Myocardial Viability in Patients with Coronary Artery Disease: New Directions and Prospects

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Key words:
Myocardial viability, nuclear techniques, stress echocardiography, prognosis.

Manuscript received:
June 26, 2001;
Accepted:
February 5, 2003.

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Over the last 20 years, it has been proven that left ventricular dysfunction after myocardial infarction in patients with acute or chronic coronary artery disease (CAD) is not necessarily an irreversible process. It appears that if there are areas within the dysfunctional segments of the myocardium which display some viability, both the regional and the global performance of the left ventricle (LV) can be restored either partially or totally, automatically or following revascularization[1-5]. Consequently, in patients with ischaemic cardiomyopathy, and particularly in those who display LV dysfunction, the identification of viability is of great clinical importance and this is due to the significant prognostic value and the therapeutic benefits in patients with viable myocardium.

In this review, an attempt is made to analyze the pathophysiology of reversible systolic dysfunction, to determine the most reliable method of identifying viable myocardium and to evaluate the prognostic significance of viability, with respect to clinical endpoints. All of these issues comprise the main aim of both current clinical and experimental research.

Pathophysiology of systolic dysfunction

Traditionally, myocardial viability consists of two conditions[6,7]:

1. Stunned myocardium, which is characterized by prolonged, post-ischaemic dysfunction, despite satisfactory reinstatement of regional blood flow, and by the automatic recovery of LV function with the passage of time.

2. Hibernating myocardium, which is characterized by an impairment of systolic function, which is due to chronic, severe reduction in coronary blood flow and which is only reversed after revascularisation.

Myocardial stunning is mainly noted in patients with a thrombolysed myocardial infarction or with prolonged episodes of unstable angina pectoris[3,4,6]. On the other hand, recent studies have cast some doubt on the theory first described by Rahimtoola[8], which states that in patients with chronic CAD, the reversible LV dysfunction is due to hibernating myocardium, which was explained as an adjustment, via down regulation, of myocardial contractility, as a result of a chronic reduction in regional blood flow[9-16]. In patients with severe LV dysfunction, determination of regional blood flow by positron emission tomography (PET) proved that in comparison to normal segments, most of the areas which were dysfunctional but regained their systolic ability after revascularisation had similar or only slightly reduced initial blood flow and at rest only a small proportion of these segments (15%) had severely reduced myocardial blood flow so as to warrant, according to the given criteria, being described as hibernating myocardium[9-14]. Nevertheless, it must be noted that the present PET technology does not allow the identification of the distribution of

areas of altered transmural myocardial blood flow. Subsequently, in these patients, despite the presence of normal transmural blood flow, a reduction in subendocardial blood flow cannot be excluded as a possible mechanism for regional systolic dysfunction. Moreover, various other studies shed light on the pathophysiology of chronic, systolic LV dysfunction, indicating that in comparison with segments with normal systolic function, the dysfunctional segments are characterized by a marked reduction in coronary dilatory reserve, which is directly related to severe disturbance of regional wall motion[11,14-16]. Consequently, it was assumed that systolic dysfunction may be a result of repeated ischaemic episodes, which are either triggered by an increase in demand or by a primary reduction in the regional oxygen supply, resulting in prolonged, post-ischaemic stunning[11,14-16]. The theory of repetitive insults as a mechanism of chronic LV dysfunction is confirmed by other studies. One such experimental study by Shen et al[17] suggests that the appearance of chronic systolic dysfunction in regions supplied by a critically stenosed coronary vessel is a result of repeated episodes of acute ischaemic dysfunction, which are caused by an increase in myocardial oxygen demand. Other clinical studies[18-20] prove that there is rapid recovery of systolic function after successful revascularisation. Despite this, in patients with chronic CAD, the extent and duration of recovery of systolic function after revascularisation differs significantly from patient to patient, while complete recovery may be attained after approximately 6 months or may even remain incomplete[21-23]. The degree of recovery is inversely proportional to the extent of structural alterations to which the myocardium is subjected. Thus, patients with partial or no recovery after revascularisation have more extensive myocyte death and greater associated transmural and subendocardial fibrosis and they have increased myocardial glycogen content, as well as reduced and disorganized systolic and cytoskeletal proteins[15,16,24-29]. Furthermore, structural proteins such as α-smooth muscle actin, cardiotenin and tinin, which under normal circumstances are only present in embryonic myocardium and lead to the hypothesis that repetitive episodes of ischaemia - reperfusion and/or chronic reduction in myocardial blood flow can cause a disturbance in the expression of myocardial genes and can lead to the final de-differentiation of myocytes[30,31]. Recently, studies in transgenic mice showed that the fragmentation of the troponin I light chain gene mimics the cellular pathophysiology of stunned myocardium phenotypically, leading to LV dilatation and failure. In patients with myocardial ischaemia who have undergone revascularisation, this may lead to similar structural changes of this protein[32]. It was thus proposed that alterations of proteins, which are part of the myocardial excitation - contraction coupling mechanism, due to changes effected on the genetic code, may play an important role in the development of post-ischaemic LV dysfunction[32]. The abovementioned process has been implicated as an additional mechanism, apart from myocyte apoptosis, responsible for LV dysfunction, and has been proven both experimentally, in models of hibernating myocardium of short and intermediate duration[33], and in patients with chronic LV dysfunction[34].

We can subsequently surmise that the pathophysiology of chronic LV dysfunction in patients with CAD is complex and consists of multiple mechanisms, including repeated episodes of myocardial stunning, chronic limitation of blood flow and changes in myocardial structure and gene expression. The relative significance of each of these mechanisms is dependent on each patient's history, the severity and duration of LV dysfunction and the extent and morphology of the coronary artery lesions. It is a fact, though, that there is need for further experimental and clinical research, in order to clarify the pathophysiology of LV dysfunction, particularly regarding the development of experimental models of chronically hibernating myocardium, an entity which would more closely resemble the true clinical process. It is also necessary to more accurately be able to determine the type, duration and reversibility of the metabolic and structural changes accompanying LV dysfunction.

Methods of detecting myocardial viability

In clinical practice, both radioisotopic techniques of imaging myocardial blood flow and metabolism[35-41] and echocardiographic techniques[3,42-44] are widely used to estimate myocardial viability. The mechanism through which these techniques detect viability reflect the varying characteristics of viable myocytes. Thus, the radioisotopic techniques which include thallium-201, technetium compounds and 18-fluorodeoxyglucose PET indicate the conservation of radioisotopic uptake and metabolism in viable cells, while echocardiography using small

doses of dobutamine (DSE) can detect residual inotropic reserve in initially asynergic yet viable segments. Both cellular metabolic activity and systolic response in dysfunctional regions of the LV are directly related to the proportion of viable myocytes[31,45-47]. On limitation is that in order for DSE to detect an inotropic response, a larger amount of viable myocardium and a greater functional integrity are required, compared to the detection of the conservation of cellular membrane integrity and metabolic activity. This is confirmed by the finding that PET and SPECT using thallium-201 detect 60-80% of the areas which contain 25-50% viable myocytes, as confirmed by subsequent histopathological examination of these regions, whereas a positive inotropic response was found in only 25% of these areas[47]. These differences have to do with the different diagnostic accuracy of echocardiographic and radioisotopic techniques in the prediction of functional recovery after revascularisation. Therefore, PET and thallium-201 SPECT using either the rest-redistribution or reinjection protocols had similar or slightly better sensitivity (80-90%) compared to DSE, in predicting functional recovery. Conversely, radioisotopic techniques overestimate the probability of functional recovery after revascularisation and consequently have lower specificity (54-73%) and overall precision compared to DSE[27,44,48-52]. Despite its clinical usefulness, DSE is not the ideal method for detecting myocardial viability and this is due to various limitations:

1. It is a subjective evaluation which is qualitative or in the best of situations only semi-quantitative in nature.

2. In the presence of haemodynamically critical stenoses the systolic response to dobutamine may be severely impaired or even absent, even in the presence of a significant amount of viable myocardium[53,54].

3. Finally, since the systolic response is mainly dependent on subendocardial integrity, in patients with a myocardial infarction which has affected 20-50% of myocardial thickness, the presence of viable myocardium in the subepicardial layer may be significantly underestimated or even not detected[54].

Recently, Lombardo et al[55] showed that the systolic response to DSE after revascularisation developed in >30% of dysfunctional segments which had neither displayed previous inotropic reserve, nor had shown any recovery at rest after revascularisation. The above finding indicates that the underestimation of epicardial viability by DSE may be clinically significant and that revascularisation may also improve segmental systolic reserve in patients who had no functional recovery at rest, by preventing further myocardial ischaemia.

Another important parameter, which determines the best method for detecting myocardial viability is the absence of a clinically accepted gold standard. In many of the studies performed, regional or global functional recovery of the LV was used as a gold standard for determining the presence of viable myocardium. Despite this, though, it might not be clinically dependable, because it may underestimate the actual quantity of viable myocardium and the beneficial effects of revascularisation with regards to symptomatic improvement, exercise tolerance and overall survival. This hypothesis is based on a recent study, which indicates that in patients with severe LV dysfunction, the failure of the overall LV function to improve after revascularisation is not related to a poorer prognosis compared to patients who displayed improvement of LV function[56]. Moreover, functional recovery after revascularisation is often progressive and may occur over several months[57,58] and this is inversely related to LV dysfunction and to the structural changes, which have resulted in the myocytes (28,29). Subsequently, the diagnostic accuracy of each method used in the prediction of post-revascularisation recovery is significantly affected by the duration of patient follow-up and by the severity of LV dysfunction[57].

Other alternative methods of estimating myocardial viability are ST segment depression at stress testing[59-64], the estimation of myocardial systolic thickening at rest[65,66] and after extrasystolic potentiation. Some studies showed that in patients with recent myocardial infarction ST segment elevation in the infarction related areas at stress testing or after dobutamine administration at DSE is often associated with a biphasic response (improvement at low doses and deterioration at high doses), which is indicative of the presence of myocardial viability. The abovementioned finding has high specificity and acceptable sensitivity for predicting LV functional recovery[59-62]. Other authors, though, have not confirmed the relationship between ST segment elevation during DSE and the presence of viable myocardium[63,64] and consequently this cannot be considered as a method of first choice for detecting viability. Recently, end-diastolic myocardial thickness measured by 2-dimensional echocardiography in patients with chronic CAD was evaluated as an indicator of the presence of myocardial viability and

was compared to DSE and to thallium-201 scintigraphy[65,66]. An end-diastolic thickness of greater than 0,6cm had high sensitivity (94%) and negative predictive value (93%) for predicting functional recovery, with an overall diagnostic accuracy similar to that of scintigraphy[66]. The specificity of this method, though, is low (48%) and consequently it should be accompanied by DSE with an aim to improve the overall diagnostic accuracy in predicting LV functional recovery[66]. On the other hand, the measurement of LV end-diastolic thickness is neither easy nor precise in all patients and may be subject to significant inter-observer variability. At the end of 1970 post-extrasystolic potentiation was proposed as a means of detecting viable myocardium[67], but its clinical application was limited, mainly because it required cardiac catheterization. New advances in both echocardiographic and radioisotopic techniques are directed towards the improved quantification of viable myocardium and the concurrent estimation of myocyte integrity, regional blood flow and function of dysfunctional but potentially viable areas of myocardium. Doppler tissue imaging may significantly aid in the quantitative estimation of regional contractility[68,69] and has been shown to provide greater sensitivity in the detection of viable myocardium, compared to DSE[70]. In patients with acute myocardial infarction or chronic LV dysfunction, contrast echocardiography using intracoronary contrast media can evaluate microvascular integrity and the preservation or lack thereof of myocardial blood flow. These are indicators of cellular viability and they predict functional recovery with a similar sensitivity but lower specificity to that of DSE[71-74]. The interventional character of this procedure, though, limits its application in clinical practice. On the other hand, recent technological advances allow the evaluation of myocardial blood flow using intravenous contrast media[75,76], an event which allows a non invasive approach to gathering information regarding both microvascular integrity, segmental blood flow and inotropic reserve, which results in an improved determination of the presence and extent of viability.

In the same way, recent studies showed that in patients with LV dysfunction, gated SPECT with tetrofosmin or with MIBI at rest or in combination with the administration of small doses of dobutamine can simultaneously evaluate the regional and the overall blood flow and contractility of the LV. These techniques have substantially improved both the specificity and the overall reliability in predicting functional recovery after revascularisation, in relation to perfusion studies[77-80]. On the other hand, fatty acid analogues, such as β-methyl-iodophenyl-pentadecanoic acid (BMIPP), combined with SPECT, may be used to observe myocardial metabolic activity at rest and during ischaemia[81,82]. Thus, gated SPECT with tetrofosmin or sestamibi, after dobutamine administration, combined with BMIPP SPECT, may facilitate the evaluation of regional systolic response to dobutamine and may detect jeopardized but viable myocardium, based on metabolic and blood flow mismatch. Preliminary results demonstrate that this combined method may be a successful tool for the detection of viable myocardium and for the reliable prediction of recovery after revascularisation[81,82].

Technological developments in the diagnostic techniques do not end at this point. The introduction of Magnetic Resonance Imaging (MRI) in cardiology promises much in the discovery of viable myocardium, as far as acutely ischemic areas and hibernating myocardium are concerned. Moreover, MRI can evaluate inotropic reserve, like echocardiography. On the other hand the use of contrast agents provides us with the possibility of characterizing the ischemic myocardial damage, including the ability of distinguishing viable from non-viable areas. So, in a recent study Klein et al[83] showed that, in 31 patients with ischemic heart failure (EF=28+/-9%), the sensitivity and specificity of MRI in detecting patients and segments with perfusion defects in which PET had matched flow/metabolism pattern was higher than 85%. Also a good correlation was found (r=0.91) in grading the severity of perfusion defects for PET and MRI. Moreover, quantitative evaluation of infarct area with MRI showed a good relationship to that obtained with PET (r=0.89).

The prognostic significance of myocardial viability and its implication in patients' management

Myocardial viability appears to have different clinical and prognostic significance in patients with normal or mildly impaired LV function from those who have severe LV dysfunction (ejection fraction <35%). In the former group, residual ischaemia remains the most important prognostic indicator, while the evaluation of myocardial viability is of lesser clinical importance[84]. Conversely, in patients with severe LV dysfunction, the presence of myo-

cardial viability has the greatest effect on prognosis and on the effectiveness of myocardial revascularisation. This is also confirmed by the finding that when comparing patients, who had viable myocardium and were managed conservatively, to patients with no viability, those who had a significant amount of viable myocardium, as seen on PET or DSE, had substantially improved survival rates after revascularisation[85-90]. Moreover, Allman et al.[91] performed a meta-analysis of 24 viability studies (3088 patients), from a MEDLINE database, which reported patient survival using thallium perfusion imaging, F-18 fluorodeoxyglucose metabolic imaging or dobutamine echocardiography. They found that in patients with viability, revascularization was associated with 79.6% reduction in annual mortality (16% vs 3.2%, $x^2=147$, $p<0.0001$) compared with medical treatment. Conversely, patients without viability had intermediate mortality, tending towards higher rates with revascularization versus medical therapy (7.7% vs 6.2%, p=NS). Patients with viability showed a direct relationship between severity of LV dysfunction and magnitude of benefit with revascularization ($p<0.001$). Moreover, there was no measurable performance difference in predicting revascularization benefit among the three investigatory techniques. The significance of quantifying myocardial viability in these patients is strongly supported by the finding that only patients who showed viability in at least 25% of LV segments on DSE had a significant improvement in overall performance, NYHA functional class and exercise tolerance, after revascularisation[88-90]. Thus, when taking into account the potential benefit and the surgical risks of revascularisation in these patients, pre-operative evaluation of the quantity of viable myocardium are of paramount importance, in order to identify the patients who will benefit in terms of both prognosis and functional recovery after surgical revascularisation. Since the consequences and the extent of viability have not been evaluated in a large population of patients with LV dysfunction, recent findings indicate that 50% of subjects with severe LV dysfunction have viable myocardium, but the extent of viability which is functionally significant is seen in less than 30% of the total population[92]. Therefore, according to the aforementioned findings, we can expect a significant benefit from surgical revascularisation in only half of all patients with myocardial viability.

Another important question which remains to be answered is when patients who have small amounts of viable myocardium may also benefit from revascularisation. Given that the benefits from revascularisation in this group are less evident, recent studies suggest that patients with a low index of viability, who did not display significant improvement of their LV function after revascularisation, may have better survival rates compared to those who were managed conservatively.

Symptomatic improvement follows a similar course as the post-operative improvement of LV function after revascularisation[56,93,94]. The benefits of revascularisation are due to various mechanisms, which include prevention of a new myocardial infarction, protection from fatal arrhythmias, which are probably caused by acute ischaemia, and limitation of LV dilatation and remodeling, which lead to worsening of cardiac failure. Since there is limited data on the effects of coronary artery bypass grafting on this subset of patients, the present indications for surgical revascularisation should be individualized, taking into account not only the presence of myocardial viability, but also other important clinical parameters, such as the presence and the severity of angina pectoris, the duration of LV dysfunction, the severity and the extent of coronary lesions, the existence of suitable target vessels for revascularisation and the presence of other medical conditions which may affect morbidity. From the above, it evident that further prospective and randomized trials are useful in this subgroup of patients, in order to compare optimal conservative therapy to surgical revascularisation, so as to evaluate when revascularisation will improve survival and functional recovery and when it may be a good alternative to heart transplantation.

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