

Clinical Decision Making Based on Cardiac Diagnostic Imaging Techniques (VI)

Assessment of Myocardial Viability in Patients Before Revascularization

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Information on myocardial viability can be useful to decide when coronary artery revascularization is indicated for patients with acute myocardial infarction (AMI) and left regional or global ventricular dysfunction. Difficulties in assessing viability arise because the same part of the ventricular wall can have a mixture of necrotic tissue and viable myocardium. Diagnostic markers of myocardial viability are: the preservation of wall thickness, the presence of contractility reserve, the presence of blood perfusion reserve, integrity of the wall cells, and preservation of cellular metabolism. Echocardiography and thallium or technetium imaging are methods currently used to assess myocardial viability because of their availability and relatively low cost. Although positron emission tomography (PET) has been considered the gold standard, its unavailability may limit its clinical use. Recent publications have demonstrated the accuracy of cardiac magnetic resonance imaging (cardiac MRI) in assessing myocardial viability, together with noninvasive procedures to study the markers of viability noted above. Late contrast enhancement with gadolinium is the most accurate and simplest method.

The late open artery hypothesis recommends, on the basis of scant evidence, systematic revascularization of the culprit artery. Although no large randomized studies focused on prognosis are available yet, several small studies provide sufficient evidence of functional recovery of viable myocardium after coronary artery revascularization of the culprit artery in patients with global or regional ventricular dysfunction. The assessment of myocardial viability to decide whether culprit artery revascularization is indicated is a strategy currently based on more evidence than the more indiscriminate recommendations based on the late open artery hypothesis.

Key words: *Myocardial viability. Myocardial infarction. Magnetic resonance. Echocardiography. Thallium. Technetium. Positron emission tomography.*

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Valoración de la viabilidad miocárdica en pacientes prerrevascularización

La viabilidad miocárdica es una información disponible que puede utilizarse para indicar la revascularización coronaria en pacientes con infarto agudo de miocardio (IAM) y disfunción segmentaria o global. Las dificultades para determinar la viabilidad vienen dadas por la mezcla de tejido necrótico y viable en el mismo segmento de la pared miocárdica. Los marcadores diagnósticos de viabilidad miocárdica son la conservación del espesor de pared, la reserva contráctil, la reserva de perfusión sanguínea, la integridad de la pared celular y la conservación de su metabolismo. La ecocardiografía, el talio y el tecnecio son los métodos utilizados hasta ahora para estudiar la viabilidad miocárdica, en parte por su disponibilidad y su bajo coste relativo. Aunque la tomografía por emisión de positrones (PET) se ha considerado el método de referencia, su escasa disponibilidad podría ser la razón de su poca utilización. Publicaciones recientes han demostrado la alta precisión de la cardi resonancia magnética para detectar viabilidad miocárdica mediante procedimientos que estudian todos los marcadores anteriormente descritos. El método de cardi resonancia del realce tardío de gadolinio es el más preciso y simple de realizar.

Según la hipótesis de la arteria abierta tardía se recomienda, con escasa evidencia, la revascularización sistemática de la arteria relacionada con el infarto. Aunque todavía no se dispone de resultados de grandes estudios aleatorios que analicen el pronóstico, numerosos pequeños estudios han demostrado suficiente evidencia de la recuperación funcional del miocardio viable tras revascularización de la arteria relacionada con el infarto en pacientes con disfunción ventricular segmentaria o global. La determinación de la viabilidad miocárdica para decidir la revascularización de la arteria relacionada con el infarto en la actualidad es una opción respaldada por más pruebas que la recomendación de revascularización sistemática que se desprende de la hipótesis de la arteria abierta tardía.

Palabras clave: *Viabilidad miocárdica. Infarto de miocardio. Resonancia magnética. Ecocardiografía. Talio. Tecnecio. PET.*

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INTRODUCTION

The first descriptions of what would today be recognized as «viable myocardium» appeared in the 1970s, when it was observed that ventricular dysfunction reverted after revascularization in some patients with antecedents of acute myocardial infarction (AMI).¹ The concept of viability is the opposite of that of necrosis, which implies an irreversible alteration in contractility.² In patients with severe left ventricular dysfunction of ischemic origin, revascularization leads to improvements in ventricular function,³ survival,⁴⁻⁸ and prognosis.⁹ Such improvements may be due to the presence of myocardial viability.

The aim of revascularizing the infarct-related coronary artery (IRCA) is to restore interrupted or reduced blood flow, as well as to achieve some degree of functional recovery, avoid ventricular remodeling, and improve prognosis. From the clinical perspective, viable myocardium can be defined as myocardium in which contractile function is expected to improve, or in which remodeling can be avoided, once blood flow has been restored.

Simple diagnostic methods such as the electrocardiogram, resting echocardiography, and ventriculography are available to detect myocardial necrosis. Although such methods are not helpful in detecting myocardial viability, even without resorting to specific diagnostic techniques, revascularization is known to improve survival in 50% of patients with severe left ventricular dysfunction of ischemic origin.¹⁰ Such improvements are due to the presence of dysfunctioning, but viable myocardium.

Assessing myocardial viability poses two difficulties. In the first place, viability is not a dichotomous concept, as there are degrees of viability ranging from complete absence to total normality. In the second place, the lack of a standard reference model means that precise assessment of myocardial viability is not possible at present, so that results obtained with current assessment methods may be open to discussion.

MECHANISMS OF VIABLE DYSFUNCTIONING MYOCARDIUM

In myocardium which suffers acute, subacute or persistent perfusion defects, nonfatal ischemia can occur, and in such cases viability is maintained but resting contractile function is altered. Responses to such nonfatal ischemia include stunning and hibernation. In both of these states, cell dysfunction may be reversed once coronary flow is restored. The terms myocardial hibernation and stunning are currently accepted within the cardiology community, although their clinical

application has been limited because they are difficult to determine precisely. The myocardium is said to be stunned when transitory postischemic contractile dysfunction is present after coronary flow has been restored.¹¹ After revascularization, contractile dysfunction persists temporarily and is followed by late recovery.¹² a situation which may be secondary to AMI or ischemia.¹²⁻¹⁴ Hibernating myocardium is believed to be the consequence of discordance between flow and function, in which contractile function is altered as a response to a reduction in blood flow.^{15,16} Various mechanisms may be responsible for flow defects, including persistent perfusion defects at rest,^{17,18} reductions in the coronary flow reserve,¹⁹ or repeated episodes of ischemia and accumulated stunning.^{15,16} Recovery of contractile function once coronary flow is restored is, however, independent of the mechanism that produces hibernation.²⁰ As with viability, hibernation should not be considered a dichotomous concept, but can be conceived of as a reaction involving progressive tissular dedifferentiation, which can eventually result in apoptosis. The more severe and longer-lasting the ischemic injury, the greater the degree of myocardial degeneration.²¹ In general, the study of viability in pre-revascularization patients means studying hibernating myocardium.

In viable myocardium, cell membrane integrity is typically retained, and there is some mitochondrial activity, together with an active glucose metabolism, existence of coronary flow, and the presence of contractile reserve.²² AMI produces irreversible myocardial damage, and the extent of this damage will determine functional recovery in the ventricular wall and the possibility of avoiding remodeling. Irreversible damage to the myocytes alters their metabolism and contractile function, and leads to their replacement with scar tissue and subsequent loss of contractile muscle mass.

IMPORTANCE OF DEFINING VIABILITY IN PRE-REVASCLARIZATION PATIENTS

Assessing myocardial viability is of particular interest in patients in whom regional contractility is severely affected, as it helps to determine which segments of ventricular wall are viable and may be suitable for revascularization. In over 50% of patients with antecedents of electrocardiographically documented infarct, viable myocardial regions and necrotic tissue exist side by side.²³ However, the prior existence of necrosis does not necessary affect segment contractility. In a prospective study, regional contractile dysfunction was observed in 33% of patients who had ischemic

cardiopathy but no electrocardiographic evidence of infarct, and functional recovery after revascularization was found to occur in 85% of the dysfunctioning segments.²⁴ From the point of view of prognosis, the most important factor is the existence of severe global ventricular dysfunction. In patients with coronary disease, depressed ejection fraction, and cardiac insufficiency — with or without angina — assessing myocardial viability can be helpful in deciding whether there is an indication for revascularization.^{25,26} The prevalence of viable myocardium in patients with ischemic cardiomyopathy and global contractile dysfunction of the left ventricle is considerable, and ranges between 29%²⁷ and 55%²⁸ depending on the series.

Determining viability in patients with left ventricular dysfunction is also important from the prognostic point of view. When treated conservatively, patients with depressed ventricular function and signs of viability have higher mortality than patients without viability.²⁹ Likewise, revascularization has been shown to improve long-term prognosis in the former group,⁹ which may be explained by an improvement in overall ventricular function in patients with viability.^{30,31} In patients with ischemic cardiomyopathy, functional recovery after revascularization is a sufficient but not necessary condition for improved prognosis, as cases in which revascularization does not increase left ventricular ejection fraction may also present a favorable course.³² Where viability is present, revascularization improves both prognosis and functional class in these patients.³³

Determining the extent of viable myocardium to be revascularized allows thresholds to be defined above which improvements in global ventricular functioning and patients' functional capacity can be expected. Studies with cardiac magnetic resonance imaging (CMRI) in patients with AMI have shown that the recovery of contractile function in ventricular segments depends on the extent of viable myocardium in the thickness of the ventricular wall.³⁴ Contractile function was recovered after revascularization in 0%, 10%, 42%, 59% and 78% of the segments where the viable proportion of wall thickness detected with CMRI was 0%, 1%-25%, 26%-50%, 51%-75% and 76%-100%, respectively. Thus, the greater the percentage of viable myocardium, the greater the improvement in ventricular function after revascularization. Studies with radioisotopic techniques have reported different thresholds for the percentage of viable myocardium that determines increases in post-revascularization ejection fraction (34.4%;³⁵ 39%;³⁶ 42%³⁷). Revascularization has also been reported to improve the level of functioning of patients with over 18% of viable myocardium.³³

DIAGNOSTIC MARKERS OF VIABILITY

Living myocardium is characterized by preserved ventricular wall thickness, the presence of contractile reserve, cell membrane integrity, active myocyte metabolism, and the existence of blood perfusion. Diagnostic techniques for studying myocardial viability are based on detecting one or more of these markers (Figure 1). The preservation of ventricular wall thickness and contractile reserve are usually investigated using echocardiography or stress CMRI. Myocyte membrane integrity and blood perfusion can be evaluated using gammagraphy with thallium or technetium contrasts, positron emission tomography (PET), and contrast CRMI. PET and CRMI spectroscopy can detect metabolic defects in nonviable myocardium.

The importance of these markers is relative, as myocardial necrosis may not be transmural and may coincide with viable myocardium in the same segment of the ventricular wall. The ideal diagnostic technique would be one which provided sufficient spatial resolution to determine the quantity of viable myocardium in the same ventricular segment. Of all the techniques mentioned, CMRI provides the best spatial resolution.

The image-based diagnostic techniques used in cardiology aim to identify the presence and extent of viable myocardium using noninvasive methods. Such techniques include dobutamine echocardiography, thallium and technetium scintigraphy, PET and more

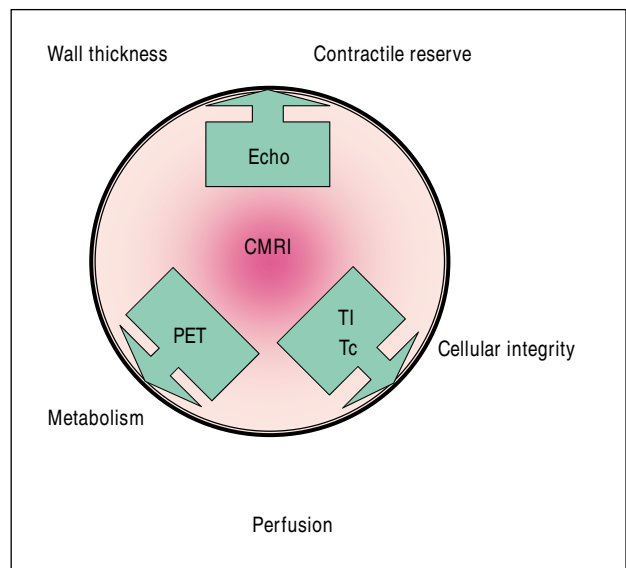


Fig. 1. Diagram showing viability markers and the techniques used to explore them. Cardiac magnetic resonance imaging (CMRI) can be used to analyze all of the viability markers shown. Tl indicates thallium; Tc, technetium; echo, stress echocardiography.

recently CMRI. The choice of technique to be used will be based on availability and experience. Because of its high sensitivity, PET has generally been considered the gold standard for determining viability; however, its limitations and cost have restricted its use. These limitations will be described later.

Markers of myocardial viability are described below:

Ventricular wall thickness

Necroscopic studies have indicated that nonviable myocardium is frequently associated with a significant thinning of the ventricular wall.^{38,39} When myocardial necrosis leads to considerable myocyte loss, a process of fibrosis begins which results in loss of myocardial wall thickness. The small number of living myocytes remaining is insufficient to recover contractility once reperfusion is achieved after revascularization.

Echocardiography

This is a quick and accessible method for estimating reductions in thickness in the akinetic or dyskinetic wall. Increased refraction may also be a sign of fibrosis. When using echocardiography, a reduction in the telediastolic thickness at rest to below 5 mm, and the presence of akinesia or dyskinesia, indicate non-viable myocardium.⁴⁰⁻⁴³ Such a finding has high negative predictive accuracy for viability, and means that more complex diagnostic procedures can be avoided. Conversely, a telediastolic thickness of over 5 mm provides a sensitive (100%), but not very specific (28%) marker of viability. Although echocardiography is accessible and economic, its limited specificity and poor reproducibility⁴⁰ mean that it is of little practical use. Where wall thickness is reduced, more specific markers need to be used.⁴⁴

Cardiac magnetic resonance imaging (CMRI)

CMRI provides a means of measuring ventricular wall thickness precisely and of assessing contractile function, without window limitations. In healthy individuals studied using CMRI, the telediastolic thickness of the left ventricular wall is greater than 5.5 mm.⁴⁵ With this technique, left ventricular wall segments with altered contractility and a telediastolic thickness of 5.5 mm or more are considered viable. This marker of myocardial viability is very sensitive (92%) but not very specific (56%), and as with echocardiography, has a high negative predictive accuracy for viability.⁴⁵

Contractile reserve

One objective of revascularizing viable myocardium is to recover contractile function. Echocardiography and stress CMRI can be used to determine the level of contractile reserve in viable myocardium, and to predict its functional recovery. However, even where contractile reserve is not shown to exist, viability may still be present. In some patients with a small proportion of viable myocardium, revascularization may not lead to recovery of contractility in the myocardial wall, but it can avoid ventricular remodeling.

Stress echocardiography

Contractile reserve is demonstrated using echocardiography in combination with stress-inducing protocols based on progressive exercise⁴⁶ (Figure 2) or continuous perfusion of drugs such as dipyridamole, nitroglycerin, postextrasystolic potentiators, enoximone and the catecholamines (including isoprenaline, adrenaline, dopamine and dobutamine). Enoximone is a positive inotropic drug which inhibits cyclic adenosine monophosphate (cAMP) phosphodiesterase, and in preliminary studies⁴⁷ in small numbers of patients, it has shown the greatest diagnostic precision of the drugs listed, with a sensitivity and specificity of 88% and 89%, respectively. However, dobutamine stress echocardiography is the most widely used and best-documented stress echocardiographic technique for detecting myocardial viability.⁴⁸⁻⁵³ Dobutamine preferentially stimulates beta-1-adrenergic receptors. At low doses (5 and 10 µg/kg/min) it produces more of an inotropic than a chronotropic effect, leading to improved contractility in the hibernating myocardium.⁵⁰ At higher doses, both the inotropic effect and heart rate are increased, thereby increasing oxygen consumption and ischemia in territories irrigated by stenosed coronary arteries.⁴⁸ When significant coronary stenosis exists, once the existence of contractile reserve has been demonstrated at low doses of dobutamine, contractility worsens at ischemic doses. The result is a two-phase response consisting of initial improvement, indicating viability, and later worsening due to the flow defects which produce the induced ischemia. Such a two-stage response is characteristic of hibernating myocardium, and predicts recovery of ventricular function after revascularization.⁵⁰ Dobutamine stress echocardiography has a sensitivity, specificity and positive predictive value of 81%, 86%, and 83%,⁵¹ respectively. The limitations in specificity are due to the poor echocardiographic window in some patients, or to operator subjectivity in the evaluation of segmentary contractility. The increasing use of harmonic image

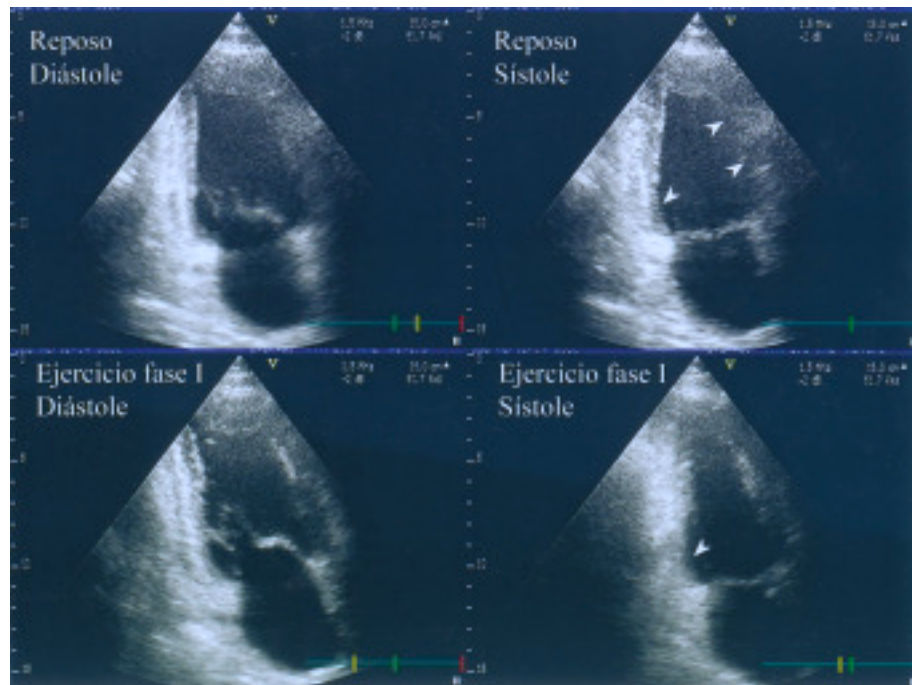


Fig. 2. Echocardiographic study using the treadmill exercise test with the Bruce protocol. An echocardiographic reading obtained with the patient standing and at rest detected akinesia of the anterior wall and basal segment of the lower wall (arrowheads). During the first 3 minute phase, contractile reserve in the viable anterior wall is revealed (no arrows), with akinesia persisting in the basal segment of the lower wall. Readings in later phases of exercise were of poor quality due to the patient's movement during fast walking.

echocardiography, the use of contrasts^{53,54} and transesophageal echocardiography⁵⁵ have notably improved the detection of the endocardial borders. Another limitation of dobutamine echocardiography is that in some segments, movement transmitted from adjacent normal segments which are hypercontractile under stress may be erroneously interpreted as an improvement in contractility. On the other hand, the small portion of viable myocardium in the involved segment may make sustained recovery of perfusion necessary to ensure partial recovery of contractile function.⁵¹ The method's limited sensitivity may also be due to the fact that significant coronary stenosis can considerably alter perfusion reserve, with a lower oxygen demand at low doses of dobutamine resulting in ischemia.

In comparison with single photon emission computed tomography (SPECT) and PET, dobutamine stress echocardiography shows greater specificity in the diagnosis of myocardial viability (81% against 73%) and lower sensitivity (84% against 90%).⁵⁶

Cardiac magnetic resonance imaging

Infarcted viable myocardium may have lost contractile function because of perfusion defects, which produce significant stenosis in the coronary artery involved. In this case, when stress is induced by progressive doses of dobutamine or exercise, the result is the two-stage response described previously. Long

experience with stress echocardiography means this procedure has been widely studied. However, some patients may not have an adequate ultrasonic window, and in these cases cardiac magnetic resonance imaging (CMRI) provides a useful alternative which has also proved reliable in identifying viable myocardium.⁴⁵ With CMRI the window for studying the heart is not limited, and equipment incorporating the latest technical advances will ensure a quick and accurate exploration. Significant systolic thickening of any segment of the akinetic or dyskinetic ventricular wall observed using stress CMRI is indicative of viability. This marker is more accurate if it is combined with the wall thickness analysis referred to earlier.⁴⁵ Although the monitoring of patients undergoing CMRI is complicated, there should be no additional risk if qualified personnel are available and adequate procedures are used.

Gated SPECT

Obtaining isotopic images of myocardial perfusion, synchronized with electrocardiogram and gated SPECT, permits the simultaneous evaluation of perfusion and contractility at a global and segmental level. When this technique was used to assess viability by studying contractile reserve during dobutamine perfusion at 10 $\mu\text{g}/\text{kg}/\text{min}$, it provided a sensitivity of 96% and a specificity of 78% (the capacity of dobutamine gated SPECT at rest to predict contractile recovery after

revascularization in dyssynergic myocardial regions⁵⁷).

Myocardial microperfusion

If contractile function is to be recovered after revascularization of the epicardial arteries, viable myocardium should have preserved myocytic cell membrane integrity, as well as a minimal level of blood microperfusion.

Isotopic techniques

Radioactive isotopes provide information on blood perfusion and myocyte integrity, both of which are important in determining myocardial viability. This technique will be discussed in more detail later, in the section on cell membrane integrity.

Cardiac magnetic resonance imaging

Damage to the cell membrane and compromised microperfusion can be detected using contrast-enhanced magnetic resonance imaging (MRI). The most frequently used contrast agents in MRI are gadolinium-based, although these are chelated to improve safety. Used in this form, the incidence of adverse events is very low and the technique is considered relatively safe. Gadolinium-based contrast agents are distributed rapidly through the vascular space before moving into the intercellular space. At the same time, they respect the intracellular space in healthy myocardium. Early MRI scanners had poor temporal resolution and did not permit effective first-pass analysis of rapidly distributed gadolinium. Nowadays, high quality images are available with a temporal resolution which more closely matches gadolinium's speed of distribution through the vascular space, thereby making exploration of myocardial perfusion possible.⁵⁸ The detection of myocardial perfusion defects using first-pass gadolinium-enhanced MRI after AMI signifies the presence of microvascular no-reflow, and thus indicates nonviable myocardium.^{59,60} The detection of perfusion defects using first-pass contrast studies indicate lack of viability, as revascularization does not lead to the recovery of contractile function in such cases.⁶¹

Perfusion echocardiography

In perfusion echocardiography, microcirculation is assessed by the use of contrasts, which are primarily intracoronary. Perfusion defects detected using this technique can identify no-reflow phenomena which are associated with poorer remodeling and poorer prognosis. The best moment at which to perform

perfusion studies after AMI is currently not clear.⁶²⁻⁶⁴ Earlier studies obtained better results when perfusion studies were performed 28 days after AMI, whereas other studies have obtained similar results when the technique was used immediately after reperfusion. Several studies have shown that intracoronary contrast techniques have limited diagnostic precision, with a sensitivity of 62%-96% and a specificity of 18%-67%.⁶⁵ Comparative studies of viability have shown that dobutamine stress echocardiography provides a more accurate method for assessing contractile reserve than contrast echocardiography, owing in particular to its greater specificity.⁶³

Cellular integrity

Cardiac magnetic resonance imaging (CMRI)

A technique of late enhancement with chelated gadolinium which produces enhancement where the greatest concentrations are found. When myocytes are irreversibly damaged and the cell membrane altered, gadolinium enters the cellular space, where it reaches high concentrations. Gadolinium also reaches high concentrations in the replacement fibrous scar tissue produced in some AMI patients. Delayed-enhancement CMRI in AMI patients who receive an injection of contrast agent produces a «bright» signal in segments of the ventricular wall where gadolinium is retained. The high concentration of contrast agent in nonviable myocardium produces a brighter image, which contrasts with viable myocardium (Figures 3 and 4). The method has been shown to be valid for detecting viable myocardium in pathological anatomy studies^{66,67} as well as in clinical studies, which have provided evidence of functional recovery in viable ventricular wall.^{34,68,69} The recovery of contractile function is directly related to the proportion of viable myocardium which is transmural. Kim et al³⁴ demonstrated that functional recovery occurs in only 0.02% of segments where hyperenhancement indicated the existence of transmural, and therefore nonviable dysfunctional myocardium. These authors established several percent intervals of viable myocardium for predicting the likelihood that contractility can be recovered. When viable myocardium composed 1%-25%, 26%-50%, 51%-75%, and 76%-100% of wall thickness, the corresponding probability of recovery were 10%, 42%, 59%, and 78%, respectively.

CMRI is highly accurate in detecting viable myocardium,^{34,61} is simple, does not require stress, uses a safe contrast agent, and is reproducible.⁷⁰ The method's good spatial resolution also permits analysis of the extent of viability defects within the ventricular

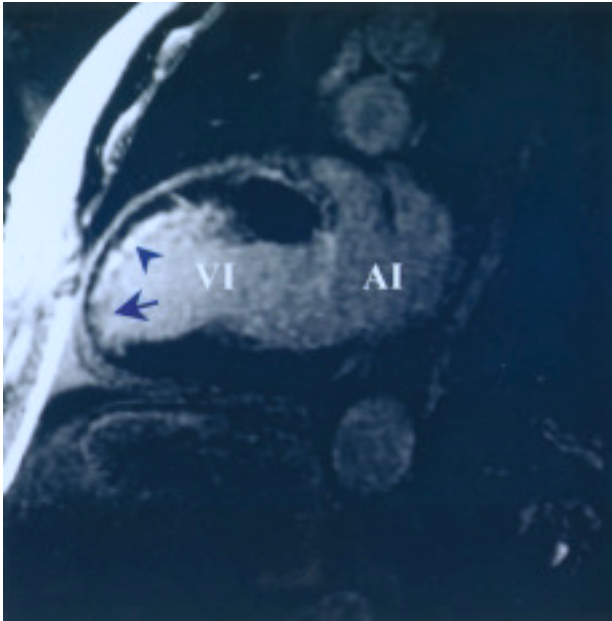


Fig. 3. Late enhancement cardiac magnetic resonance imaging with gadolinium to analyze myocardial viability in a patient with a previous clinical history of anteroapical acute myocardial infarct. Using a two-chamber view, nontransmural enhancement can be seen in the anterior wall of the left ventricle, indicating <50% absence of viability (arrowhead), and lack of viability in 90% of the thickness of the apex (arrow) can be seen. Functional recovery is not possible in the apex, whereas it is possible in the rest of the anterior wall (arrowhead). La indicates left atrium; Lv, left ventricle.

wall, by distinguishing between subendocardial, subepicardial and transmural alterations.⁷¹ CMRI provides images with good anatomic resolution and allows viable and nonviable myocardium to be clearly distinguished. Within the near future, late-enhancement CMRI with gadolinium may well become the gold standard method in the study of myocardial viability, particularly as it provides better anatomic resolution than isotopic methods. In an animal study,⁷² late-enhancement CMRI detected subendocardial infarct in 92% of segments, whereas SPECT was only able to

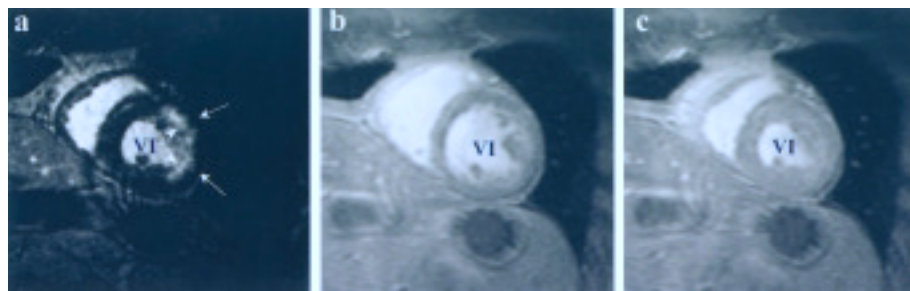
detect this type of infarct in 28% of the segments. Both techniques are, however, very sensitive in detecting transmural AMI (97% and 98%, respectively). CMRI's better spatial resolution also makes it more accurate in detecting subendocardial defects than PET.⁷³

Isotopes

Thallium-201 is a monovalent cationic radionuclide analog of potassium. Uptake of thallium-201 in cardiac myocytes depends on both coronary flow and cell membrane integrity. Intracellular uptake of thallium-201 is actively produced by the Na⁺/K⁺ATP-ase pump, although given the small size of the cation, uptake is also produced by a passive diffusion mechanism. In myocardial regions with adequate flow, thallium-201 uptake is fast, and high concentrations are quickly reached, with speed of uptake being directly proportional to the coronary flow. In regions with depressed flow, tissue dedifferentiation, or both, thallium-201 uptake is slower, and final concentrations are lower.⁷⁴ After uptake by the myocytes, a process of cation exchange between the cells and the blood pool is initiated which is known as redistribution.⁷⁵ The process is generally considered complete after 3-4 h, although its duration depends on the regional coronary flow: in regions with greatly reduced blood flow, the process may last up to 24 h. Reinjecting a small dose of thallium-201 intensifies redistribution, and provides better contrast between regions with normal and non-normal uptake.⁷⁶ Late redistribution and redistribution-reinjection techniques are both highly sensitive for diagnosing viability in dysfunctional myocardial segments (Figure 5), and both have shown high levels of agreement with the results of PET [¹⁸F]fluorodeoxyglucose (PET-FDG) testing.⁷⁷

Thallium's limitations in diagnosing viability derive from its biophysical characteristics. Its low emission energy makes it more liable to show false uptake

Fig. 4. a) Late enhancement cardiac magnetic resonance imaging with gadolinium used to analyze myocardial viability in a patient with a prior clinical history of acute myocardial infarct in the lateral wall of the left ventricle and revascularization of the circumflex artery. The short axis view shows enhancement in the subendocardial region and lack of viability (arrowheads) in 50% of the wall thickness in the lateral wall of the left ventricle. The subepicardial portion (50%) of the wall thickness is viable (arrows). Figures b) and c) correspond to the same view as a) and show dynamic images in diastole (a) and systole (b), illustrating recovery of contractility after revascularization. Lv indicates left ventricle.



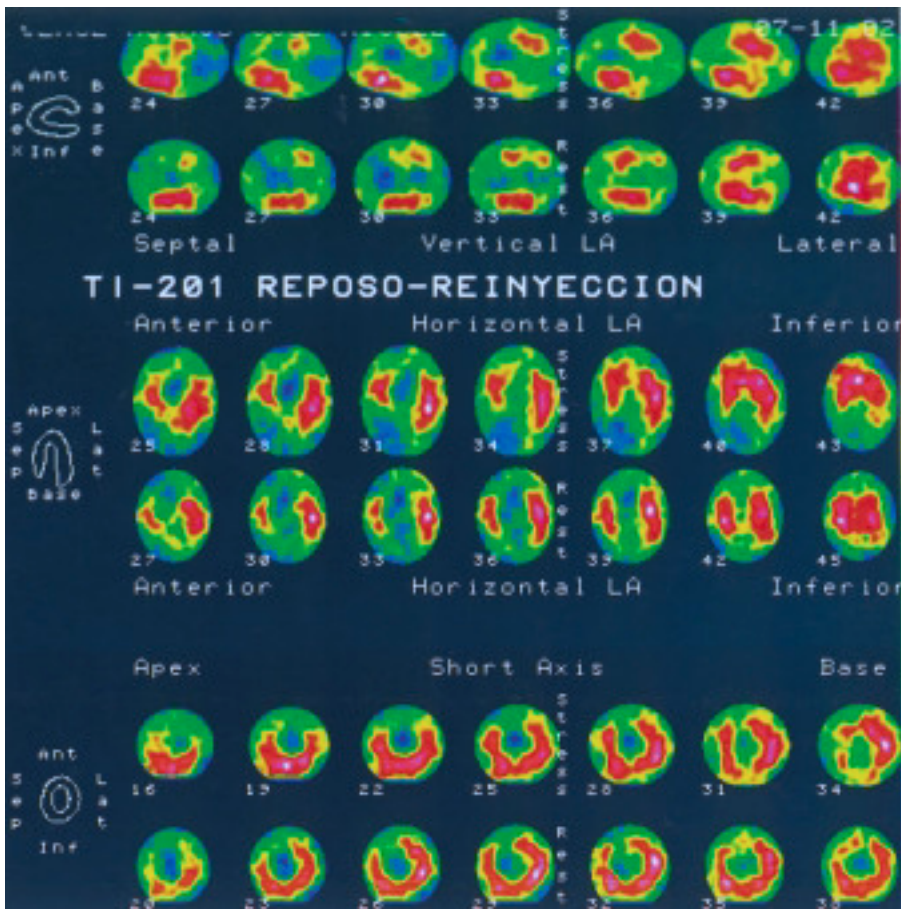


Fig. 5. Single photon tomography with thallium -210, using a 4-h rest-reinjection-redistribution protocol. The resting study (upper rows erroneously marked as stress by the automatic reader, but actually performed at rest) shows substantial and extensive capture defects in the anteroapical region of the left ventricle. In the redistribution study performed 4 h after reinjection (lower rows marked as rest) no improvement is observed in the anteroapical region with capture defects, indicating lack of viability in those areas.

defects due to attenuation artefacts. A more accurate assessment of viability requires quantification of the relative uptake of thallium-201 in dysfunctioning myocardial segments. The threshold for viability has generally been situated at 50% of maximum uptake, although where baseline activity is close to 50%, it is preferable to assess the degree to which thallium-201 is redistributed, independently of the baseline value. In this situation, viability is indicated where there is substantial redistribution, and vice versa.⁷⁸

Compounds marked with technetium-99m have greater photonic energy and a lower half-life (6 h) than thallium, which means that this marker is better detected by SPECT gamma cameras. Of all of the technetium-based compounds, the two most widely used are technetium-99m-sestamibi, and technetium-99m-tetrofosmin. Both are lipophilic compounds with considerable cardiac affinity, whose distribution in the myocardium is directly proportional to the regional coronary flow. Both compounds do, however, have a tendency to saturation where coronary flow levels are high. Technetium-99m enters the myocyte by passive diffusion via the cell and mitochondrial membrane. Its fixation, which is over 90% intramitochondrial,

depends on maintaining the polarity of the transmembrane potential; in other words, it requires metabolic activity to be maintained in the mitochondria. In this case redistribution does not occur and the compound remains inside the cell without returning to the blood pool. The biggest difference between the two technetium-based compounds is that tetrofosmin provides a quicker heart-lung contrast for image acquisition.⁷⁴

The main limitation of these compounds in diagnosing myocardial viability is that they are excellent markers of coronary flow: as no redistribution effect is produced, it is not possible to determine whether hypofixation is due to hypoperfusion or cellular necrosis. If these two compounds are to be adequate indicators of viability, it is essential to monitor relative levels of activity in the different myocardial regions being studied. Myocardial regions shown with FDG to have less than 30% activity are not considered viable. Two studies have correlated technetium-99m-sestamibi activity at rest with the amount of tissular fibrosis and regional functional recovery after revascularization, and both concluded that technetium-99m-sestamibi activity is inversely correlated with the

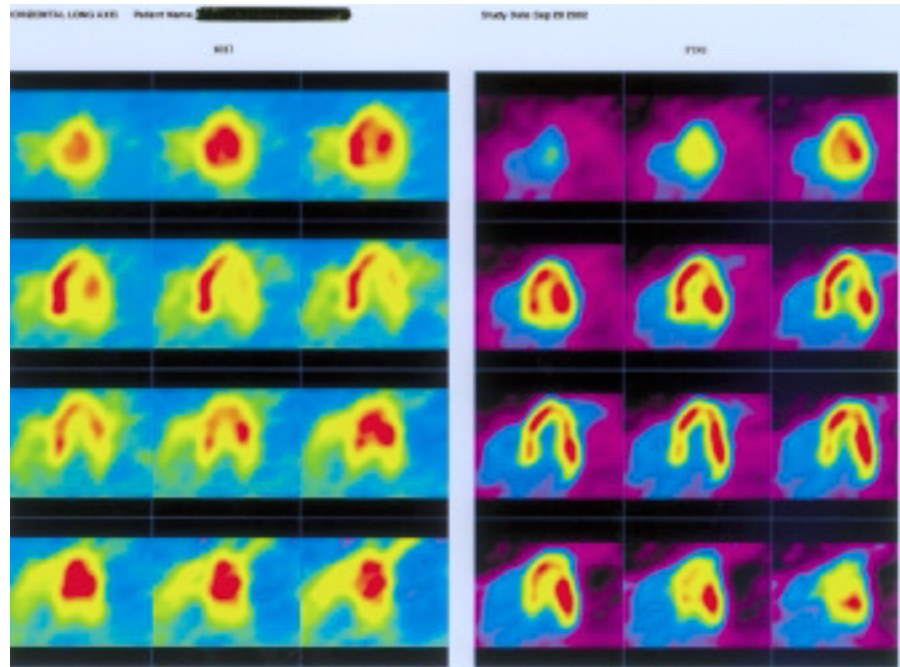


Fig. 6. Positron emission tomography (PET) images using ammonia (NH₃) and glucose metabolism (FDG) perfusion in four-chamber views of the heart. The lateral wall and apex of the left ventricle show a perfusion defect with NH₃ and metabolism with FDG which indicates viability. (Images courtesy of Dr. A. Maldonado of the Madrid Complutense PET Center.)

amount of fibrosis, and that activity cut-off points between 50 and 55% adequately predicted functional recovery of dysfunctional segments after revascularization.^{79,80}

Cellular metabolism

Positron emission tomography

Positron emitters are short half-life radionuclides which are generally synthesized in a cyclotron. The annihilation of positrons they produce generates two high-energy photons which are released at 180° to each other and travel in opposite directions. The simultaneous detection of two photons at 180° forms the basis of PET cameras. The principal positron emitters used to assess myocardial viability are FDG and ¹³N-ammonia. The first detects myocardial glucose metabolism, whereas the second is used to assess coronary flow. Since the early 1980s, a pattern of increased glucose metabolism together with reduced coronary flow has been observed in dysfunctional ischemic myocardium. This pattern of flow-metabolism dissociation is indicative of myocardial viability⁸¹ (Figure 6), and in order to assess myocardial viability it may be sufficient to analyze glucose metabolism in the myocytes. Metabolic images obtained with FDG have a sensitivity of 88%, a specificity of 73%, a positive predictive value of 82% and a negative predictive value of 83% for determining the viability of dysfunctional myocardial regions. Numerous studies have also

demonstrated the FDG's capacity to predict recovery of global contractile function after revascularization.⁵⁶ The main disadvantage of PET studies is their high cost and limited availability. However, metabolic studies can currently be performed without the need for a PET gamma camera or cyclotron. Fluorodeoxyglucose relatively long half-life (2 h) means it can be used in conventional centers which may be some distance from the cyclotron. On the other hand, gamma cameras with high energy physical or electronic collimators may be available for FDG studies. SPECT-FDG has been described as being more sensitive in detecting viability than stress-redistribution-reinjection thallium-201, and several studies have demonstrated excellent agreement between SPECT-FDG and PET-FDG.⁸²

Cardiac magnetic resonance imaging (CMRI)

Viability may be lacking due to reduced or nonexistent metabolic activity at the cellular level, an aspect which can be studied using CMRI. The spectra distinguish high-energy phosphorous-31 atoms forming adenosine triphosphate (ATP) from low energy atoms of creatine phosphate (CrP). In myocardium with low metabolic activity, the ATP/CrP ratio is reduced, making it less likely to recover its contractile function.⁸³ Although technically possible, this type of spectroscopy analysis is not practical for clinical use, and is currently only used in clinical research.

CLINICAL UTILITY OF ASSESSING MYOCARDIAL VIABILITY

Several studies in small numbers of patients have shown that revascularization of the IRA in viable myocardium leads to recovery of contractile function, both when ventricular function is preserved and when it is severely impaired. A recent meta-analysis by Allman et al included 24 studies which analyzed the prognostic benefit of coronary revascularization in the presence of myocardial viability and ventricular dysfunction.⁸⁴ The studies included a total of 3088 patients, and the results of the meta-analysis indicated that patients with viability who received medical treatment had greater annual mortality (15.8%) than patients without viability (16% vs 6.2%; $P=0.001$). Furthermore, patients with viability who were revascularized had lower annual mortality (15.8%) than those without viability (3.2% vs 7.7%; $P<0.0001$). The same study demonstrated that better prognosis in revascularized patients with viability was inversely related to the ejection fraction: the lower the ejection fraction, the greater the benefit of revascularization. However, there was no association between benefit and ejection fraction when revascularization was performed in patients without viability. At present, no prospective, randomized studies are available which demonstrate better prognosis in patients in whom revascularization of the IRA has been performed, and in which myocardial viability and

systolic function are preserved. On-going, prospective, randomized trials with sufficient numbers of patients will undoubtedly provide more evidence regarding the prognostic role of myocardial viability assessment. Such studies include the Surgical Treatment for Ischemic Heart Failure (STICH) and the Desobstruction Coronaire en Post-Infarctus (DECOPI) trials. Until results become available, however, Allman et al's meta-analysis provides some evidence of contractile recovery in viable myocardium, and improved prognosis.⁸⁴

Myocardial hibernation represents a higher level of myocardial aggression than stress-induced ischemia, and in patients with AMI and demonstrated residual ischemia, this is an accepted indication for coronary revascularization. Until recently, however, determining the existence of myocardial hibernation as an aid to decision-making regarding revascularization was not a routine part of clinical practice, and detection of viability was restricted to patients with severe ventricular dysfunction. There is currently sufficient evidence for the recovery of contractile function in viable segments of the ventricular wall after revascularization of the IRA in patients with preserved ventricular function (Figure 7). The alternative to assessing viability is the systematic revascularization of the IRA recommended by the late open artery hypothesis,⁸⁵ a recommendation based on several nonrandomized studies which showed a better long-term prognosis with revascularization of the IRA. However, the GUSTO I study did not confirm the benefits of open IRA one year after the AMI. Other randomized studies have presented inconclusive results,⁸⁶⁻⁸⁸ or better prognosis in patients with delayed revascularization of the IRA.^{89,90}

In spite of the large number of studies indicating the usefulness of assessing viability, the limited availability of PET, the relatively low specificity of stress-based isotopic techniques and the reduced sensitivity of dobutamine echocardiography have probably led to the assessment of viability being underused to date in clinical practice. The recent appearance of CMRI as an accurate method for determining myocardial viability may change this, especially as it is a simple and safe technique, which does not require stress, has greater spatial resolution (Figures 2 and 3), and increased sensitivity. CMRI could be considered the gold standard for the study of myocardial viability, and the detection of viability using this technique may alter decision-making processes in patients with AMI without severe ventricular dysfunction. The detection of viability in a myocardial segment could be an indication for the revascularization of the culprit artery and, in all likelihood, would reduce ventricular remodeling and

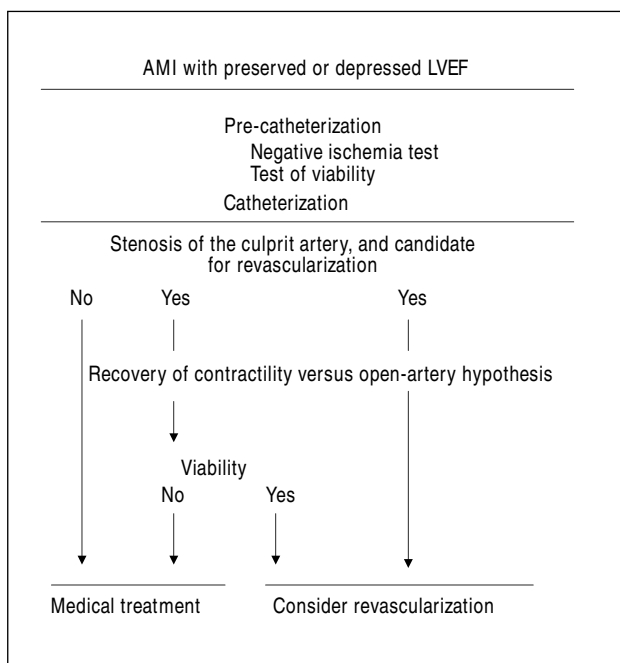


Fig. 7. Decision-making algorithms in pre-revascularization patients. LVEF indicates left ventricle ejection fraction; AMI, acute myocardial infarct.

improve prognosis. On-going prospective studies will provide definitive evidence of the clinical value of viability assessment in patients with or without severe ventricular dysfunction.

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