Myocardial viability in ischemic heart disease: new directions and perspectives

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Key words:
Dobutamine echocardiography; Left ventricular dysfunction; Myocardial viability; Prognosis.

In patients with ischemic heart disease detection of myocardial viability is of major clinical and prognostic importance and may significantly affect therapeutic decisions. Reversible left ventricular dysfunction may be due to different pathophysiological mechanisms, including myocardial hibernation and stunning, structural and ultrastructural myocardial changes and alterations in gene expression leading to myocardial cell dedifferentiation. Each of these mechanisms may have different importance related to the clinical history of the patient and severity and duration of left ventricular dysfunction and may significantly influence the extent and time course of functional recovery after myocardial revascularization. In the clinical arena detection of myocardial viability is currently based on the use of nuclear techniques, which show preserved tracer uptake and metabolism in viable myocardium and echocardiographic methods, which detect residual contractile reserve. Both techniques show a similar sensitivity in predicting functional recovery after revascularization, but dobutamine echocardiography has a higher specificity and therefore may be clinically more useful. Due to the limitations of current nuclear and echocardiographic methods in detecting myocardial viability, new developments are directed towards better quantification of viable myocardium and simultaneous assessment of myocardial metabolism, perfusion and function. Doppler tissue imaging, intravenous contrast echocardiography and ECG-gated SPECT with combined evaluation of metabolism and perfusion seem to be the most promising and cost-effective methods for a comprehensive assessment of myocardial viability. The major prognostic importance of myocardial viability in patients with severe left ventricular dysfunction is demonstrated by the fact that patients with a significant amount of viable myocardium have a marked survival benefit from revascularization and an improvement in left ventricular function and NYHA functional class compared with those without or only marginal viability. Thus, in patients with severe dysfunction preoperative quantification of viable myocardium is of utmost importance to identify patients who can benefit from revascularization. In patients with lesser amount of viable myocardium the possible beneficial effect of revascularization on survival, even in the absence of significant improvement in ventricular function, is yet to be demonstrated and should be assessed in future prospective clinical trials.

(Ital Heart J 2001; 2 (2): 93-99)

Received September 13, 2000; revision received November 30, 2000; accepted December 14, 2000.

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Over the past 20 years it has been clearly demonstrated that in patients with acute and chronic coronary artery disease (CAD) left ventricular (LV) dysfunction following myocardial necrosis is not necessarily an irreversible process. When viable myocardium is present in dysfunctional areas, partial or even complete recovery of regional and global LV function may occur spontaneously or after revascularization[1-5]. Therefore, in patients with ischemic heart disease and more so in those with depressed LV function, the detection of viable myocardium has become of great clinical importance, due to the major prognostic role and therapeutic implications of myocardial viability. The pathophysiology of reversible contractile dysfunction, the definition of the most accurate and cost-effective method for the identification of viable myocardium and the assessment of the prognostic impact of viability on major clinical endpoints, which will all be discussed in this review, are at present the main focus of clinical and experimental research.

Pathophysiology of contractile dysfunction

Viable myocardium traditionally encompasses two different pathophysiological conditions[6,7]: stunned myocardium is characterized by prolonged postischemic dysfunction despite restoration of adequate regional blood perfusion and by spontaneous recovery of function over time; hibernating myocardium is characterized by impaired contractile function due to a chronic and severe reduction in regional coronary blood supply and can recover only after coronary revascularization. Stunning has been recognized as the most important mechanism of reversible dysfunction after reperfused acute myocardial infarction or prolonged episodes of unstable angina[3,4,6]. On the other hand, recent studies have challenged the concept popularized by Rahimtoola[8] that in patients with chronic CAD, reversible LV dysfunction was due to myocardial hibernation, viewed as a down-regulation of myocardial contractility in response to chronic regional hypoperfusion[9-16]. In patients with severe LV dysfunction, measurement of regional blood flow by positron emission tomography (PET) has demonstrated that, compared to normal segments, the majority of dysfunctional areas showing contractile recovery after revascularization has similar or only mildly reduced baseline regional blood flow and that in basal conditions only a small proportion of segments (15%) has a severely reduced myocardial perfusion thus meeting the criteria for hibernation[9-14]. However, it should be recognized that current PET technology does not allow detection of alterations in transmural blood flow distribution. Hence, in these patients, despite normal transmural flow, a reduction in subendocardial blood flow cannot be ruled out as a mechanism of regional impairment in contractility. Further insight into the pathophysiology of chronic contractile dysfunction has been provided by other studies showing that, compared with segments with normal contractile function, dysfunctional segments are characterized by a more severe reduction in coronary vasodilator reserve and that the severity of wall motion abnormalities correlates directly with the degree of impairment of coronary vasodilator reserve[11,14-16]. Thus, it has been hypothesized that contractile dysfunction may be due to repetitive episodes of myocardial ischemia, either induced by increased myocardial demand or by a primary reduction in regional coronary blood supply, leading to prolonged postischemic stunning[11,14-16]. The hypothesis of repetitive stunning as a mechanism of chronic LV dysfunction is supported by other evidence. An experimental study by Shen and Vatner[17] indicates that the onset of chronic hypocontractility in regions supplied by a critically stenosed coronary artery is preceded by repeated episodes of acute ischemic dysfunction triggered by an increase in myocardial oxygen demand. Clinical studies[18-20] demonstrate rapid recovery of contractile function after successful coronary revascularization. However, in patients with chronic CAD, the extent and time course of contractile recovery after revascularization are variable and recovery may require up to 6 months or may be incomplete[21-23]. The degree of recovery is inversely correlated with the extent of structural and ultrastructural myocardial changes. Patients with incomplete or no recovery after revascularization show a greater extent of myocyte loss and of transmural and subendocardial fibrosis, an increase in glycogen myocardial content and a reduction and disorganization of contractile and cytoskeletal proteins[15,16,24-29]. Moreover, structural proteins such as α-smooth muscle actin, cardiotenin and titin, that are normally present only in fetal myocardium, are expressed in the hibernating myocardium, leading to the hypothesis that repetitive ischemia-reperfusion and/or chronic hypoperfusion may interfere with myocardial gene expression and cause myocardial cell dedifferentiation[30,31]. Recently, it has been demonstrated that in transgenic mice, truncation of the thin filament protein troponin I reproduces the cellular pathophysiology of stunned myocardium leading to cardiac dilation and failure and that in humans myocardial ischemia and reperfusion can lead to similar structural changes in this protein[32]; therefore, it has been hypothesized that post-translational alterations in proteins involved in excitation-contraction coupling can play a major role in the development of post-ischemic LV dysfunction[32]. Besides, myocyte apoptosis has been documented both in experimental models of short- and medium-term hibernation[33] and in patients with chronic LV dysfunction[34] and may be another mechanism responsible for LV contractile dysfunction. Thus, there is growing evidence that in patients with CAD the pathophysiology of chronic LV dysfunction is complex and encompasses several mechanisms including repetitive stunning, chronic hypoperfusion and alterations in myocardial structure and gene expression. The importance of each of these mechanisms is variable depending on the clinical history of the patient, the severity and duration of LV dysfunction and the extent and type of coronary lesions. Further experimental and clinical research is therefore required to elucidate the pathophysiology of chronic LV dysfunction through the development of experimental models of long-term hibernation that more closely mimic the clinical situation. More precise assessment of the type, time course and reversibility of the metabolic, structural and ultrastructural changes associated with chronic LV dysfunction is also necessary.

Detection of myocardial viability

In the clinical arena both nuclear techniques with perfusion and metabolic imaging[35-41] as well as echocardiographic methods[3,42-44] have been widely used for the detection of myocardial viability. The mechanisms by which these techniques identify viable myocardium reflect the different characteristics of viable myocytes: nuclear methods including thallium-201 or 99m-technetium (Tc) sestamibi SPECT and fluorodeoxyglucose PET demonstrate preserved tracer uptake and metabolism in viable cells while low-dose dobutamine stress echocardiography (DSE) can detect the residual contractile reserve in basally asynergic but viable regions. Both the cellular metabolic activity and the contractile response in dysfunctional areas are directly correlated with the amount of viable myocytes[31,45-47]; however, a contractile response to DSE requires a greater amount of viable myocardium and a higher degree of myocyte functional integrity than do preserved membrane integrity and metabolic activity. This is shown by the finding that PET and thallium-201 SPECT detect viability in 60 to 80% of the areas containing 25 to 50% of viable myocytes, while a positive response to inotropic stimulation is found in only 25% of these areas[47]. These differences may account for the different accuracy of the echocardiographic and nuclear techniques in predicting functional recovery after coronary revascularization: PET and thallium-201 SPECT with rest-redistribution or reinjection protocols have shown similar or slightly better sensitivity (ranging from 80 to 90%) than low-dose DSE in predicting recovery; however, the radionuclide techniques overestimate the probability of functional improvement after revascularization and therefore have a lower specificity (ranging from 54 to 73%) and overall accuracy than DSE[27,44,48-52]. Despite its clinical usefulness, DSE is not the ideal method for detecting myocardial viability due to several limitations: first, it is a subjective and qualitative or at best semiquantitative technique; second, in the presence of critical flow-limiting coronary stenosis the contractile response to the drug may be blunted or abolished even in the presence of a substantial amount of viable myocardium[53,54]; finally, since the contractile response is mainly dependent on the integrity of the subendocardial layers, in patients with an infarction involving 20 to 50% of the wall thickness, the presence of viable myocardium in the subepicardial layers can be significantly underestimated or even missed by DSE[54]. Recently Lombardo et al.[55] have shown that after revascularization the contractile response to DSE developed in > 30% of dysfunctional zones showing no previous contractile reserve and no baseline recovery after revascularization; this finding suggests that underestimation of epicardial viability by DSE may be clinically relevant and that by preventing myocardial ischemia, revascularization may also improve the regional contractile reserve in patients with no baseline functional recovery.

Another critical issue in determining the best method for detecting myocardial viability is the lack of an accepted clinical gold standard. In most studies recovery of regional or global LV function after revascularization has been used as a gold standard to define the presence of myocardial viability. However, this may be clinically inaccurate as it may underestimate the actual amount of viable myocardium and the benefit of revascularization in terms of improved symptoms, exercise capacity and survival. This hypothesis is supported by a recent study showing that in patients with severe LV dysfunction lack of improvement of global LV function after coronary revascularization is not associated with a poorer prognosis compared to patients with improved LV function[56]. Moreover, functional recovery after revascularization is often gradual and may take several months[57,58] and is inversely correlated with the impairment of LV function and with the structural and ultrastructural changes of myocardial cells[28,29]; thus, the diagnostic accuracy of any method employed for the prediction of recovery after revascularization is critically influenced by the timing of follow-up and the severity of LV dysfunction[57].

Alternative methods for evaluating myocardial viability include stress-induced ST-segment elevation[59-64], baseline wall thickness evaluation[65,66] and post-extrasystolic potentiation[67]. Several studies have shown that in patients with recent myocardial infarction dobutamine- or exercise-induced ST-segment elevation in the infarct area is frequently associated with a biphasic response indicative of a viable jeopardized myocardium and that it has a high specificity and an acceptable sensitivity for predicting functional recovery[59-62]; however, other authors did not find a significant association between DSE-induced ST-segment elevation and the presence of a viable ischemic myocardium[63,64]. Thus, the significance of ST-segment elevation during stress is still controversial and may vary in relation to the extent of infarction. For this reason, ST-segment elevation during exercise or DSE cannot be considered a first-line method for detecting myocardial viability. Recently myocardial end-diastolic wall thickness measured by two-dimensional echocardiography has been evaluated as a marker of myocardial viability in patients with chronic CAD and compared to DSE and thallium scintigraphy[65,66]. An end-diastolic wall thickness > 0.6 cm showed a high sensitivity (94%) and negative predictive value (93%) for predicting functional recovery, with an overall diagnostic accuracy similar to that of thallium scintigraphy[66]. However, the specificity of the method is low (48%) and it should be associated with DSE in order to improve its overall diagnostic accuracy in predicting recovery[66]; moreover, measurement of the end-diastolic wall thickness is neither feasible nor accurate in all patients and may be subject to a significant interobserver variability. In the late 1970s post-extrasystolic potentiation has been proposed to identify myocardial viability[67], but its clinical applicability was limited mainly because of the need of cardiac catheterization.

The new developments both in echocardiographic and nuclear techniques are directed towards better quantification of viable myocardium and simultaneous assessment of myocardial cell integrity, regional perfusion and function in dysfunctional but potentially viable regions. Pulsed-wave Doppler tissue imaging can provide quantitative evaluation of regional myocardial contractility[68,69] and has been shown to have a higher sensitivity for detecting viable myocardium than DSE[70]. In patients with acute myocardial infarction or chronic LV dysfunction, myocardial contrast echocardiography using intracoronary contrast agents can assess microvascular integrity and preserved myocardial perfusion. These are markers of cell viability and predict subsequent functional recovery with a similar degree of sensitivity but lower specificity than DSE[71-74]. However, its invasive character limits its clinical application. Recent technological advances allow the assessment of myocardial perfusion by echocardiography using intravenous contrast agents[75,76]. Thus, data on microvascular integrity, regional perfusion and contractile reserve can be non-invasively acquired at the same time to better define the presence and extent of viability. Similarly, recent studies show that in patients with LV dysfunction ECG-gated SPECT using 99m-Tc-tetrofosmin or Tc-sestamibi performed at rest and during low-dose dobutamine infusion can simultaneously evaluate both regional and global perfusion and motion. These techniques significantly improve the specificity and overall accuracy in predicting functional recovery after revascularization compared to perfusion studies alone[77-80]. SPECT performed using fatty acid analogues, such as beta-methyl-iodophenyl-pentadecanoic acid (BMIPP) can be used to monitor myocardial metabolic activity at rest and during myocardial ischemia[81,82]. Combined with ECG-gated tetrofosmin or sestamibi SPECT during dobutamine infusion, BMIPP SPECT may permit assessment of the regional contractile response to dobutamine and identify jeopardized but viable myocardium on the basis of a mismatch between metabolism and perfusion; preliminary results suggest that this combined approach can be a useful tool for the detection of viable myocardium and for the accurate prediction of recovery[81,82].

Prognostic significance and therapeutic implications of myocardial viability

Myocardial viability appears to have a different clinical and prognostic significance in patients with normal or only mildly depressed LV function compared to those with severe LV dysfunction (LV ejection fraction < 35%). In the former, myocardial ischemia remains the most important prognostic determinant and the assessment of myocardial viability is of minor clinical importance[83]. In patients with impaired LV function, myocardial viability has a major impact on prognosis and on the effectiveness of myocardial revascularization. This is confirmed by the finding that, compared to those with viability who are treated with medical therapy or to those without viability, patients with a significant amount of viable myocardium at PET or DSE have a marked survival benefit from revascularization[84-89]. The critical importance of quantifying myocardial viability in these patients is emphasized by the finding that only patients with at least 25% of viable LV segments at DSE have a significant improvement in global LV function, NYHA functional class and exercise capacity after revascularization[87-89]. Thus, given the potential benefit but also the increased surgical risk of revascularization in these patients, the preoperative assessment of the amount of viable myocardium is of utmost importance for the identification of those patients who may benefit both prognostically as well as functionally from revascularization. Although the prevalence and extent of myocardial viability has not been assessed in large populations of patients with LV dysfunction, recent data suggest that 50% of patients with severely impaired LV function have viable myocardium, but the extent of viability is functionally significant in less than 30% of the overall population[90]. According to these figures only about half the patients with myocardial viability can be expected to derive significant benefit from myocardial revascularization.

An important question that remains to be answered is whether patients with a smaller amount of viable myocardium can also benefit from myocardial revascularization. Although the beneficial effects of revascularization are less pronounced, recent studies suggest that patients with a lower viability index who do not show a significant improvement in global LV function after revascularization also have a better survival rate than that reported for similar patients treated medically. The symptomatic improvement is similar to that of patients with postoperative improvement in LV function[56,91,92]. The beneficial effects of revascularization may be due to several mechanisms, including prevention of myocardial infarction, protection from fatal arrhythmias triggered by acute myocardial ischemia and limitation of further LV dilation and remodeling that in turn lead to worsening of heart failure. Because only limited data on the effects of coronary bypass surgery in this subgroup of patients are available, at present the indication to myocardial revascularization should be individualized and take into account not only the presence of myocardial viability, but also other important clinical variables such as the presence and severity of angina, the duration of heart failure, the severity and extent of coronary artery lesions, the suitability of target vessels for revascularization and comorbidity. Prospective randomized studies comparing optimal medical therapy with myocardial revascularization in this subset of patients would be useful to assess whether myocardial revascularization improves survival and functional status and whether it may be a valuable alternative to cardiac transplantation.

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