Role of Imaging in Ablation Therapy of Ventricular Arrhythmias
– Focus on Cardiac Magnetic Resonance Imaging –
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Cardiac magnetic resonance imaging (MRI) has a central role in the management of patients with ventricular arrhythmias. Cardiac MRIs help to identify patients with risk for life-threatening arrhythmias. Delayed enhancement identifies scar tissue within the heart. Because scar harbors the arrhythmic substrate in patients with structural heart disease, areas of delayed enhancement can be targeted in order to eliminate ventricular arrhythmias with catheter ablation procedures. In this article, we will discuss the role of MRI in diagnosing different forms of non-ischemic cardiomyopathy and its role in risk stratification. Furthermore, we will discuss the role of MRI in imaging of the arrhythmogenic substrate in patients with structural heart disease. (Circ J 2012; 76: 1292–1298)

Key Words: Cardiomyopathy; Delayed enhancement; Magnetic resonance imaging; Myocardial infarction; Ventricular arrhythmia

Magnetic resonance imaging (MRI) allows for exact anatomic reconstruction of cardiac anatomy, and can be used in conjunction with delayed enhancement to localize scar tissue. Delayed enhanced MRI is considered the gold standard for imaging of scar tissue (Figure 1). In patients with structural heart disease, ventricular arrhythmias originate from scar tissue. Furthermore, in the presence of ventricular arrhythmias, cardiac MRI helps to rule in or rule out the presence of structural heart disease. In this article, we will focus on the use of delayed enhanced MRI to identify scar tissue in various cardiomyopathies, and the potential value for mapping and ablation of ventricular arrhythmias. Furthermore, we will discuss the value of MRI for ruling out structural heart disease.

Delayed Enhancement
Gadolinium, which is used as a contrast agent, accumulates in areas of scar. It is unable to cross the cell membrane, and in the normal myocardium, tissue volume is mainly intracellular. Therefore, when delayed imaging of the myocardium after administration of gadolinium is performed, the myocardium is unenhanced. In the presence of scar, however, if imaging is performed 10–15 min after contrast administration, contrast material accumulates in areas where extracellular space is increased. In the setting of acute myocardial infarction (MI), myocardial necrosis results in disruption of myocyte membranes, allowing increased space for the distribution of gadolinium. In the setting of chronic MI, collagenous scar tissue has replaced the necrotic tissue and the increase in interstitial tissue increases the volume of distribution for gadolinium, resulting in hyperenhancement. Initial studies used a signal intensity of 2–3 standard deviations (SDs) above normal-appearing myocardium in order to define the presence of delayed enhancement.1 Animal studies in the setting of chronic MI have shown that the presence of delayed enhancement corresponds to irreversibly injured areas as defined by triphenyltetrazolium chloride.1 There is almost exact concordance between the area and shape outlined by delayed enhancement and the histopathology, when high-resolution ex-vivo MRI is performed.1

MRI Technology
A T1-weighted inversion recovery imaging sequence has been designed for use after administration of intravenous gadolinium. The inversion time is chosen individually to null the signal of the normal myocardium. In the setting of acute or chronic MI, gadolinium accumulates in the necrosis/scar zone and presents as a bright or enhanced signal as compared to the normal myocardium, which remains dark or nulled.2 Typically, delayed enhanced sequences are acquired by 2-dimensional (D) imaging. A 3D inversion recovery prepared gradient echo sequence has the advantage of achieving higher spatial resolution, thereby enhancing the ability to detect smaller lesions that might otherwise have been missed by 2D imaging.3

Quantification of Delayed Enhancement
The amount of delayed enhanced tissue in the myocardium increases the volume of distribution for gadolinium, resulting in hyperenhancement. Initial studies used a signal intensity of 2–3 standard deviations (SDs) above normal-appearing myocardium in order to define the presence of delayed enhancement.1 Animal studies in the setting of chronic MI have shown that the presence of delayed enhancement corresponds to irreversibly injured areas as defined by triphenyltetrazolium chloride.1 There is almost exact concordance between the area and shape outlined by delayed enhancement and the histopathology, when high-resolution ex-vivo MRI is performed.1

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has been assessed qualitatively by visual assessment or quantitatively by using different thresholding techniques. The original studies used a signal intensity of 2–3 SDs above that of normal myocardium for the definition of MI or scar tissue. These studies were performed with high-resolution ex-vivo MRI without any cardiac motion. In-vivo imaging, however, results in increased blurring of images due to cardiac motion. In the border zone, if well-demarcated scar tissue borders normal myocardium, averaging areas with normal and abnormal voxels will result in an intermediate signal intensity. This phenomenon is described as partial volume averaging and can affect determination of the scar size; if, for example, a lower SD (eg, SD of 2) is used to define scar, this may result in an overestimation of the scar size due to partial volume averaging in the border zone. Therefore, higher signal intensities (up to 6 SD) have been used for quantification of scar. If, however, there are large areas with intermediate signal intensity, this may result in an underestimation of the scar size. An alternative method for scar quantification uses a threshold >50% of the maximal signal intensity within scar. This method – the full-width-half-maximum method – has shown a good correlation between actual infarct size and imaging-determined infarct extension in an animal study.

**Figure 1.** Inferoseptal myocardial scar in a patient with post-infarction ventricular tachycardia. (Top) Short-axis images of delayed enhanced magnetic resonance imaging of an inferoseptal scar. (Bottom left) 3-dimensional reconstruction of the endocardial scar (red) and the normal left ventricular endocardium (blue). (Bottom right) Electroanatomic map of the inferoseptal scar. The scar is color-coded red, normal myocardium is color-coded purple. The 4 blue tags indicate the isthmus where an effective ablation was performed for this patient’s ventricular tachycardia. (Adapted from Desjardins with permission.)

**Limitations of MRI**

MRI is contraindicated in patients with implanted pacemakers or implanted cardiac defibrillators. Limited data, however, have shown that if appropriate precautions are taken, MRI can still be safely performed in patients with implanted cardiac devices. MRI-conditional pacemakers have been developed and released in the United States. However, image distortion due to artifacts originating from device generators and leads will remain an issue for cardiac imaging.

In the setting of advanced renal failure, patients are at risk of developing nephrogenic systemic fibrosis when exposed to intravenous gadolinium, particularly when the glomerular filtration rate is <30 ml/min.

The low spatial resolution of in-vivo imaging limits identification of the arrhythmogenic substrate in post-infarction patients. The spatial resolution in humans is approximately 1.5x1.8x6 mm. Surviving myocardial bundles are in the submillimeter range, and imaging of these structures remains a challenge. In ex-vivo MRI, spatial resolution is close to the myocyte level, with a spatial resolution of 50x50x50 µm.

Often, only focal delayed enhancement can be identified, and detection of diffuse fibrosis is currently still limited. Be-
cause often the fibrotic process is not as extensive as post-infarction scarring, but instead limited to increased collagenous tissue deposited around individual viable cells, the signal intensity is closer to that of normal tissue.

**Electroanatomic Mapping**

A 3D reconstruction of cardiac anatomy combined with electrophysiological information is the basis for mapping and ablation of complex ventricular arrhythmias. Exact identification of the catheter tip in 3D space, combined with the ability to characterize tissue viability based on bipolar voltage information, has hugely improved our ability to navigate catheters within the cardiac chambers, along with acquiring essential information about tissue integrity. This has proven to be particularly helpful in the presence of arrhythmias originating from scar tissue. Scar tissue can be identified by voltage mapping, and validation studies have confirmed that low voltage corresponds to the presence of scar defined by delayed enhanced MRI (Figure 1). Electroanatomic mapping can be performed if a particular cardiac chamber can be reached and mapped with a mapping catheter, and, therefore, does not face the same limitations and contraindications as cardiac MRI. Adequate catheter contact with the myocardial wall, however, is a requirement for an adequate voltage map.

**MRI and Electroanatomic Mapping**

Integration of both imaging modalities has been used to focus on the arrhythmogenic substrate that is predominantly confined to scar tissue. Image registration has been mainly accomplished post-hoc with customized software, but can also be easily achieved with the vendor-supplied integrated segmentation tool (eg, CARTO Merge). Although analysis is mostly accomplished post-hoc, the registration process can take place during the mapping procedure, focusing the mapping effort on the myocardial scar tissue. This can be accomplished with a positional error <5 mm (Figure 2). Because in most cardiomyopathies arrhythmias originate from scar tissue, registration of the scar not only helps to focus on a particular part of the heart, it can also be used to plan an ablation procedure in patients with scar tissue and ventricular tachycardia (VT); that is, if the scar is predominantly located in the endocardium, an endocardial ablation is most likely to eliminate VT, whereas an epicardial procedure is often required in the presence of scar tissue with an epicardial distribution (Figure 3). In the setting of an intramural scar, ablations from the endocardial and epicardial aspects may be required in order to eliminate VT. Because these procedures can be very complex, adequate planning ahead of time is important for achieving the best possible procedural outcome.

**MRI and Arrhythmogenic Right Ventricular Dysplasia (ARVD)**

Cardiac MRI plays a key role in the diagnosis of ARVD. High-resolution cine imaging is widely considered the gold standard for the quantitative assessment of right ventricular (RV) volume and systolic function. The high spatial and temporal resolution enables a detailed assessment of the RV for regional wall motion abnormalities. The modified Task Force Criteria include an assessment of a combination of RV function and wall mo-
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tion abnormalities. RV volumes have been adjusted for body surface area and sex. Previous criteria that included wall thinning, and fatty infiltrations, as well as wall motion abnormalities such as hypokinesis, have been abandoned for akinetic and dyskinetic wall motions (Figure 4) in order to achieve higher specificity. Fibrofatty tissue has been described in ARVD, and delayed enhanced MRI has also been found to indicate scar tissue in this particular cardiomyopathy. Inducibility of VT does correlate with the presence of delayed enhancement. No series, however, has described the use of MRI in defining the arrhythmogenic substrate in patients with ARVD. Possible reasons include difficulties in imaging the thinner wall of the RV, as well as differences in the optimal inversion times of the RV, if nulling is performed based on the left ventricle (LV). Correlations of abnormalities within the MRI and electrophysiologic findings such as low voltage areas have been done in a qualitative manner in small series of patients.

MRI and Hypertrophic Cardiomyopathy (HCM)

The presence of delayed enhancement in patients with HCM (Figure 5) has been reported to correlate with the presence of ventricular arrhythmias and to be associated with subsequent sudden cardiac death. However, because of the lack of prospective studies with sufficient size and follow-up duration, its discriminant ability as a single risk factor has not been established. A recent meta-analysis of 4 studies involving 1,063 patients with HCM demonstrated that the presence of delayed enhancement correlated with cardiac death, heart failure death, and all-cause mortality and tended to predict sudden death/aborted sudden death. Mapping and ablation procedures of VT have been reported in a few patients with HCM. However, the value of MRI for correlating the location of scar tissue with the origin of ventricular arrhythmias remains to be determined. Although no series has been reported in which MRI was used to map VT in patients with HCM, the finding that the majority of VTs have critical zones in the area where the interventricular septum inserts into the LV–RV junction corresponds to prior reports of MRI data indicating that this is often an area of fibrosis in patients with HCM. Because detailed mapping within the septum has not been performed, it cannot be ruled out that the interventricular septum actually hosts most of the arrhythmogenic substrate.

MRI and Other Forms of Non-Ischemic Cardiomyopathy

Delayed enhanced MRI has been used to differentiate various forms of cardiomyopathy and to be associated with subsequent sudden cardiac death. However, because of the lack of prospective studies with sufficient size and follow-up duration, its discriminant ability as a single risk factor has not been established. A recent meta-analysis of 4 studies involving 1,063 patients with HCM demonstrated that the presence of delayed enhancement correlated with cardiac death, heart failure death, and all-cause mortality and tended to predict sudden death/aborted sudden death. Mapping and ablation procedures of VT have been reported in a few patients with HCM. However, the value of MRI for correlating the location of scar tissue with the origin of ventricular arrhythmias remains to be determined. Although no series has been reported in which MRI was used to map VT in patients with HCM, the finding that the majority of VTs have critical zones in the area where the interventricular septum inserts into the LV–RV junction corresponds to prior reports of MRI data indicating that this is often an area of fibrosis in patients with HCM. Because detailed mapping within the septum has not been performed, it cannot be ruled out that the interventricular septum actually hosts most of the arrhythmogenic substrate.
form adequate scar imaging with cardiac MRI to assess the etiology of the cardiomyopathy prior to implantation of a cardioverter defibrillator.

Identification of scar tissue in patients with idiopathic dilated cardiomyopathy or cardiac sarcoidosis has been useful in assisting with mapping and ablation of ventricular arrhythmias.\textsuperscript{14} We demonstrated\textsuperscript{14} that the location of the scar corresponds to the location of the arrhythmogenic substrate (Figure 3). If the scar was located endocardially, all arrhythmias were mapped to the endocardium. In the case of an epicardial scar, the origin of the arrhythmias was always in the epicardium, but in the case of intramural scars, only arrhythmias in which the scar extended to the endocardium or epicardium could be mapped and ablated from the endocardium or epicardium, respectively. Because mid-wall delayed enhancement is the hallmark of idiopathic dilated cardiomyopathy, the findings of this study explain the lower success rate of VT ablation in this subgroup of patients with non-ischemic cardiomyopathy.\textsuperscript{37,38} Our study\textsuperscript{14} highlights the importance of scar imaging in the setting of non-ischemic cardiomyopathy in order to plan and optimize an ablation procedure. If adequate imaging can be performed (ie, there is no contra-indication for cardiac MRI), an epicardial procedure may not be necessary, especially if the scar does not involve the epicardium. Furthermore, our study\textsuperscript{14} demonstrated that VT was only inducible in patients with delayed enhancement. In the remaining patients, a reversible form of cardiomyopathy secondary to frequent premature ventricular complexes (PVCs) was present, and LV function improved after successful PVC ablation. In patients with idiopathic PVCs, the arrhythmogenic substrate could not be detected with delayed enhanced MRI, suggesting that scar tissue is not involved in the arrhythmogenic substrate.

**MRI and Prior MI**

The amount of scar tissue detected by delayed enhanced MRI has been shown to correlate with the presence of inducible VT and prognosis in patients with prior infarctions.\textsuperscript{39,40} Those studies support that there may be a critical burden beyond which spontaneous VT and/or inducible VT tend to occur; the critical burden based on these small reports is in the range of 10–15% of the total LV mass. A prospective study that aimed to assess the value of scar quantification for risk stratification in patients with prior MI ([DETERMINE], (http://clinicaltrials.gov NCT00487279)) was terminated prematurely due to lack of enrollment. Delayed enhanced MRI has been used to iden-
tify the arrhythmogenic substrate in post-infarction patients, confirming that scar tissue harbors the arrhythmogenic substrate in such patients. Myofibers surviving within the infarcted scar have been found to represent the cellular substrate of VT in post-infarction patients. Detection of these myofibers within scar is possible with high-resolution ex-vivo MRI, where a very high special resolution can be achieved in the absence of a moving heart. Schelbert et al in their high-resolution ex-vivo animal study showed that areas of intermediate signal intensity corresponded to surviving muscle bundles within scar. However, when they used retrospective degradation of the MR images to obtain a lower resolution comparable to that of clinical scans, areas of intermediate signal intensity were often due to volume averaging. Further animal experiments where post-infarction VTs were mapped demonstrated that with high-resolution MRI, viable myofibers could be detected within the isthmus area of a post-infarction scar. The isthmus architecture based on this study has been described as complex interwining 3D layers or canals of viable myocardium.

We could demonstrate that in patients with post-infarction ventricular arrhythmias from the papillary muscles, tissue heterogeneity within the papillary muscles contained the arrhythmogenic substrate. Recent clinical reports have also assessed the presence of tissue heterogeneity using different cut-off values for signal intensity within the area of delayed enhancement. No uniformly accepted definition of infarct heterogeneity exists. One method used the signal intensity of 3 SDs beyond the signal intensity of normal myocardium to define the “infarct core”. A signal intensity between 2 and 3 SDs beyond that of the normal myocardium was defined as the “infarct periphery” and there was a correlation between the amount of infarct periphery and cardiovascular death. The full-width half maximum method determines the maximal signal intensity of an area with delayed enhancement, and defines the infarct core as an area where the signal intensity is >50% of the maximal signal intensity and the grey zone as an area with a signal intensity <50% of the maximal intensity, being greater than the peak signal intensity of remote normal myocardium. Tissue heterogeneity was associated with inducibility of VT. Predictive data based on scar heterogeneity have been confirmed in another study that used a different definition for the assessment of heterogeneity, however.

More recently, differences in signal intensities within scar tissue have been correlated with “channels” in the electroanatomical voltage maps of post-infarction patients, and have been found to indicate critical areas for post-infarction VT within the Scar tissue. Lower signal intensities within scar are thought to indicate surviving muscle bundles within dense scar tissue. Caution, however, needs to be taken with this method, because this has not yet been confirmed by other studies. Desjardins et al did not find any differences in signal intensity at sites critical for post-infarction VT compared to other sites within the scar, and volume averaging also may account for lower signal intensities, especially in the border zone of the infarct.

MRI and Frequent PVCs

In a prior study of patients with non-ischemic cardiomyopathy and ventricular arrhythmias, only patients with myocardial scar as defined by delayed enhanced MRI had inducible VT. In the absence of myocardial scar, patients were non-inducible, and the reason for the development of cardiomyopathy was the presence of frequent PVCs. PVC-induced cardiomyopathy is a form of cardiomyopathy that can be reversed by suppression of the PVCs. The absence of scar in the setting of frequent PVCs and cardiomyopathy suggests that the cardiomyopathic process is most likely due to the frequent PVCs, and suppression of the PVCs with medication or ablation of the PVCs should strongly be considered. The presence of scar in the setting of frequent PVCs, however, does not exclude the possibility of a detrimental effect of PVCs resulting in further deterioration of myocardial function. A scar that is out of proportion to the ejection fraction in a patient with frequent PVCs suggests that frequent PVCs may be the reason for the deterioration of cardiac function.

Conclusions

Cardiac MRI is very helpful in identifying the arrhythmogenic substrate in patients with structural heart disease. The presence of delayed enhancement indicates myocardial scar tissue; in a patient with VT, regardless of the type of structural heart disease, delayed enhancement most likely indicates the arrhythmogenic substrate. In the absence of high-resolution MRI that allows adequate imaging in the submillimeter range in the beating human heart, differences in signal intensity may indicate tissue heterogeneity. This may further help to divide the scar into areas that do and do not contain viable myocardium, which will further help to better identify and characterize the arrhythmogenic substrate of VT in patients with structural heart disease.

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References


