical group when ventricular function is depressed[19-22], operative mortality in unselected patients remains high[23,24]. These patients often present with symptoms of congestive heart failure and despite severe multivessel disease are often not highly symptomatic of angina[1,25,26]. Identification of myocardial viability in this subgroup is critical because of the increased risks associated both with revascularization as well as continued medical therapy[27] and the relatively high attrition rate on follow-up despite surgery[20].

One plausible explanation for the high mortality in this cohort is that some patients without viable myocardium were operated on. Conversely, successfully revascularized patients have a medium-term survival equivalent to that of transplanted patients[23,28-30]. The improved postoperative outlook in patients with contractile reserve suggests that determination of myocardial viability may be a useful strategy to select those most likely to benefit from revascularization[23,31,32]. The demonstration of viable myocardium in regions of severe asynergy may also reassure surgeons that coronary artery bypass grafting (CABG) will improve ventricular function; those with irreversibly damaged myocardium would then have the option of cardiac transplantation.

METHODS OF ASSESSING VIABILITY

Conventional indices

Traditional indices of myocardial necrosis have not proven to be universally reliable. Brunken *et al* found that the majority of chronic electrocardiographic Q-wave regions had persistent metabolic activity despite reduced regional perfusion[33], suggesting that most infarcted areas contain viable myocytes. Montalescot *et al* demonstrated that Q-wave regions could regain contractile function following percutaneous transluminal coronary angioplasty (PTCA) in 15 patients with single vessel disease (>70% stenosis) and a Q-wave infarction of more than 6 weeks' duration[34]. Despite the absence of prior clinical and scintigraphic evidence of myocardial ischemia, dilatation of the infarct-related lesion resulted in improved regional wall motion and increased thallium-201 (^{201}Tl) uptake in the infarct zones.

Assessment of regional anatomy and function do not always reliably distinguish viable myocardium from dead tissue. Lewis *et al* found resting segmental wall motion abnormalities on echocardiography in 1/3 of patients without a previous symptomatic myocardial infarction (MI) or ECG Q-waves who were being evaluated for coronary artery disease[35]. Subsequent improvement of contractile function in 85% of revascularized territories suggested to these authors that many of the abnormally contractile segments were hibernating. It needs to be noted however that the majority of these revascularized segments were hypokinetic rather than akinetic. Other investigators have previously shown that resting akinesia or even dyskinesia may improve following revascularization[36,37]. While studies using magnetic resonance imaging (MRI) indicate that non-viable myocardial regions are generally thin and lack systolic thickening[38,39], the converse is not always true. Using positron emission tomography (PET) and spin-echo gated nuclear MRI techniques, Perrone-Filardi *et al* showed that metabolic activity is present in many myocardial segments with reduced end-diastolic wall thickness and absent wall thickening[40].

The presence of viable myocardium may be inferred by an ischemic response to exercise testing because only viable tissue will develop ischemia and produce electrocardiographic abnormalities. However, the significance of some of these changes,

including ST segment elevation in the province of infarcted leads, is unclear. ST segment elevation in this setting has been ascribed primarily to mechanical factors[41,42] while others consider this finding indicative of transient ischemia[43,44]. A recent investigation using ^{201}Tl scintigraphy suggests that in the early post-myocardial infarction period at least, ST segment elevation in infarct-related leads is indicative of residual viable myocardium[45]. Both viewpoints may not be incompatible because depending on the age of the infarct, the degree of vessel patency, and extent of collateral circulation, there may be varying amounts of residual viable tissue in the peri-infarction zone[46].

Information derived from coronary arteriography is of limited value in predicting myocardial viability. It is likely that myocellular survival depends not only on patency of the coronary arteries[47] but also on the adequacy of collateral circulation which is underestimated by arteriography[48]. Even when angiographic collaterals are present, they are a non-specific marker for viability, implying therefore that revascularization of collateralized asynergic regions subtended by occluded arteries may not always result in functional benefit[49]. Sabia *et al* for instance, found the improvement in wall motion following PTCA to correlate poorly with baseline angiographic collateral flow[48].

Positron emission tomography

Various imaging methods have been used to identify potentially reversible myocardial dysfunction. Of these positron emission tomography (PET) scanning using a perfusion tracer (commonly nitrogen-13 ammonia) to provide regional flow information in conjunction with a metabolic marker [fluorine-18 fluoro-2-deoxy-D-glucose (FDG)] to demonstrate areas of altered glucose metabolism is the *de facto* gold standard test of myocardial viability[50]. Tillisch *et al* showed that a perfusion-metabolism mismatch by PET scanning predicted functional recovery with 85% accuracy following CABG; the negative predictive value was 92%[51]. PET has also been reported to predict successful coronary revascularization in patients with "ischemic cardiomyopathy" referred for cardiac transplantation[23]. However, the cost of this imaging modality is prohibitive, limiting its use to a few institutions. Furthermore, PET/FDG imaging for viability may yield spurious results in up to one in five patients because of dependence of FDG uptake on a number of metabolic variables such as local insulin concentration[52,53].

In addition, the benefit of intervention following demonstration of myocardial viability by PET when other diagnostic tests are negative is not established. Certainly, it is not always clear that "metabolically active" dysfunctional myocardium will recover after revascularization. In one post-MI series for example, glucose uptake was demonstrated in some (presumably infarcted) segments which remained non-contractile following revascularization[54]. Experimental studies have also shown that some myocardial regions become incapable of thickening if a threshold percentage of transmural irreversible injury is exceeded[55]. Hence, the greater "sensitivity" of PET in detecting viable myocardium may not always translate into greater functional improvement following intervention, as recently confirmed by Knuuti *et al*[56]. Furthermore, Gould has pointed out that although the majority of post-infarction regions may be viable by PET, the residua of viable tissue is often too small to warrant any intervention[53]. In addition, Marwick *et al* have shown that complete reversal of ischemic metabolic dysfunction is not achieved in a significant proportion of previously "hibernating" segments which regain contractile function following revascularization[57]. All these observations cast doubt on the importance of detecting abnormal myocardial metabolism alone and emphasize the need for more specific indications for intervention.

Thallium scintigraphy

In nuclear cardiology laboratories, ^{201}Tl imaging is most routinely employed for the evaluation of myocardial viability. ^{201}Tl was initially developed as a perfusion tracer, but as a potassium analogue it is also a marker of viability because only cells with intact membranes retain the tracer. In myocardial scar tissue, ^{201}Tl is not taken up to the same extent as normal myocardium because of markedly diminished blood flow. Conversely, there may be little uptake of ^{201}Tl in non-viable areas despite increased flow. Because the uptake of ^{201}Tl is influenced by flow (as well as derangements in intracellular metabolism), some under-perfused persistent imaging defects may in fact represent areas of viable tissue.

The reduced sensitivity of conventional ^{201}Tl imaging vis-a-vis PET[58,59] and its imprecision in de-

tecting viable myocardium[36,60] is well recognized. Various modifications of the ^{201}Tl protocol involving either reinjection immediately after stress-redistribution imaging[61–64] or delayed redistribution imaging[60,65] have been proposed to enhance the sensitivity of this test. Quantitation of the degree of reduction in ^{201}Tl uptake in "irreversible" defects has also been shown to be useful in predicting myocardial viability[62,66] and a combination of these techniques may allow detection of viable myocardium with a sensitivity approaching PET[62]. Such protocols, however, are more time-consuming, and in the case of late redistribution imaging, may result in suboptimal image quality.

Recently, stress and rest technetium-99m (^{99m}Tc) hexakis-2-methoxy-isobutyl-isonitrile (MIBI) imaging has been used to identify viable myocardium[67]. Human studies, however, suggest that MIBI is primarily a perfusion and not a viability tracer[68-70]. In the context of chronic ischemic ventricular dysfunction, the use of this tracer is potentially disadvantageous as it does not substantially redistribute over time. Dilsizian *et al* have demonstrated that same day MIBI imaging incorrectly identifies over a third of myocardial regions as being irreversibly damaged compared to ^{201}Tl redistribution-reinjection and PET[69]. On the contrary, Udelson *et al* found both agents to be comparable in predicting reversibility of regional wall motion abnormalities following revascularization[71]. These authors suggest that the sensitivity of ^{99m}Tc-MIBI imaging may have been enhanced by quantitative analyses of regional MIBI activity and alterations in the kinetics of this tracer at low flow rates. A recent ACC/AHA Task Force Report acknowledges this lack of consensus over ^{99m}Tc-MIBI scintigraphy for viability and the need for more data in this regard[72].

Patients with severe LV dysfunction may not have adequate exercise capacity and in these situations, rest-redistribution ^{201}Tl imaging is an attractive option to exercise-redistribution-reinjection techniques[73,74]. Furthermore, there is concern from work by Cloninger *et al* that following stress, even delayed ^{201}Tl imaging may overestimate the frequency of myocardial scarring[75]. Using rest-redistribution ^{201}Tl imaging in 21 patients with a mean ejection fraction of 27%, Ragosta and coworkers found the predictive value of a positive preoperative viability scan for segmental functional improvement to be 73% and that improvement in global LV function could be expected if a significant number of asynergic segments show preserved ^{201}Tl uptake[74]. The value of this test has since been corroborated by other investigators[76,77]. Currently, the rest-redistribution ^{201}Tl protocol is recommended for evaluation of LV dysfunction if the clinical question is primarily one of viability[78].

Dobutamine echocardiography

Over the past 2 decades, a number of investigators have observed improvement in systolic thickening of post-ischemic myocardium subjected to an inotropic stimulus, whether this be exercise[37], post-extrasystolic potentiation[79], epinephrine[80] or dopamine[81–83]. It was later shown using radionuclide angiography that dobutamine could effect a similar improvement, even in regions that were initially akinetic or dyskinetic[84]. While dobutamine echocardiography (DE) is currently an established non-invasive method for detection of coronary artery disease[85,86], its role in discriminating viable from necrotic myocardium is still evolving. Recognition of segmental viability with dobutamine infusion rests on the fact that low doses increase cardiac contractility via β_1-adrenergic stimulation without the significant increases in heart rate and myocardial oxygen consumption incurred with higher doses of this agent[87]. A number of investigators have demonstrated the utility of DE in determining contractile reserve and therefore myocellular integrity, both in the post-infarction setting and in patients with chronic LV dysfunction (**Table 1**)[54,88–93].

In a landmark paper, Piérard *et al* reported a good correlation between augmented wall thickening with low dose DE and FDG uptake in 17 patients following thrombolytic therapy[54]. None of their patients were revascularized and four of the five patients predicted to have contractile reserve had previously suffered a non-Q wave infarction. Smart *et al* subsequently confirmed low-dose DE to accurately predict reversible myocardial dysfunction following thrombolysis[88]. Again not surprisingly, the patients who had improved wall motion on follow-up study were more likely to have suffered a non-Q MI. As 57% of their patients were not revascularized at the time of the follow-up echocardiogram, the late improvement observed in this study suggests that DE was able to identify stunned myocardium. Barilla *et al* studied 21 patients with an anterior MI and noncontractile but vi-

Table 1 Use of dobutamine echocardiography for determining contractile reserve

Author (year)*)	*n*	Post-MI	Doses used (μg/kg/min)	Independent technique
Afridi (1995)[93]	20	No	2.5–40	None
La Canna (1994)[92]	33	No	5, 10	None
Charney (1994)[91]	17	No	5, 10	^{201}Tl scintigraphy
Cigarroa (1993)[90]	49	No	5, 10, 15, 20	None
Smart (1993)[88]	51	Yes	4, 12, peak	None
Barilla (1991)[89]	21	Yes	5, 10	None
Pierard (1990)[54]	17	Yes	5, 10	PET

*): Reference No.
n=number of patients; MI=myocardial infarction; ^{201}Tl=thallium-201; PET=positron emission tomography

able myocardium by low-dose DE[89]. Thirteen of their patients who underwent CABG had a greater improvement in LV function over time compared with medically treated patients. This study was not randomized and importantly, the echocardiographic reading was not blinded. Despite the caveats, this report suggests that low-dose DE may be useful not only for identification of stunned myocardium (which recovers spontaneously), but also in detecting severely ischemic but viable tissue.

Investigation into the contractile response of chronically hibernating myocardium to dobutamine stimulation has been hampered by lack of a satisfactory animal model. However, Schulz *et al* were able to demonstrate augmentation of contractile response in ischemic myocardium with abnormal LV function in a short-term animal model of hibernation[94]. Conversely, McGillem *et al* found that doses of 10 μg/kg/min of dobutamine depressed regional function in the presence of a subcritical lesion causing more than 80% impairment of reactive hyperemia[95]. There is therefore a theoretical concern that even low doses of dobutamine may increase metabolic demand in chronically ischemic dysfunctional myocardium and mask a contractile response.

In addition, previous reports suggest that the pathophysiological responses to dobutamine are prominently linked to heart rate. For instance, Willerson *et al* demonstrated concomitant increases in heart rate and epicardial ST segment elevation in dogs infused with 20 μg/kg/min of dobutamine[96]. Other investigators have found a dose of 12 μg/kg/min to be associated with tachycardia and the likelihood of ischemic injury[97]. A recent report of paradoxical improvement in wall motion at 40 μg/kg/min dobutamine infusion during fixed electronically paced rhythm (which limits any increase in myocardial oxygen consumption) lends further credence to the importance of the heart rate response[98]. Because of these observations, most clinical studies examining myocardial hibernation have used low dobutamine infusion rates of 5 to 10 μg/kg/min . In theory, higher doses of dobtamine may enhance test sensitivity provided heart rate does not increase disproportionately. Conversely, the use of increasing doses of dobutamine in the presence of severely reduced coronary reserve may induce ischemia of hibernating segments and potentially reduce test sensitivity[92], particularly if a biphasic contractile response is not appreciated[93].

Despite these concerns, a number of studies suggest that DE may be of value in predicting functional recovery following CABG in patients with impaired cardiac function. Cigarroa *et al* found DE to effectively predict improvement in regional LV wall thickening following revascularization in 25 patients with EF<45% and no recent MI or symptoms of unstable angina[90]. Most of the patients felt not to have contractile reserve, however, had improved wall thickening scores following revascularization, albeit to a non-significant level. This may be related to the performance of follow-up echocardiography at a relatively early 4 weeks. While revascularization of chronically "hibernating" myocardium generally results in rapid functional improvement[10,14,99–102], delayed recovery up to 12 months has been reported[103]. It appears that recovery of function following revascularization is dependent not only on restoration of blood flow (which leads to early recovery of function) but also on the degree of stunning following reperfusion[103] and/or repair of functionally damaged viable myocytes. This latter phenomenon where myocytes

have critically reduced inorganic phosphate stores and hover between hibernation and cellular death has been termed "embalmment" by Bashour and Mason[104].

La Canna *et al* retrospectively studied 33 patients and no recent MI with depressed ventricular function (EF $<50\%$) and found DE to have a sensitivity and specificity for predicting recovery of function in akinetic myocardial segments of 87% and 82%, respectively[92]. The vast majority of these hibernating segments improved immediately following CABG, consistent with previous observations[10]. Equally impressive figures were obtained by Marzullo *et al* in a smaller study comparing DE and quantitative rest ^{201}Tl and rest ^{99m}Tc-MIBI scintigraphy in 14 patients with chronic LV dysfunction undergoing revascularization[77]. These investigators found low dose DE to be as sensitive and specific in detecting contractile reserve as delayed (16 hours) ^{201}Tl imaging. Afridi *et al* reported the sensitivity and specificity of DE for prediction of wall motion recovery after PTCA in patients with chronic ischemic LV dysfunction to be 74% and 73%, respectively[93]. In contrast to previous studies, these investigators used high doses (up to 40 μg/kg/min) of dobutamine and found a "biphasic" or worsening contractile response to be most indicative of segmental viability.

Others

Magnetic resonance imaging

Assessment of regional wall thickness in chronic ischemic heart disease using high definition MRI may be helpful in the evaluation of myocardial viability. It is likely that asynergic myocardium less than 6 mm thick represents irreversibly scarred or damaged tissue[105]. Baer *et al* found excellent concordance (96%) between segmental viability as graded by end-diastolic wall thickness using MRI and ^{99m}Tc-MIBI uptake on single photon emission computed tomography (SPECT)[106]. However, a recent study of 25 patients with ischemic LV dysfunction found many thinned, akinetic segments on spin-echo gated MRI to be metabolically active by PET[40]. In addition, there was an only weak correlation between FDG activity and end-diastolic wall thickness. It is unclear from this latter study, however, if any of the patients enrolled had recent infarction which potentially could account for the discrepant findings.

Imaging after nitroglycerin administration

The use of nitroglycerin (NTG) to evaluate myocardial viability dates back to the mid-seventies[107,108]. Bodenheimer *et al* found a good correlation between improved contractile function following NTG administration during ventriculography and histologic evidence of viability[108]. Whether NTG unmasks contractile reserve by opening up collateral channels is unclear. This method, however, did not achieve popularity because of the imaging technique involved *i.e.* contrast ventriculography. With the ability to directly visualize wall thickening non-invasively by two-dimensional echocardiography, the effect of NTG on asynergic myocardium can easily be examined. Indeed, Tei *et al* noted that up to 28% of akinetic segments and 6% of dykinetic regions exhibited improved wall motion after NTG[109]. More recently, He *et al* demonstrated that NTG administered immediately post-exercise during ^{201}Tl reinjection imaging enhanced the detection of viable myocardium; 26% of "fixed" segmental defects after standard 4-hour redistribution imaging were deemed reversible using the NTG/reinjection protocol[110].

WHICH DIAGNOSTIC TEST?

Studies investigating the utility of viability testing are subject to potential bias in that patients are likely to undergo revascularization only if clinically warranted or if they have had a positive test result (in either case viable myocardium is likely to be present). In the light of current knowledge, however, PET and rest-redistribution ^{201}Tl imaging appear to be comparable diagnostic standards. If ischemia is an important question, either exercise ^{201}Tl imaging (with reinjection if severe persistent defects are observed) or exercise ^{99m}Tc-MIBI scintigraphy may be more appropriate investigations[111]. DE is an attractive option as it directly assesses contractile state, in contrast to PET and ^{201}Tl scintigraphy which reflect myocardial perfusion and metabolic function but do not provide direct information on contractility. There are, however, theoretical concerns that DE may underestimate contractile reserve[95] as well as conflicting data on the utility of this procedure[112]. Indeed, some investigators believe that low-dose DE augments contractile function only of stunned and not hibernating myocardium[112,113]. Clearly, the role of DE in assessment of myocardial hibernation needs to be clarified.

Whether any one particular technique is adopted

depends largely on test accessibility as well as familiarity with the procedure. It is also important to recognize that different techniques may provide dissimilar but nonetheless relevant information. For instance, in a study of 21 patients with LV dysfunction and a mean ejection fraction of 35% undergoing CABG, DE more reliably predicted intraoperative functional improvement compared to rest-redistribution ^{201}Tl imaging while 8% of akinetic segments deemed viable by the latter technique did not exhibit early recovery but regained contractile function up to 12 months later[76]. This as alluded to earlier may be related to the phenomenon of cardiac "embalmment"[104].

In a report evaluating several measures of viability in 17 patients with severe resting wall motion abnormalities, Meza *et al* found DE to be inferior to ^{99m}Tc-MIBI SPECT for identifying viable myocardium[112]. Low-dose DE was similarly less sensitive than reinjection ^{201}Tl-SPECT in a study of 20 patients with chronic ischemic LV dysfunction; however, it was considerably more specific in predicting functional recovery[113]. Essentially similar findings were reported by Charney *et al* in a small study involving patients with chronic coronary artery disease[91]. On the other hand, Gerber *et al* found DE to be equally sensitive and a more accurate predictor of viability than exercise-redistribution-reinjection ^{201}Tl-SPECT[114]. These disparate results are no doubt in part related to the characteristics of the study population and methodologies employed. In general, although the sensitivity of DE for detection of segmental viability may be lower than radionuclide techniques, its focus on actual contractile function may result in equivalent or greater specificity[115].

FUTURE DIRECTIONS

Clinical role of viability testing

Given the current concern over escalating health care costs, it is imperative that new techniques for determining myocardial viability be assessed as to their utility and clinical relevance, not only to choose the most cost-effective diagnostic procedure but more importantly, to optimise the selection of patients most likely to benefit from revascularization. Prospective investigations systematically comparing multiple modalities to obviate comparisons across studies may be necessary to address this issue. It is also important to establish if viability testing provides information (additional to existing clinical and investigative data) which should alter clinical decision making. For instance, while it may be worthwhile pursuing the issue of viability in an asymptomatic patient with severe LV dysfunction and coronary artery disease, there appears little justification for doing so in a patient with limiting effort angina[116].

It appears intuitive but certainly not established practice to select patients for revascularization based on a prospective determination of myocardial viability. In a study by Eitzman *et al* examining the clinical outcome of patients with advanced coronary artery disease who underwent PET, it was noted that 39% of patients had viability data that was at variance with the clinical decision to offer or withhold revascularization[117]. Uncontrolled studies suggest that viability testing prior to CABG in patients initially referred for orthotopic heart transplantation contributes to an impressively low operative mortality and morbidity and good medium-term functional outcome[23,118]. Further clinical observations and possibly prospective trials[119] are necessary to determine if such an approach influences post-operative outcome.

The presence of a significant amount of viable myocardium may in itself constitute a risk factor for recurrent cardiac events. Di Carli *et al* followed 93 patients with ischemic cardiomyopathy for a mean interval of 14 months and found a survival advantage in patients with "mismatch" who had surgery instead of conservative treatment[120], findings consistent with previous observations that the outcome of patients with chronic coronary artery disease is dependent on the amount of LV myocardium at risk[121]. Tamaki *et al* found an increase in FDG uptake to be superior to clinical, angiographic and radionuclide variables in predicting a cardiac event in 84 patients with a prior MI followed for an average of 23 months[122]. In multivariate analyses, only FDG uptake and angio-graphic variables had independent prognostic value. If borne out, these data suggest that there may be merit to revascularization on the basis of a perfusion-metabolism "mismatch" (or corresponding indexes of myocellular integrity) and emphasize the need for reliable methods of routine determination of myocardial viability.

Myocardial contrast echocardiography

An exciting development on the horizon of viabil-

ity research is the potential role of myocardial contrast echocardiography (MCE). MCE visualizes the territory of a coronary artery following the intracoronary injection of microbubbles[123–126]. Ito *et al* demonstrated that in patients with anterior MI receiving either intracoronary thrombolysis or emergent PTCA, myocardial contrast perfusion rather than patency of the infarct-related artery predicted recovery of LV function at 1 month follow-up[127]. In a quarter of their patients, myocardial perfusion was absent despite reflow being achieved in the occluded vessel within 6 hours of symptom onset. While the mechanism of this "no reflow" phenomenon is unclear, loss of microvascular integrity with increased impedance to flow appears to be an important contributory factor[128–130]. The importance of microvascular integrity in determining myocellular viability following acute MI has since been confirmed by other investigators[131].

The role of MCE in identifying myocardial viability in chronic ischemic heart disease may reside in the determination of microvascular integrity either anterogradely or retrogradely via collateral channels. In this regard, MCE is superior to conventional angiography which demonstrates only primary epicardial collaterals[132]. The extent of contrast perfusion by MCE has been shown to directly correlate with improvement in regional LV function following angioplasty in patients with recent MI[48]. In chronically ischemic segments, the demonstration of microvascular collateral flow using MCE may, by extrapolation from post-MI studies, indicate tissue viability and hence, the likelihood of salvage following revascularization. In addition, the logistics of MCE are such that it can readily be performed in the catheterization laboratory following routine coronary angiography. This method of assessing viability potentially provides a simple solution to what is often an important clinical dilemma. In a prospective study of patients with severe LV systolic dysfunction by Meza *et al*, MCE was found to be superior to DE in identifying viable myocardium[112]. A number of studies are currently under way to further define the role of MCE in this setting.

CONCLUSIONS

Non-invasive assessment of myocardial viability remains a challenging problem. There is a need to identify a technique that is cost-effective, conveniently performed, and amenable to rapid interpretation. While PET and nuclear techniques currently represent the diagnostic state-of-the-art, there remains the promise of echocardiographic modalities which potentially satisfy many of the aforementioned prerequisites. In order for the clinical role of these tests to expand, future research should focus not only on their diagnostic power, but also their incremental value over conventional decision-making as well as their ability to predict cardiovascular outcome.

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