

Assessment of myocardial viability with cardiac magnetic resonance imaging

Kardiyak manyetik rezonans görüntüleme ile miyokardiyal canlılığın değerlendirilmesi

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ABSTRACT

With the rapid evolution of cardiovascular magnetic resonance imaging (MRI) techniques, cardiovascular MRI has become an important noninvasive diagnostic tool in cardiovascular disease. Cardiac MRI can provide high quality diagnostic information about cardiac and valvular function, coronary anatomy, coronary flow reserve and myocardial perfusion, myocardial viability, contractile reserve and cardiac metabolism. Besides, MRI can also provide prognostic information for certain cardiac diseases. Assessment of the viable myocardium is one of the major issues of the invasive cardiology. Viable myocardium has the potential for contractile recovery after reperfusion. The identification of viable myocardium is useful in predicting which patients will benefit from revascularization and have improved left ventricular ejection fraction and survival. The focus of the present article is on the clinical role of cardiac MRI in the detection of viable myocardium. (*Anadolu Kardiyol Derg 2008; 8: Suppl 2; 71-6*)

Key words: Cardiac magnetic resonance imaging, myocardial viability, delayed enhancement

ÖZET

Kardiyovasküler manyetik rezonans görüntüleme (MRG) alanında yaşanan hızlı gelişmelerle birlikte kardiyak MRG kardiyovasküler hastalıkların tanısında ve değerlendirilmesinde önemli bir noninvazif araç haline gelmiştir. Kardiyak MRG kalp ve kapak fonksiyonları, koroner anatomi, koroner akım rezervi ve miyokardiyal perfüzyon, miyokardiyal canlılık, kontraktıl rezervi ve kardiyak metabolizmanın değerlendirilmesinde tanılal bilgi sağlar. Ayrıca, bazı kardiyovasküler hastalıkların prognozu hakkında da önemli bilgiler verir. Canlı miyokardın belirlenmesi invazif kardiyolojinin önemli konularındadır. Reperfüzyon sağlandıktan sonra canlı miyokardın kontraktıl fonksiyonlarında toparlanma olur. Canlı miyokardın tanımlanması hangi hastaların revaskülarizasyondan yarar görerek sol ventrikül ejeksiyon fraksiyonunun iyileşeceği ve yaşam süresinin uzayacağıın belirlelenmesinde önemlidir. Bu derlemenin konusu canlı miyokardın tanımlanmasında kardiyak MRG'nin rolüdür.

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Anahtar kelimeler: Kardiyak manyetik rezonans görüntüleme, miyokardiyal canlılık, geç kontrast

Introduction

Imaging has become an important part of diagnosing ischemic heart disease. Imaging of ischemic heart disease is not limited to the mere visualization of coronary arteries for detection of stenotic coronary arteries. Accurate and early identification of viable myocardium is also important, especially for treatment modalities and prognosis.

Dysfunctional, but viable myocardium has the potential for contractile recovery after reperfusion (1). It is important to distinguish viable myocardium from necrotic tissue in order to

determine preoperatively the benefit of a revascularization procedure. Revascularization may improve ejection fraction and exercise capacity in patients with chronic ischemic left ventricular dysfunction and viable myocardium. In patients with significant viable myocardium, the annual mortality rate was found higher in those treated medically compared to those who had successful revascularization (2). The location of viable myocardium, particularly in the subepicardial location, may have an important influence on long-term ventricular geometry and function (3). The removal of the possible adverse effects of hibernating myocardium on ventricular remodeling,

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electrophysiological stability, and/or diastolic dysfunction may lead to additional improved survival (4). On the other hand, the annual mortality rate after revascularization is higher in patients with no significant myocardial viability when compared to those with viable dysfunctional myocardium (2).

There are several non-invasive methods for assessing myocardial ischemia and viability including positron-emission tomography (PET), single-photon-emission computed tomography (SPECT), dobutamine stress echocardiography, and cardiovascular magnetic resonance imaging (MRI). Cardiac MRI has the unique ability of reliable and accurate assessment of myocardial viability and scar burden, coronary perfusion, and contractile reserve with optimal image quality and low inter- and intra-observer agreement (5-7).

The introduction of gradient-echo MRI made it possible to acquire images of the same plane at multiple time points throughout the cardiac cycle. The images can be viewed on a cinematic display so that cardiac motion can be visualized. Fast gradient-echo techniques with k-space segmentation allow the acquisition of a cine sequence during a breath-hold of approximately 15 seconds. Gradient-echo MRI provides a naturally high level of contrast between intracavitary blood and myocardium permitting exact and reproducible determination of wall thickness and systolic wall thickening, which are indicative of residual viability. MRI is not only limited to observations of regional myocardial function at rest, but also can provide information about functional reserve in response to pharmacologic stress like dobutamine. MRI can detect viable myocardium by analyzing the changes of global and regional function during inotropic stimulation with dobutamine. Dynamic contrast-enhanced MRI can identify viable myocardium by identifying regions with abnormal wash-in/wash-out profiles. Necrosis-specific MRI contrast media can determine the necrotic zone. Tissue perfusion, cellular integrity and cellular membrane function can also be assessed by cardiac MRI.

Delayed-enhancement cardiac MRI

It has been known for many years that regions of acute and chronic myocardial necrosis such as myocardial infarction and myocardial fibrosis exhibit higher signal intensity on T1-weighted MRI following intravenous administration of extracellular contrast agents such as gadolinium-chelate (Gd). Numerous studies of myocardial infarction have been performed using a variety of pulse sequences to differentiate injured from normal myocardium. Delayed-contrast enhanced MRI allows assessment of myocardial viability in patients with acute and chronic ischemic heart disease.

Delayed-enhancement cardiac MRI was first described by Kim et al. (8) in a canine model, where a good correlation was demonstrated between hyperenhancement on MRI and irreversible damage at pathology. Since then, the delayed-enhancement MRI technique is becoming widely used to assess myocardial viability. It has certain advantages over dobutamine stress echocardiography, positron-emission or single-photon-emission computed tomography as it can be

performed under resting conditions and there is no patient exposure to radiation.

Delayed-enhancement MRI can provide information about myocardial viability, contractile reserve, perfusion, metabolism, and electromechanical mapping (9). Typically, the heart is imaged at 15-30 minutes after intravenous administration of Gd and nonviable fibrotic tissue is demonstrated as "hyperenhanced". In myocardium with increased extravascular space or abnormal contrast wash-in and washout characteristics, an increase in the signal intensity in a T1-weighted MRI is observed. It is believed that hyperenhancement of myocardial fibrosis with Gd is due to a combination of delayed wash-in and wash-out kinetics of nonviable tissue and different volumes of distribution of Gd in viable and nonviable regions (10-13) (Fig. 1). Gadolinium-chelate diffuses into interstitial space, but can not pass into intracellular space. There is an increase in the interstitial space due to the loss of sarcomere membrane integrity in acute myocardial infarction or presence of fibrotic tissue in chronic myocardial infarction. After administration of Gd, it diffuses rapidly into the interstitial space. As interstitial space is increased in areas of myocardial scar, an increased volume of distribution of Gd occurs in both chronic and a cutely infarcted myocardium resulting in hyperenhancement relative to viable myocardium (12, 13) (Fig. 2). The hyperenhanced regions have sustained irreversible ischemic injury.

Previously, 2D MRI imaging sequence with high spatial resolution images were used, which was time-consuming and difficult for patients as it was necessitating multiple, successive breath-holds to generate a set of MRI of entire heart. Therefore, 3D acquisition sequences have been developed with which a complete volume can be acquired within one breath hold.

It should be kept in mind that contrast enhancement of the myocardium is not a specific sign for myocardial infarction. The presence of hyperenhancement on postcontrast T1-weighted images only suggests that the normal fluid

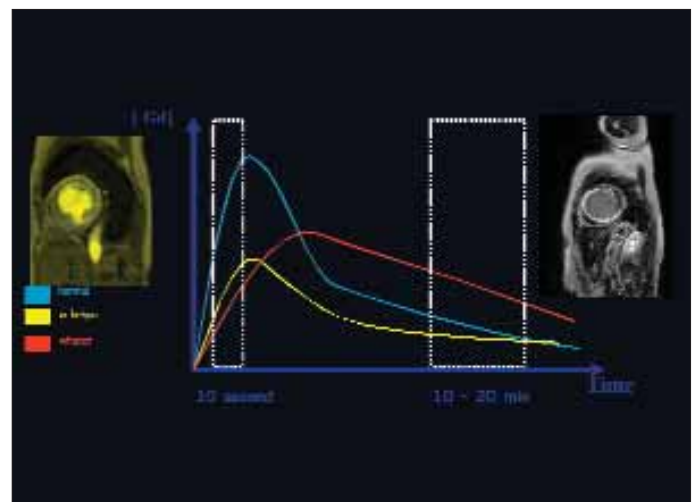


Figure 1. Time course of Gadolinium-chelate during delayed enhancement cardiac magnetic resonance imaging

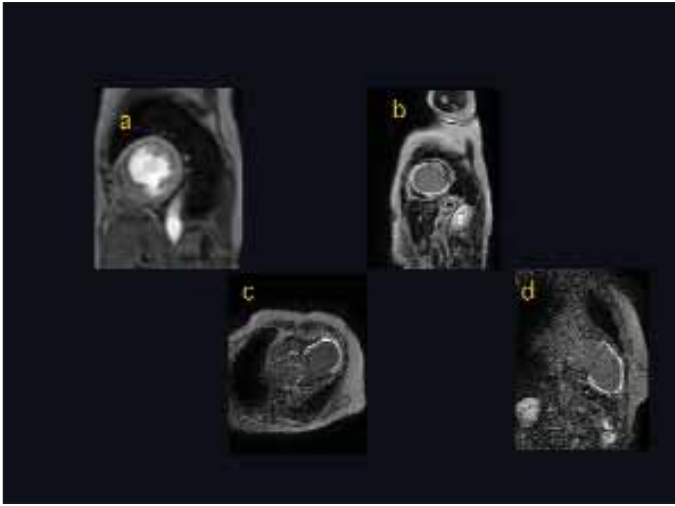


Figure 2. Delayed enhancement cardiac magnetic resonance imaging demonstrating subendocardial first-pass defect a. in the short-axis and multiple hyperenhancement area b. in the short-axis projection, c. 4-chamber projection and d. 2-chamber long axis projection

homeostasis within the heart has been altered due to rupture of cell membranes or ultrastructural changes in myocytes organization. Both interstitial fibrosis and replacement fibrosis hyperenhance similarly. Delayed hyperenhancement has been described in myocarditis, infiltrative cardiomyopathy, pericardial inflammation, hypertrophic cardiomyopathy and cardiac masses (14).

Assessment of myocardial viability and contractile reserve

Delayed-enhancement cardiac MRI gives information about irreversibly injured myocardium. The extent of hyperenhancement on a segmental or regional basis is a critical determinant of contractile recovery (15-17). Rehwald et al. (18) demonstrated that Gd levels were more than doubled in acutely infarcted nonviable areas and were 4-fold higher in chronically infarcted regions compared to remote regions while the concentration of Gd was not elevated after reperfusion in "at-risk" peri-infarction zones. This work confirms that elevations in myocardial Gd are confined to regions of histologically defined irreversible ischemic injury.

In a study by Hillenbrand et al. (17), it was found that when the segmental transmural extent of hyperenhancement was <25%, the majority (87%) of segments improved function, whereas when the extent of hyperenhancement was >75%, functional recovery was unlikely, with intermediate degrees of hyperenhancement resulting in intermediate likelihood of recovery. Similarly, in a study with patients suffering acute myocardial infarction, it was found that the best predictor of global improvement at 2 to 3 months after myocardial infarction was the extent of dysfunctional myocardium without or with <25% hyperenhancement (15). The absence of hyperenhancement in dysfunctional segments had a sensitivity of 82% for predicting contractile recovery (19).

Hyperenhancement is specifically localized to acutely infarcted myocardium and chronic scar tissue and has high accuracy for predicting functional recovery. In addition to hyperenhancement, hypoenhancement is also of clinical importance. Hypoenhancement, which is seen 1 to 2 minutes after contrast injection, defines areas of microvascular obstruction or no-reflow areas. The high spatial resolution of contrast cardiac MRI allows identification of hypoenhanced areas in patients with acute myocardial infarction. Wu et al. (20) found that the hypoenhanced area with microvascular obstruction was a significant marker of postinfarction complications.

Combination of delayed-enhancement cardiac MRI and assessment of segmental wall motions by cine MRI yields better information about contractile reserve. In general, presence of mild degrees of hyperenhancement (<25% of the segment) with normal wall motion or segmental dysfunction indicates that the segment will recover contractile function while presence of higher degrees of hyperenhancement (>75% of the segment) strongly suggests that the segment will not recover contractile function (21). The outcome after revascularization is less clear in dysfunctional segments that show intermediate degrees of hyperenhancement (>25% and <75%).

In cases with intermediate degrees of hyperenhancement, transmural extent of infarction may help to understand if dysfunctional segments are viable and have the ability to recover function. The extent of transmural scarring is associated with the degree of recovery of contractile reserve. In a study by Gerber et al. (9), it was found that segments with transmural hyperenhancement showed no significant inotropic reserve when assessed with low-dose dobutamine-tagged MRI, and nontransmural hyperenhancement was associated with contractile reserve, consistent with residual viability.

Assessment of inotropic reserve with low-dose dobutamine is also important in cases with intermediate degrees of hyperenhancement to define the viable myocardium. The value of assessing inotropic reserve in the detection of viable myocardium by low-dose dobutamine stress echocardiography is well established (22). Recent studies have shown that low-dose dobutamine MRI also enables assessment of coronary viability accurately (23, 24). Dobutamine MRI allows better endocardial definition and substantially reduces the incidence of poor-quality studies (23). Baer et al. (25) showed that both low-dose dobutamine transesophageal echocardiography and low-dose dobutamine MRI had similar positive and negative predictive accuracies for the prediction of left ventricular functional recovery after revascularization.

Dobutamine stimulates the beta-receptors of myocytes and increases the contractility. Two general responses can be detected with dobutamine-stress testing. In the presence of a hemodynamically significant coronary artery stenosis, the increase in blood flow is not sufficient to match the increased myocardial oxygen demand in the area supplied by the stenotic coronary artery. This in turn will cause regional wall motion abnormality at the tissue contracting normally at the rest. The second response seen with dobutamine is directly

related to assessment of myocardial viability in patients with a recent myocardial infarction or chronic left ventricular dysfunction due to coronary artery disease. Tissue that contracts normally during rest can be considered viable, whether or not it is supplied by a stenotic coronary artery. However, a hypokinetic myocardium observed at rest is considered viable (or hibernating myocardium) if dysfunctional segments will functionally improve with low dose dobutamine infusion. Further dobutamine infusion will result in a worsening of segmental function due to the limited contractility reserve.

Viable myocardium in patients with a chronic myocardial infarction is characterized by preserved wall thickness and a dobutamine-inducible contraction reserve. On the hand, scar formation is characterized with wall thinning and absence of dobutamine response. In general, viability is defined as an end-diastolic wall thickness of ≥ 5.5 mm and evidence of dobutamine-induced systolic wall thickening of >1 mm. Cwajg et al. (26) showed that a combination of end-diastolic wall thickness by echocardiography and inotropic reserve had a sensitivity of 88% for detecting viability. They also demonstrated that an end-diastolic wall thickness of 6 mm was associated with no functional recovery.

Coronary flow reserve and metabolism

Impaired coronary flow reserve and metabolic down-regulation are characteristic findings in myocardial hibernation. Thus, assessment of coronary flow reserve and metabolism may help in identification of myocardial hibernation. Coronary flow can be assessed by coronary Doppler flow wire or positron emission tomography (PET). The latter also allows direct quantification of coronary metabolism and has demonstrated clinical importance in assessing metabolic changes of dysfunctional yet viable myocardium. However, PET is expensive and not widely available and coronary Doppler flow wire measurements are invasive and impractical for repeated evaluations. Coronary metabolism, coronary arterial flow and coronary flow reserve can also be measured by cardiac MRI.

To assess the myocardial perfusion with MRI, the first-pass of contrast medium is monitored through the heart. A bolus injection of MRI contrast media is generally used for perfusion studies to obtain pure first-pass transit of contrast through the myocardium. Maximum enhancement, transit time and upslope of enhancement are evaluated. Analysis of the MRI perfusion images can be qualitative, semiquantitative or quantitative. Hundley et al. (27) performed cine velocity-encoded phase-contrast MRI measurements of flow in the left anterior descending coronary artery at rest and after administration of intravenous adenosine and found a good correlation between MRI results and intracoronary Doppler velocity and flow measurements. Nagel et al. (28) demonstrated that MRI-determined perfusion reserve had a sensitivity of 88% and a specificity of 90% in detecting significant coronary stenosis.

An important indicator of myocyte death and lack of cell membrane integrity is loss of Na/K-ATPase function and intracellular-extracellular ion homeostasis. Ionic shift resulting from loss of cellular integrity has been used to study myocyte necrosis. In normal myocardium, the intracellular sodium concentration is usually less than that in the extracellular space because of active transport across intact cell membranes. During ischemia, the intracellular sodium concentration rises and remains elevated in irreversible myocardial injury. Using ^{23}Na MRI, it was shown that regions of acutely or chronically infarcted myocardium were clearly visible as areas of increased signal (29). Kim et al. (30) studied the use of Na^+ imaging and found good correlation with histochemical assessment of infarct size.

Necrosis specific MRI contrast agents have also been investigated. Gadolinium-chelate mesoporphyrins such as Gadophrin-2 and Gadophrin-3 provided strong and persistent enhancement of acutely infarcted tissue on conventional T1-weighted spin-echo images (31). However, chronically injured myocardium did not enhance with necrosis-specific contrast agents, presumably because there are no binding sites in scar tissue (32). Thus, these agents might be useful for studying acute myocardial infarction, infarct healing, and possibly for estimating infarct age in combination with Gd-enhanced MRI. To distinguish reversible from irreversibly injured myocardium, several investigators administered Gd mesoporphyrin and nonspecific extracellular MRI contrast media in a double-contrast imaging protocol. Saeed et al. (33) demonstrated that the size of Gadophrin-2 enhanced regions closely matched the size of infarction defined by histochemical staining while the zone delineated by Gd-DTPA on conventional T1-weighted spin-echo images overestimated the true infarct size but was more closely related to the area at risk. It was concluded that the Gd-DTPA-enhanced region encompassed viable and nonviable portions and that the difference in size demarcated by the two compounds could be used to characterize the peri-infarction zone.

Advantages of cardiac MRI

There are limited prognostic data in patients with myocardial viability as assessed by cardiac MRI. However, there is a wealth of literature on the use of scintigraphic techniques (PET and SPECT) and dobutamine stress echocardiography for identifying high-risk patients who will benefit from revascularization. In general, SPECT perfusion studies and delayed-enhancement cardiac MRI have greater sensitivity but lower specificity for identifying viable myocardium compared with techniques including dobutamine MRI and dobutamine stress echocardiography, which detect contractile reserve (34, 35). Results of contractile reserve with dobutamine protocols are similar in the majority of studies for both dobutamine MRI and dobutamine stress echocardiography.

Delayed-enhancement MRI has shown excellent accuracy in the delineation of scar when compared with scintigraphic

techniques. Klein et al. (36) studied 31 patients with ischemic cardiomyopathy and found a close correlation between the extent of myocardial scar identified by delayed-enhancement MRI and PET. In addition to determination of infarct mass, they also found that delayed-enhancement MRI identified subendocardial scar more frequently than PET and end-diastolic and end-systolic wall thickness and wall thickening at rest in combination with delayed-enhancement MRI gave better results for viability. Similarly, Wagner et al. (37) compared delayed-enhancement MRI with SPECT and found that subendocardial infarcts were detected by delayed-enhancement cardiac MRI in 92%, whereas SPECT detected only 28%.

Mahrholdt et al. (5) compared the clinical reproducibility of infarct size by DE-MRI with the reproducibility of SPECT imaging. They found that the size of chronic infarcts showed no significant change in size between 10 and 30 minutes after contrast administration and compared favorably with quantification by SPECT.

Conclusion

Accurate quantification of areas of scar and viable tissue is clearly important in predicting mortality and identification of patient who will benefit from revascularization. Revascularization of even relatively small areas of dysfunctional, but viable myocardium may be clinically beneficial in selected patients. The excellent spatial resolution and tissue characterization enables MRI to detect viable myocardium accurately. Cardiac MRI provides a unique tool to assess multiple interrelated clinical markers of viability in a single test. Preserved wall thickness and contractile reserve can be assessed by cine magnetic resonance qualitatively and quantitatively. Contrast enhanced MRI provides information on tissue perfusion and cellular integrity and membrane function. Considering the greater spatial resolution compared with PET and the wealth of correlative pathological data, cardiac MRI has the potential to replace or complement other commonly used techniques in the diagnosis of viable and irreversibly damaged myocardium.

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