Current perspective

The expanding role of cardiovascular magnetic resonance in the identification of myocardial viability

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Cardiovascular magnetic resonance (CMR) is becoming a widespread diagnostic tool available to cardiologists to image different cardiovascular diseases. Among the main applications CMR has proven to be useful in the evaluation of patients with coronary artery disease. Particularly important seems the evaluation of coronary artery disease patients with left ventricular dysfunction. As a matter of fact CMR can identify myocardial viability by using different methods. CMR can accurately measure diastolic wall thickness and demonstrate a contractile reserve in segments with wall motion abnormalities when coupled to low-dose dobutamine infusion. In both applications CMR has proven to be superior to other diagnostic tools that use the same target of viability. By using gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) administration it has recently been shown that CMR can accurately detect myocardial viability. In fact, irreversibly damaged myocardial segments show a delayed hyperenhancement compared to normal segments. Due to its excellent spatial resolution one of the most important information that CMR offers in this application is the transmural extent of necrosis/viability that no other method can offer. The available data suggest that Gd-DTPA CMR could be superior to any other currently used methods in the identification of both stunning and hibernation.

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Introduction

Cardiovascular magnetic resonance (CMR) is a non-invasive imaging technique currently used in clinical cardiology. By offering high-quality anatomic and functional images from the heart, valves, and vessels CMR provides relevant information in several clinical conditions[1]. As it is based on the magnetic properties of the tissues examined and does not employ X-ray radiations CMR is considered a completely non-invasive diagnostic tool and, as for echocardiography, it can be safely used without significant limitations even for follow-up studies. CMR has proven useful in several different cardiac diseases and in several instances provides unique diagnostic information[2-4]. CMR measurements of left and right ventricular volumes as well as left ventricular mass are precise and accurate and currently represent the gold standard for other imaging modalities[5-7]. Since its introduction in the clinical field CMR has become a fundamental diagnostic tool in cardiovascular imaging and clinical cardiology[8,9].

In coronary artery disease CMR has been extensively used to image both irreversibly damaged and normal myocardium. Both ischemic and viable myocardium can be identified. By coupling cine-CMR with dobutamine administration it is possible to identify and differentiate normal from infarcted myocardium as well as dysfunctional albeit viable segments. Recently by using gadolinium-based chelates several studies have indicated how CMR can detect irreversibly damaged myocardial regions. On late gadolinium images these appear as areas of hyperenhancement compared to normal non-hyperenhanced myocardium. With this method, defined as delayed contrast enhancement (DEMR), viable myocardium can be described quantitatively and qualitatively. Due to its high spatial resolution viable myocardium can be easily measured and its transmural distribution precisely assessed. DEMR identifies small scars more frequently than positron emission tomography (PET) thus suggesting that CMR may even be superior to nuclear studies in detecting viability[10].

CMR is nowadays considered among the best imaging modalities to detect and describe viable myocardium. By using different markers CMR can in fact describe viability in different terms: anatomical,

functional, and histological. This information is relevant to the clinician. In this article we will briefly review the main information available on the ability of CMR to detect and describe viable myocardium by using the different available imaging techniques.

Viability and wall thickness-wall thickening

The presence of a previous myocardial infarction (MI) can be shown by CMR as regions of decreased wall thickness as compared to non-infarcted regions[11] (Figs. 1 and 2). Depending on the size and the its transmural extent the infarct can be seen by using different technical approaches. As expected a non-transmural infarct does not significantly affects the end-diastolic wall thickness (DWT) and is suspected only when a decreased systolic wall thickening can be documented. On the contrary a large transmural necrosis is identified both as a region of decreased or absent wall thickening as well as a region of decreased DWT[12,13]. With the current technology wall thickness and wall thickening are not usually used to describe a previous MI. Such demonstration is neither sensitive nor specific for a previous MI[14]. Nevertheless wall thickness and systolic thickening are related to myocardial viability. Baer et al.[15], using gradient-echo CMR, evaluated 35 patients with previous MI by comparing DWT with viability as assessed by ^{18}F-fluoro-2-deoxyglucose (FDG)-PET. Wall thickness showed a 72% sensitivity, 89% specificity, and 91% positive predictive accuracy in detecting residual viability. When wall thickening was < 1 mm and DWT ≤ 5.5 mm, viability was present only in a minority of segments. In a subsequent study the same authors evaluated DWT as a predictor of contractile recovery after coronary revascularization. A DWT ≥ 5.5 mm showed a sensitivity of 92% although only a specificity of 56% in predicting functional recovery.

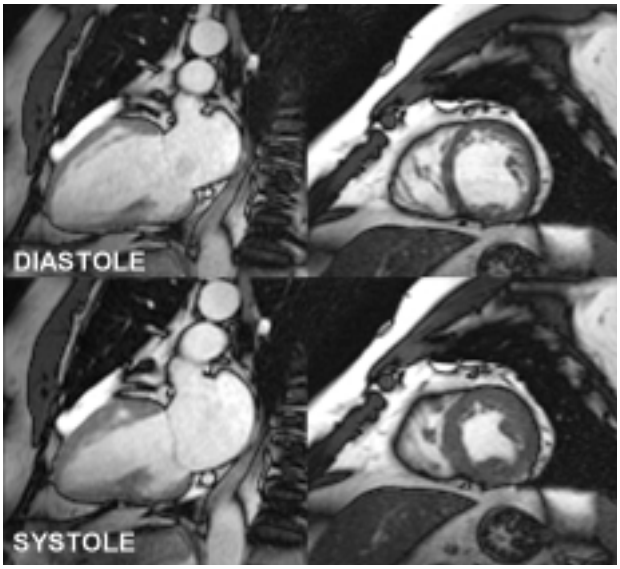

Figure 1. *A coronary artery disease patient with previous (healed) myocardial infarction of the basal inferior wall. Balanced fast-field echo series. Long-axis* (left) *and short-axis* (right) *view of the left ventricle. Note the systolic thickening of the anterior and lateral wall compared to the absence of systolic change of the infero-basal wall. The latter looks also thinner compared to the other segments.*

Viability and dobutamine cardiovascular magnetic resonance

Early studies coupling CMR and pharmacological stimulation were performed in coronary artery disease patients starting in the early 1990s[16-20]. Functional studies of the left ventricle both at rest and during drug infusions are today available in a very short time. The speed of acquisition and presentation of the images allows to depict the whole left ventricular regional wall motion in less than 1 min. Both adenosine stress, dipyridamole, and dobutamine stress CMR are commonly performed for diagnostic purposes[21].

The demonstration of a contractile reserve in myocardial segments with abnormal function represents a way to demonstrate the presence of residual viability. This can be accomplished by using low-dose dobutamine infusion and evaluating the left ventricular wall motion. The first papers to describe the feasibility of

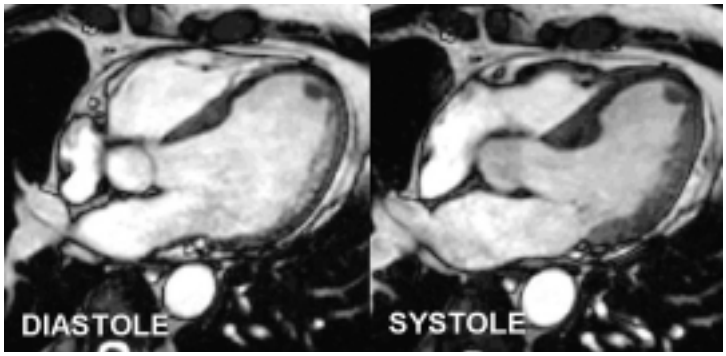

Figure 2. *Patients with previous antero-septal and apical myocardial infarction. Balanced fast-field echo cine series. Modified 4-chamber view. Note the thinning of the antero-septal wall, the lack of systolic change, and the presence of an aspect compatible with a mural thrombus.*

such an approach were published in 1995. Dendale et al.[22] in patients with recent MI and Baer et al.[15] in patients with chronic coronary artery disease showed the feasibility and utility of such an approach.

By using low-dose dobutamine and FDG-PET Baer et al.[15] showed that a 1 mm systolic wall thickening had a sensitivity of 81%, a specificity of 95%, and an accuracy of 79% in detecting viability. In patients with dysfunctional segments and undergoing coronary artery bypass surgery, it was demonstrated that a systolic wall thickening ≥ 2 mm had a sensitivity of 84%, a specificity of 94%, and an accuracy of 91% in predicting the functional recovery[22]. Others have also confirmed the ability of low-dose dobutamine in evaluating myocardial viability[23-26]. It should be stressed however that when echocardiography can be performed without limitations due to a poor acoustic window the results obtained can be quite similar. This has also been confirmed in some investigations. In a recent study comparing low-dose dobutamine CMR and low-dose dobutamine transesophageal echocardiography both techniques showed similar accuracy (88 vs 83%) although CMR showed a superior specificity (92 vs 83%)[27].

Currently the clinical use of low-dose dobutamine CMR is not yet fully defined. On one side when dobutamine CMR is used to perform a pharmacological stress test, low-dose dobutamine may be also used when dysfunctional segments are present. Also low-dose dobutamine CMR should be considered when echocardiography does not provide optimal information. In this case the information offered is at least as accurate as that offered by using transesophageal echocardiography as imaging tool. Finally, as we will see, low-dose dobutamine CMR has recently gained new attention in patients having dysfunctional segments and intermediate degree of transmural scar as imaged after gadolinium chelate administration.

Delayed enhancement

The ability of CMR to image MI has recently received an enormous attention by both researchers and clinicians. By using gadolinium chelates (i.e. intracellular contrast agents) and a T1-weighted image acquisition, CMR detects even very small amounts of irreversibly damaged myocardium. This is a relatively simple and very accurate method that offers an outstanding tool to evaluate all the main different pathological states of the myocardium.

Since its early application it has been shown that CMR could identify acute MI due to the changes induced by the ischemic damage on T2-weighted and T1-weighted images[28-30]. Also CMR could detect MI on T1-weighted images following contrast agent administration[31-33]. Since these early observations several studies have been performed using a variety of pulse sequences with and without contrast agent administration to differentiate injured from normal myocardium[34-36]. More recently T1 weighting has been achieved with an inversion-recovery fast low-angle shot pulse sequence (acronyms are IR-FLASH, IR-TFE, IR-TGE) that yields the best results in terms of image quality. The method is defined by several acronyms. The one we are using here is DEMR.

It is now well established that the irreversibly damaged myocardium appear as regions of late contrast hyperenhancement when imaged by CMR with the IR-TFE technique[37-39]. Currently these imaging sequences are acquired after a careful setting of the inversion time while the patient holds his/her breath. The inversion time has to be chosen individually so to null the signal from the normal myocardium, typically between 150 and 300 ms. Recently DEMR has been simplified by both improving the speed of choice of the correct inversion time and by significantly decreasing the imaging time (i.e. with a three-dimensional volume acquisition). The usual dose of the gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) is 0.2 mM/kg in a single dose and the imaging starts after 10 min. The time window for the examination is limited as the kinetics of the tracer changes significantly after few minutes. Several technical factors may affect image quality but, in spite of these limitations DEMR is a widely used and very powerful diagnostic tool.

The hyperenhanced region almost perfectly fits the infarct zone as described by specific infarct staining of the anatomic specimen such as the triphenyl tetrazolium chloride-stained myocardium (Fig. 3)[38]. Also it has been demonstrated that gadolinium myocardial concentrations are exclusively associated with irreversible ischemic injury as defined by histology and by regional electrolyte concentrations[40].

The causes for the increased contrast concentration in the region of myocardial necrosis are different and not fully elucidated. The disruption of the sarcolemmal membranes increases the distribution volume of Gd-DTPA that is an extracellular agent. The contrast enters the necrotic cells and so its concentration increases in regions where there is an acute MI. However, cell death leads to a change in composition of the damaged myocardium with increased extracellular space. This in turn is occupied by more contrast compared to the viable myocardium. The latter mechanism seems to be more important in explaining the DEMR of chronic infarcts. Finally, the damaged myocardium shows a different wash in/wash-out kinetics of gadolinium compared to the normal tissue[41,42].

DEMR accurately determines the presence, location, and transmural extent of healed Q wave and non-Q wave MI[43,44]. When compared to single photon emission computed tomography (SPECT) results CMR detects transmural infarcts to the same extent. However, due to its superior spatial resolution, CMR systematically detects subendocardial infarcts that are missed at SPECT (Figs. 4-6)[45]. The ability to image even very

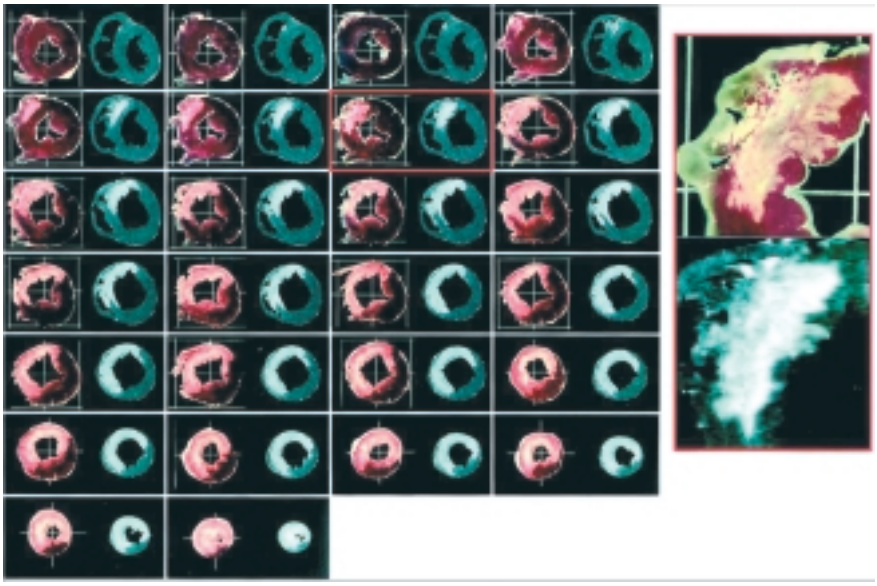

Figure 3. *Comparison of ex vivo magnetic resonance images with triphenyl tetrazolium chloride-stained (infarct avid stain) slices in one animal at 3 days after infarct. Slices are arranged from base to apex starting in upper left and advancing left to right, then top to bottom. Right, magnified view. Note the close relationship between the results of delayed contrast enhancement and triphenyl tetrazolium chloride. Reproduced with permission from Kim et al.[38].*

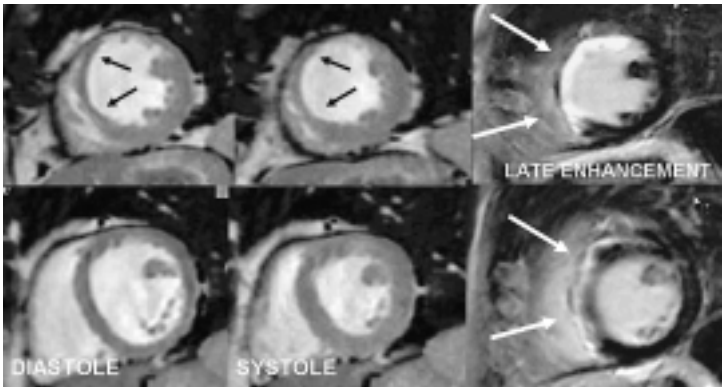

Figure 4. *A patient with previous anteroseptal myocardial infarction. Balanced fast-field echo series in the short axis at different levels of the left ventricle. Note the absence of thickening in the most apical short-axis image* (dark arrows). On the right *are shown the corresponding delayed enhancement images. Note the presence of areas of hyperenhancement* (arrows) *which appear to be transmural in the upper image and non-transmural in the lower image. It is readily appreciated how the transmural pattern of delayed contrast enhancement is associated with a thin wall and lack of systolic thickening.*

small lesions has been also confirmed in patients after percutaneous coronary interventional procedures[46]. CMR has shown that mild elevations of creatine kinase-MB or troponin I after such procedures are the results of discrete small infarctions that can be seen by DEMR even when ECG and wall motion appear normal[47]. The extent of DEMR does not appear to be constant at different time intervals since the acute phase of MI. While in chronic MI the size of abnormal DEMR is reproducible, the abnormal DEMR present in the acute phase significantly decreases in time[48]. By using DEMR it is possible to distinguish transmural from non-transmural lesions (Fig. 7). Also one can evaluate the relationship between the transmural extent of the abnormal DEMR and function. Animal studies have thus shown that the inotropic reserve is confined to dysfunctional myocardium with normal contrast enhancement[49,50]. Also, the inotropic response in delayed hyperenhanced myocardium is influenced by transmurality of necrosis: wall thickening relates inversely to the extent of transmural DEMR.

Assessment of myocardial viability by delayed enhancement

In the setting of acute MI a variable amount of jeopardized myocardium may show a preserved metabolic activity and contractile reserve and subsequently recovery in function. Such regions of myocardium are

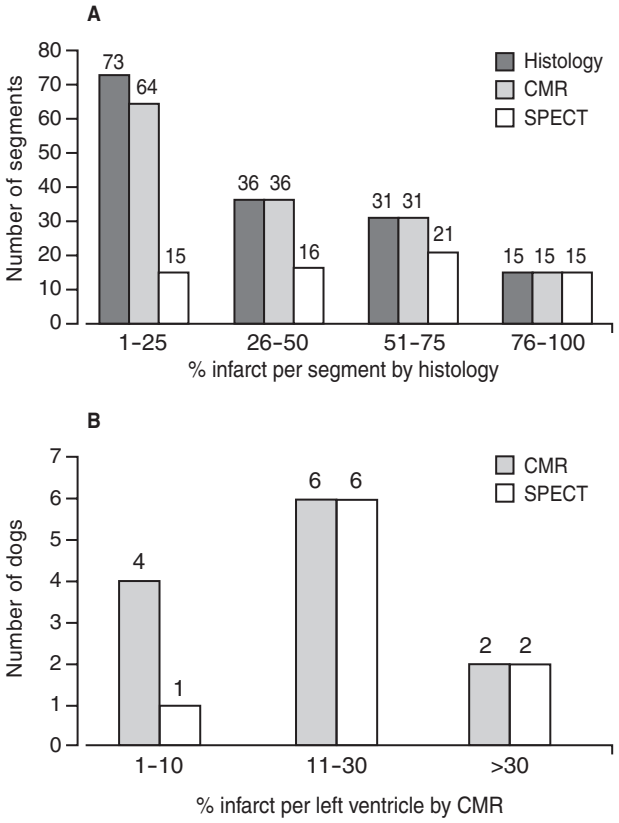

Figure 5. *Comparison of single photon emission computed tomography (SPECT) and cardiovascular magnetic resonance (CMR) in detecting the infarct of animals. Note the good agreements of the two methods in detecting infarct sizes > 10% of the left ventricle. Below this threshold CMR still performs very well while SPECT misses 75% of the infarcts. Reproduced with permission from Wagner et al.[45].*

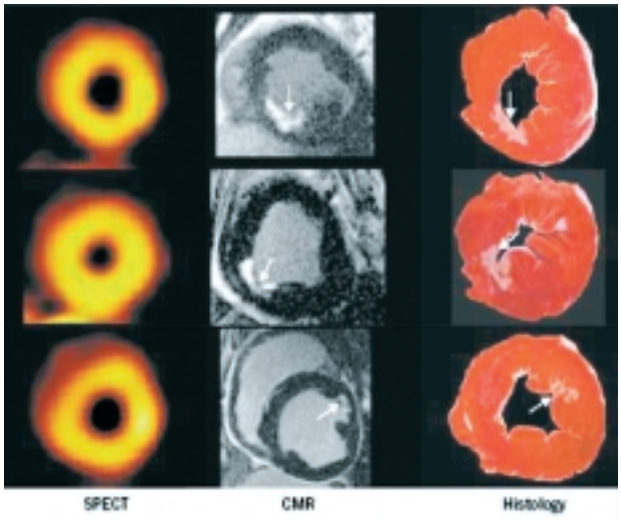

Figure 6. *Short-axis views from three dogs with subendocardial infarcts. Delayed contrast enhancement are shown in the* middle panel. *Cardiovascular magnetic resonance (CMR) detects even very small infarcts while single photon emission computed tomography (SPECT) shows normal perfusion. Reproduced with permission from Wagner et al.[45].*

dysfunctional albeit viable and are known as regions of myocardial stunning[51,52]. As delayed hyperenhancement is strictly related to irreversibly damaged myocardium, DEMR can be used to distinguish reversible from irreversible ischemic injury independent of wall motion and infarct age. Early investigations in the animal model have shown that early restoration of flow in the setting of an experimental acute MI decreases the transmural extent of hyperenhancement and is associated with future improvement in contractile function[39].

In patients with both reperfused and non-reperfused acute MI the presence of dysfunctional but viable segments can be correctly detected by DEMR[53]. The likelihood of functional improvement is heavily affected in a stepwise manner to the presence and transmural distribution of the left ventricular hyperenhancement. Regions with transmural hyperenhancement > 75% have a low probability of recovery compared to regions with ≤ 25% of transmural distribution. This relationship has been confirmed in different studies[54,55] (Fig. 8)[54,55,56].

In the chronic setting, viable but dysfunctional myocardium is also identified as hibernating myocardium[57-59]. While the hallmark of viability by PET imaging is the presence of residual metabolic activity in dysfunctional segments, hibernating myocardium can be identified by CMR as regions without contrast hyper-

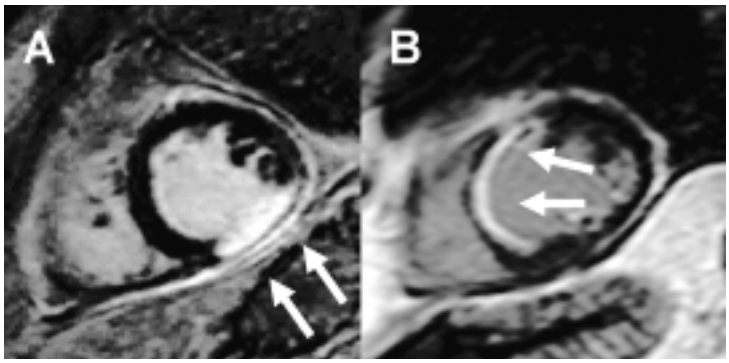

Figure 7. *Transmural* (A) *and non-transmural* (B) *"chronic" myocardial infarction. In* panel A*, the inferior wall shows an hyperenhancement involving all the layers of the myocardium. Note also the lack of enhancement at this stage in the remaining myocardium. In* panel B*, the antero-septal wall shows non-transmural delayed contrast enhancement. This represents non-transmural scar.*

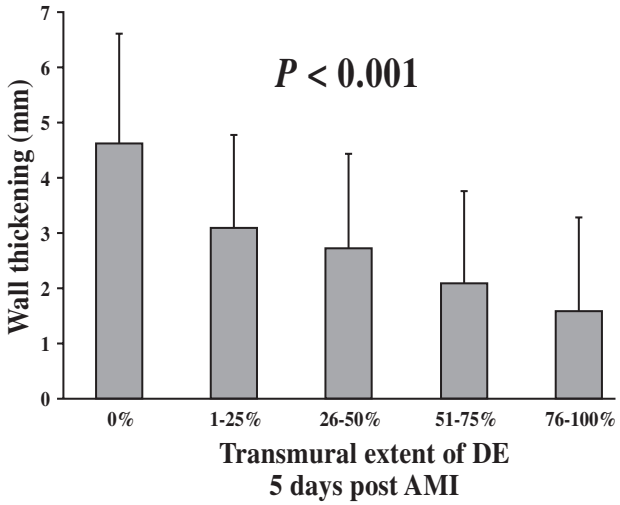

Figure 8. *Relationship between the transmural extent of delayed enhancement (DE) and wall thickening. Note the inverse relationship between systolic thickening and percentage of transmural extent of scar. AMI = acute myocardial infarction. Reproduced with permission from Baks et al.[56].*

enhancement and decreased or absent systolic thickening. It is noteworthy that it was a very early report from Fedele et al.[60] to show the potential of contrast enhanced CMR to detect viable myocardium.

The relationship between the metabolic activity of left ventricular dysfunctional segments as measured by PET and DEMR was investigated by Klein et al.[10] in 31 patients with severe left ventricular dysfunction and heart failure. The presence of scar identified as contrast hyperenhancement was closely related with PET data. Hyperenhanced regions of the left ventricle correlated well with areas of decreased flow and metabolism. However, CMR appeared to show scar more frequently than PET as 55% of segments showing a subendocardial hyperenhancement by CMR were classified as normal by PET. These data were interpreted as the result of the better spatial resolution of CMR compared to PET scan.

An early study from Ramani et al.[61] showed that in coronary artery disease patients and left ventricular dysfunction the presence of hyperenhanced segments by DEMR was common. Dysfunctional segments showed a variable amount of hyperenhancement. Viable segments as recognized by both thallium-201 scintigraphy and dobutamine echocardiography showed lack of hyperenhancement while hyperenhancement was associated with non-viability. In a cornerstone study, the same group studied the ability of DEMR CMR to predict the contractile recovery after surgical or percutaneous revascularization in 41 patients with left ventricular dysfunction[62]. They identified a total of 804 dysfunctional segments before intervention. The likelihood of improvement in regional contractility after revascularization decreased progressively as the transmural extent of hyperenhancement increased (Fig. 9). Contractility increased in 256 out of 329 segments (78%) with no hyperenhancement before revascularization, but in only 1 out of 58 segments with hyperenhancement ≥ 75% of the myocardial wall (Fig. 9). Recently DEMR has been evaluated in patients with left ventricular dysfunction undergoing only coronary artery bypass surgery[63]. Fifty-two patients were studied before and after 6 months after bypass surgery. Preoperatively, 611 segments (21%) had abnormal regional function, and 421 segments (14%) showed hyperenhancement. At 6 months 57% of dysfunctional segments improved. Also in this investigation a strong relationship was found between the transmural extent of hyperenhancement and the recovery in regional function.

The relationship between the extent of delayed hyperenhancement in myocardial dysfunctional segments and their contractile recovery after interventions has also been examined for the effect of medical therapy. Bello et al.[64] studied 45 patients with heart failure and left ventricular dysfunction. They found an inverse relationship between the extent of hyperenhancement and the likelihood of contractile improvement after 6 months of beta-blocker administration. They found improved contractility in 56% of regions with no contrast enhancement but in only 3% of those with > 75% of transmural hyperenhancement.

From these studies DEMR appears to be a powerful diagnostic tool to detect viability. The presence and extent as well as the transmural distribution of hyperenhancement has thus been shown to represent a direct

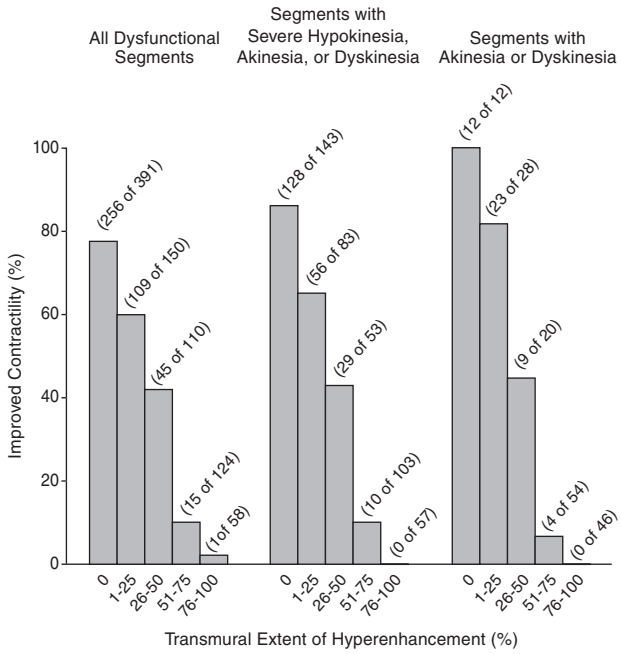

Figure 9. *Relationship between transmural extent of delayed contrast enhancement and functional recovery after revascularization. Note the inverse relationship between the transmurality of scar by of delayed contrast enhancement and the likelihood of functional recovery. Adapted with permission from Kim et al.[62].*

sign of myocardial scarring. Non-hyperenhanced myocardial regions represent viable myocardium and therefore with a very high likelihood to recover in function after medical, interventional, or surgical interventions. When regions of scar are present, a transmural distribution of hyperenhancement virtually rules out any possibility of recovery in function. Intermediate transmural presence of scar may yield unpredictable results. In these cases the combined use of DEMR and low-dose dobutamine CMR seems to possess additional value. In particular segments with similar amount of hyperenhancement may have a completely different behavior after revascularization. In these subgroups low-dose dobutamine magnetic resonance imaging seems to add significant information by showing a contractile reserve in those who will recover after coronary artery bypass surgery[65,66].

First-pass gadolinium and assessment of viability

First-pass analysis of the signal intensity after gadolinium peripheral injection has been used to evaluate myocardial viability. A bolus injection of Gd-DTPA or its analogues determines changes in the magnetic properties of blood by shortening the T1. By using T1-sensitive magnetic resonance sequences it is possible to identify on a beat-to-beat basis the changes in signal intensity of the blood and draw time-intensity curves. The time course and intensity of the signal from the myocardium is related to myocardial perfusion. An altered pattern of perfusion can be detected during pharmacological stress-induced maldistribution of flow in patients with obstructive coronary artery disease but can also be seen because of microvascular obstruction in the early phase of MI. An abnormal perfusion pattern can also be seen in patients with chronically occluded epicardial vessels. Myocardial viability has been evaluated by first-pass studies only in patients with recent acute MI. In this setting viability is related to myocardial stunning. In a recent paper from Baks et al.[56], 22 patients with recent MI and treated by primary angioplasty were studied by both first-pass and delayed enhancement and related to subsequent outcome. The information obtained by the first-pass study was able to predict the functional recovery although less precisely than DEMR. Lund et al.[67] showed that there is a substantial similarity between the extent of microvascular obstruction during the first-pass study with areas of hypoenhancement at DEMR. Microvascular obstruction was mainly seen in large infarcts and therefore was related to a poor recovery in function in the following months.

Regions of DEMR can also be detected in other diseases, namely in many conditions affecting primarily the myocardium. In suspected myocarditis DEMR is a frequent finding and is related to active inflammation[68]. The distribution of abnormal enhancement is different from that found in MI as it is mainly located in the subepicardial layer. Interestingly the presence of DEMR in the acute phase is not related to decreased function while in the chronic phase its persistence is associated with myocardial dysfunction. This behavior most probably reflects the different meaning of DEMR in the acute vs the recovery setting.

Blood oxygen level-dependent imaging

Blood oxygen level-dependent imaging (BOLD) can be used as an alternative way to evaluate the presence of viable myocardium by CMR. The principle relies upon the magnetic properties of hemoglobin. Oxyhemoglobin and deoxyhemoglobin are diamagnetic and paramagnetic, respectively. The prevalence of one over the other determines small local field inhomogeneities that can be used to generate differences in contrast. Changes in blood flow, volume, and oxygen consumption cause variations in local magnetization[69-71]. This approach has been used to detect the presence of viable myocardium in patients with chronic coronary artery disease[72]. This method is yet under investigation.

Pitfalls and strengths of cardiovascular magnetic resonance

While BOLD imaging is yet an investigative method, both dobutamine and contrast studies are performed in several centers throughout the world. Contrast studies do not require any particular attention or preparation of the patient. On the contrary dobutamine as well as other stress studies require the use of magnetic compatible infusion pumps to inject the drug intravenously and special systems to monitor the patient. Monitoring of the patients is usually granted by the use of systems that allow repeated blood pressure measurements and non-invasive evaluation of oxygen saturation. The ECG of the patient is necessary for the acquisition of the images but unfortunately is usually limited to one trace only and the signal is distorted by the magnetic field. As a result a full monitoring of the patients' conditions is not achievable. Another potential problem is related to the heart rate increase provoked by some drugs as in the case of dobutamine. At the concentrations needed to evaluate viability this however does not usually represent a problem.

When performing a viability study by CMR it should always be considered that several important information can be achieved during the same session of examination at no or at very low extra cost. In first place anatomy and function of the left ventricle are always evaluated, usually in the first part of the examination. Delayed imaging can be performed by injecting the amount of due contrast in two separate boluses (one during stress and the remaining after the end of stress)

when it is desirable to evaluate myocardial flow reserve. A perfusion stress study requires a few minutes and can be performed by using adenosine or dipyridamole. Thus in the same session of examination it is possible to obtain several different information and consider this both separately or together in a comprehensive fashion that is unique among the currently available imaging techniques.

Conclusions

Although CMR can detect and evaluate myocardial viability by different techniques the best available and most promising method is the one based on DEMR. By evaluating the delayed contrast-enhanced images, CMR represents a powerful diagnostic tool able to detect and quantitate scar directly. As viable myocardium does not show hyperenhancement CMR is able to accurately differentiate reversibly from irreversibly injured myocardial segments. The available data show that CMR is superior to other currently used techniques to detect both scar and viable myocardium. Combining the use of delayed enhancement and low-dose dobutamine CMR seems the best way to predict the functional recovery after revascularization in patients with hibernating myocardium.

CMR is currently considered among the techniques available for clinical use in cardiology and in detecting viability[73-75]. Therefore CMR should be considered among the established methods to evaluate myocardial viability in coronary artery disease patients. As recently pointed out, if CMR is available to the clinician a precise role for this technique can be foreseen and DEMR should be considered class I for viability studies[76]. This appears to be particularly important in patients with heart failure and a suspicion for the presence of viable myocardium.

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