Visualization and Temporal/Spatial Characterization of Cardiac Radiofrequency Ablation Lesions Using Magnetic Resonance Imaging

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Background—The purpose of this study was to describe a system and method for creating, visualizing, and monitoring cardiac radiofrequency ablation (RFA) therapy during magnetic resonance imaging (MRI).

Methods and Results—RFA was performed in the right ventricular apex of 6 healthy mongrel dogs with a custom 7F nonmagnetic ablation catheter (4-mm electrode) in a newly developed real-time interactive cardiac MRI system. Catheters were positioned to intracardiac targets by use of an MRI fluoroscopy sequence, and ablated tissue was imaged with T2-weighted fast spin-echo and contrast-enhanced T1-weighted gradient-echo sequences. Lesion size by MRI was determined and compared with measurements at gross and histopathological examination. Ablated areas of myocardium appeared as hyperintense regions directly adjacent to the catheter tip and could be detected 2 minutes after RF delivery. Lesions reached maximum size ≈5 minutes after ablation, whereas lesion signal intensity increased linearly with time but then reached a plateau at 12.2±2.1 minutes. Lesion size by MR correlated well with actual postmortem lesion size and histological necrosis area (55.4±7.2 versus 49.7±5.9 mm², r=0.958, P<0.05).

Conclusions—RFA can be performed in vivo in a new real-time interactive cardiac MRI system. The spatial and temporal extent of cardiac lesions can be visualized and monitored by T2- and T1-weighted imaging, and MRI lesion size agrees well with actual postmortem lesion size. MRI-guided RFA may be a useful approach to help facilitate anatomic lesion placement and to provide insight into the biophysical effects of new ablation techniques and technologies. (Circulation. 2000;102:698-705.)

Key Words: catheter ablation ■ magnetic resonance imaging ■ histopathology ■ fluoroscopy

Since its initial description in 1982,1 radiofrequency ablation (RFA) has evolved from a highly experimental technique to its present role as first-line therapy for most supraventricular arrhythmias, including atrioventricular nodal reentrant tachycardia, the Wolff-Parkinson-White syndrome, and focal atrial tachycardia.2-5 More recently, the clinical indications for RFA have expanded to include more complex arrhythmias that require accurate placement of multiple linearly arranged lesions rather than ablation of a single focus.6 In contrast to catheter ablation of accessory pathways and atrioventricular nodal reentrant tachycardia, for which detailed mapping is necessary to identify appropriate sites for energy delivery, sites for catheter ablation of atrial flutter and atrial fibrillation, for example, are identified almost entirely on an anatomic basis. Although the feasibility of anatomy-based catheter ablation has been demonstrated with standard catheter ablation techniques, these procedures are extremely time-consuming, require prolonged fluoroscopy exposure, and have been associated with a high incidence of complications. For these reasons, there is general agreement that new approaches to facilitate anatomy-based catheter ablation are needed.

The purpose of this study was to explore the potential role of MRI to guide a comprehensive interventional electrophysiology study in vivo. MRI offers several specific practical advantages over other imaging modalities for guiding and monitoring therapeutic interventions, including (1) real-time catheter placement with detailed endocardial anatomic information, (2) rapid high-resolution 3D visualization of cardiac chambers, (3) high-resolution functional atrial imaging to evaluate atrial function and flow dynamics during therapy, (4) the potential for real-time spatial and temporal lesion moni-
toring during therapy, and (5) elimination of patient and physician radiation exposure. No studies to date, however, have evaluated the potential use of MRI to guide ablation therapy in the heart. Accordingly, the purpose of this study was to (1) develop and characterize a novel MR ablation system capable of guidance, delivery, and monitoring of cardiac RF thermal therapy; (2) quantify temporal and spatial MR signal changes in cardiac tissue after RF-induced thermal damage; and (3) correlate MR lesion size with postmortem lesion size and quantitative histological markers of cell death.

Methods

MRI System

Experiments were performed in a short 1.5-T closed-bore real-time interactive cardiac MRI system (Signa LX, General Electric Medical Systems) with a standard cardiac phased-array coil. This new system overcomes the limitations of conventional MR systems that rely on static scanning protocols by providing rapid data acquisition, data transfer, image reconstruction, and real-time interactive control and display of the imaging slice, while allowing for direct access to the groin or neck for catheter insertion and manipulation. The real-time hardware platform consists of a work station and bus adapter that can be added to conventional scanners. Details of this system have been described elsewhere.7,8

RFA System

RFA was performed with a standard clinical RF generator (Atakr, Medtronic) with open-loop control. The generator was located outside the scan room and was electrically interfaced to the animal via nonmagnetic 7F ablation catheters (Bard Electrophysiology). These custom catheters are fabricated with woven Dacron bodies, copper wires, and 4-mm gold electrodes and therefore do not result in image distortion.

A technical limitation of RF energy delivery and electrophysiological signal acquisition in the scanner is electromagnetic interference. Although the frequency of the RF generation unit (~500 kHz) is well below the 64-MHz proton precession frequency at 1.5 T, higher harmonics of the RF signal can produce significant image degradation. To overcome this problem, special RF filters and shielding were designed and constructed to suppress these harmonic signals and permit simultaneous RFA and electrophysiological monitoring during imaging. These multistage, low-pass filters consist of an arrangement of nonmagnetic electrical components that achieve a cutoff frequency of ~10 MHz. The output from the RF generator is directed to the ablation catheter through these fully shielded filter assemblies that pass through an electric patch panel between the scan and console rooms. The dispersive ground electrode consists of a large conductive-adhesive pad that is attached to the skin of the animal to complete the circuit. Intracardiac electrogram (IEGM) tracings were acquired with the same catheters via a large-surface-area skin patch at a power of 20 W for 60 seconds. To avoid electrode coagulum formation, impedance was monitored by an automatic open-loop feedback system that terminated RF delivery if the impedance exceeded 220 Ω. The isolated slice and 2 immediately adjacent slices were then subsequently imaged once every 2 minutes over 20 minutes with a T2-weighted fast spin-echo (FSE) sequence to monitor temporal signal change and lesion growth over time (TR = 5 ms, TE = 68 ms, echo train length = 16, field of view = 22 cm, slice thickness = 7 mm, 256×128 matrix, tip angle = 13°, readout bandwidth = 31.0 kHz). Once electrode-wall contact was visualized and confirmed by IEGM tracings, the catheter was imaged to isolate the optimal tomographic slice containing the catheter electrode. After baseline images were acquired for this slice prescription, RFA was performed in the right ventricle between the distal electrodes and a large-surface-area skin patch at a power of 20 W for 60 seconds. To avoid electrode coagulum formation, impedance was monitored by an automatic open-loop feedback system that terminated RF delivery if the impedance exceeded 220 Ω. The isolated slice and 2 immediately adjacent slices were then subsequently imaged once every 2 minutes over 20 minutes with a T2-weighted fast spin-echo (FSE) sequence to monitor temporal signal change and lesion growth over time (TR = 5 ms, TE = 68 ms, echo train length = 16, field of view = 22 cm, slice thickness = 7 mm, 256×192 matrix, readout bandwidth = 62.5 kHz). After this imaging series (30 minutes after ablation), 0.3 mL/kg of gadolinium-DTPA was administered as a bolus injection into an intravenous line, and the same slice was imaged every 30 seconds over 12 minutes with the same T1-weighted gradient-echo sequence as described above with a tip angle of 40°.

Postmortem Examination

After the experiment, the animals were killed by an overdose of anesthesia, and the hearts were excised and sectioned through the right ventricular lesion into slices corresponding to the tomographic MR imaging slices. Lesion location, morphology, width, length, and transmural extent were determined and recorded at gross examination, and right ventricular lesions were photographed for later comparison with MR images. Sections from thermally damaged tissues were bisected longitudinally and submitted for histological staining (Masson’s trichrome and hematoxylin-eosin). Specimens were then analyzed under light microscopy at ×40 to characterize global morphological changes8 (eg, delineated cell junctions and nuclei and interstitial edema) for determination of the degree of heat-induced cell damage and necrosis.

Data Analysis

To determine the temporal response of cardiac tissue after RF delivery, lesion signal intensity, length, width, and area were
measured directly from MR images with an offline quantitative analysis package (Scion Image for Windows). Each parameter was measured 10 times for each time frame from baseline to 20 minutes after ablation. Mean signal intensity from region of interest (ROI) measurements was then normalized (mean ROI signal intensity at time t divided by the baseline signal intensity) and plotted as a function of time. A similar method was used after gadolinium injection on T1-weighted imaging. In addition, IEGMs were analyzed before and after ablation for changes in signal amplitude and waveform shape. For accurate and consistent determination of MR lesion size by free-hand planimetry, it was necessary to establish quantitative exclusion criteria regarding the spatial distribution of signal intensity through the lesion. This was achieved by rejecting pixel values around the periphery of the lesion that were less than the normal myocardium signal intensity plus 1 SD of the background noise as determined from ROI intensity measurements. Lesion parameters at gross examination were measured independently of MR hand-planimetered lesion parameters and compared.

Statistical Analysis
Changes in mean signal intensity and IEGM before and after ablation were considered significant at a level of \( P < 0.05 \) in a paired t test. Lesion area measurement comparisons between MR and gross examination were analyzed by linear regression with a paired t test at a level of \( P < 0.05 \).

Results

Catheter Placement
An MR fluoroscopy sequence was used to successfully position the nonsteerable catheter at atrial and ventricular target sites in all animals. In 3 animals, MR-guided catheter placement was attempted to target the inferior lateral wall of the right atrium from a jugular access (Figure 2). Images were acquired without breath-hold once every heartbeat with 1-second updates. Details of the right atrial anatomy could be appreciated in all animals, and several major endocardial anatomic landmarks were successfully identified, including the superior and inferior venae cavae, atrial septum, right atrial appendage, coronary sinus, eustachian ridge, fossa ovalis, and tricuspid valve. The catheter remained in the imaging plane throughout the entire navigation sequence in 2 of 3 animals. Contact between the electrode and tissue could be visualized without significant electrode artifact (Figure 2f), and inferolateral wall catheter localization was successful and reproducible in each animal. Right ventricular ablation sites were successfully targeted in all animals, and the electrode-tissue interface was clearly visualized during FGRE imaging (Figure 3a), with visual catheter stability confirmed by high-fidelity IEGMs (amplitude = 10.7 mV) as shown in Figure 3b.

MRI Lesion Visualization and Temporal Signal Response
Lesions were successfully created and visualized at right ventricular target sites in all animals. Ventricular lesions appeared as clearly delineated hyperintense regions directly adjacent to the ablation catheter tip and were detectable 2 minutes after RFA (Figure 4). The lesion signal intensity response is shown in Figure 4c at a temporal resolution of \( \approx 2 \) minutes, with the first 3 time points representing baseline myocardial signal intensity before ablation. Mean intensity increased linearly over the first 10 minutes and was then followed by a plateau. Mean FSE signal intensity 15 minutes after ablation was \( 1.9 \pm 0.4 \) times greater than the baseline signal intensity.
myocardial intensity ($P<0.05$), and the mean time to signal plateau was $12.2\pm 2.1$ minutes. FSE imaging time averaged 1.72 minutes for a 2-slice acquisition. Approximately 30 minutes after this imaging protocol, FGRE images of the same tomographic slice were acquired before and after injection of 7 mL peripheral gadolinium (Figure 5a and 5b). The lesion border was clearly demarcated 60 seconds after contrast injection. Intensity-versus-time data for the contrast-enhanced lesion (temporal resolution $\approx 30$ seconds) indicated a rapid initial uptake of gadolinium and a gradual washout over the next several minutes (Figure 5c). Data for an adjacent region of native myocardium indicated a significantly lower level of enhancement that followed a similar temporal course over the same imaging interval ($1.13\pm 0.12$ versus $1.55\pm 0.16$, $P<0.05$). Under MR fluoroscopy guidance, the catheter was moved from the right ventricular apex and repositioned on the right ventricular free wall. FSE images before and after RF delivery are shown in Figure 6 with the respective IEGM tracings. A large lesion was visualized directly adjacent to the ablation catheter tip and demonstrated a temporal response similar to those measured in right ventricular apex lesions, with peak intensity occurring $\approx 11$ minutes after ablation. IEGM amplitude decreased from a mean preablation value of 10.3$\pm 3.1$ mV to 2.2$\pm 3.3$ mV after RF delivery ($P<0.05$). Figure 7 is a series of lesion profile plots that characterize the spatial and temporal formation of ventricular lesions. A lesion profile is simply a plot of signal intensity over a fixed spatial domain passing through the lesion, as illustrated by Figure 7a for a single time frame. The 3-D surface plot represents a series of these profiles in time, where the z axis represents the color-coded signal intensity and the x and y axes represent position and time after RF delivery, respectively. The lesion grew dramatically in signal intensity and size from the baseline level shown by the arrow. Maximum signal intensity and lesion area were achieved $12.2\pm 2.1$ and $5.3\pm 1.4$ minutes after RF delivery, respectively.

**Correlation With Gross and Histopathological Examination**

Direct visual comparison of right ventricular lesions at gross examination and those derived by MR 10 minutes after ablation demonstrated similar lesion geometries (Figure 8). Lesion width and length measured at gross examination correlated well with MR-derived measurements (width: $6.7\pm 0.5$ versus $7.1\pm 0.9$ mm, $P<0.05$; length: $9.4\pm 1.5$ versus $9.9\pm 0.9$ mm, $P<0.05$). MR lesion depth could be assessed quantitatively in 3 animals and also agreed well with gross examination measurements (depth: $3.4\pm 2.1$ versus $3.1\pm 1.2$ mm, $P<0.05$). All lesions were composed of a series of 3 concentric elliptical zones of damage: a dark inner portion representing a region of coagulative necrosis (zone 1), a surrounding pale peripheral circular zone of hemorrhage that extended $\approx 4$ mm from the center of the lesion (zone 2), and an outermost area consisting of a thin purple rim.
extending an additional 2 to 3 mm (zone 3). Low-power trichrome-stained histological specimens clearly demarcated the pathological lesion from native undamaged tissue in all animals. A strong agreement and correlation were observed (Figure 9) between the spatial extent of right ventricular MRI-derived lesions and the actual extent of damage measured at gross and histopathological examination (55.4±7.2 versus 49.7±5.9 mm, r=0.958, P<0.05).

Discussion

Main Findings
In this study, we describe a novel MRI-compatible interventional electrophysiology hardware system used in conjunction with a newly developed real-time interactive cardiac MRI system to characterize the temporal and spatial development of cardiac lesions after RFA. Our findings indicate that (1) MR images and IEGMs can be acquired during RFA therapy by use of specialized RF filters, (2) nonmagnetic MR-compatible catheters can be successfully placed at right atrial and right ventricular targets by use of fast MR imaging sequences with interactive scan plane modification, (3) regional changes in ablated cardiac tissue are detectable and can be visualized with FSE and FGRE images, and (4) the spatial extent of heat-induced necrosis can be accurately quantified by MRI immediately after thermal damage. These results may have significant implications for the guidance, delivery, and monitoring of cardiac ablation therapy by interventional MRI.

MR-Guided Catheter Placement
Right atrial and ventricular sites were successfully targeted in all animals by use of nonsteerable catheters with real-time MR fluoroscopy pulse sequences. The high-resolution images of endocardial anatomy combined with the ability to interactively modify the scan plane considerably improved targeting and accurate lesion placement, because standard fluoroscopic views could be defined in real time by use of a graphical interface. Accurate atrial catheter placement has clinical importance for the study of a variety of supraventricular arrhythmias as the relationship between endocardial anatomy and arrhythmia substrate becomes increasingly appreciated. Current techniques to map and identify arrhythmogenic foci are based on low-resolution voltage maps generated by catheter movements under x-ray fluoroscopy. In addition to limited anatomic information, catheter manipulation under x-ray fluoroscopy can be arduous and poorly reproducible. Anatomic MRI-guided electrophysiological mapping may significantly improve the localization accuracy of critical arrhythmogenic substrate and allow acquisition of true electroanatomic data.

Another important feature of MR-guided catheter placement is the ability to visualize the electrode–endocardial tissue interface, which has been shown to increase lesion size by improving the efficiency of RF tissue delivery. Although traditional indicators of electrode contact, such as fluoroscopic catheter stability and IEGM amplitude, are useful, these parameters are relatively insensitive indicators of electrode-tissue contact. An important limitation of passive MR catheter tracking, however, is the need to manipulate the catheter within the imaging slice (typically 5 to 10 mm wide), which may be especially difficult during catheter placement in geometrically complex vessels and cardiac chambers, in which catheter curvature and loops are common. To improve the accuracy of MRI catheter positioning, we are currently developing active tracking techniques that provide the x, y, z space coordinates of the ablation catheter tip, which can then be superimposed on interactive 3D images of the atrial chambers.

In Vivo Lesion Visualization
Perhaps one of the greatest advantages of MRI-guided therapy is the ability to visualize and monitor lesion formation with high temporal and spatial resolution. In this study, right ventricular lesions were created and visualized with both a T2-weighted FSE sequence and a gadolinium-enhanced T1-weighted FGRE sequence. Lesions imaged with FSE appeared immediately as elliptical, hyperintense regions directly adjacent to the catheter tip; however, zones of reversible and irreversible damage were not visible. FGRE contrast-enhanced lesions 30 minutes after ablation showed...
rapid uptake of gadolinium after injection and represented the affected area similar to FSE images. The mechanisms of lesion enhancement for these 2 sequences are quite different and may lend insight into the biophysics of in vivo tissue damage and lesion formation.

**FSE Imaging**

MRI is able to detect 1 or more specific changes in T1 and T2 relaxation parameters resulting from heat-induced biophysical changes in cardiac tissue, such as interstitial edema, hyperemia, conformational changes, cell shrinkage, and tissue coagulation. Reviewing this general inventory of effects in the context of parameters detectable by MRI, acute interstitial edema is most likely responsible for the hyperintense regions representing the spatial extent of the anatomic lesion. The delayed lesion response after ablation over 10 to 12 minutes is consistent with the temporal physiology of local acute interstitial edema and probably represents the time required for hydrostatic and osmotic capillary pressures to equilibrate.

**Contrast-Enhanced FGRE Imaging**

Although ablation lesions were not visible by T1-FGRE imaging alone, the spatial extent of the lesion was clearly demarcated with this sequence after peripheral administration of gadolinium-DTPA. This enhancement is distinctly different from the dynamic lesion detection described for T2-FSE images and can be explained by considering the physical and physiological mechanisms by which gadolinium achieves enhanced signal intensity in injured myocardium. Gadolinium-DTPA exerts its signal-enhancing effect by interacting with water protons and inducing a shorter T1 relaxation time. In uninjured myocardium, this large molecule cannot penetrate cell membranes and is therefore restricted to the extracellular space. After endocardial ablation, however, damaged/ruptured cell membranes allow diffusion and penetration of the contrast agent into the intracellular space.

**Figure 7.** a. Right ventricular apex lesion showing spatial location of intensity profile line and (b) resulting intensity vs location data for a single point in time during temporal assessment of lesion. c. 3D surface plot showing temporal and spatial development of right ventricular lesions, created by plotting several intensity profiles in time. Maximum lesion size and peak signal intensity occurred ~5 and 12 minutes after ablation, respectively.

**Figure 8.** Direct visual comparison of right ventricular apex lesion appearance (a) at gross examination and (b) by MRI. Abbreviations as in previous figures.

**Figure 9.** Comparison of MR and postmortem lesion area.

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\begin{align*}
    y &= 0.8049x + 0.1367 \\
    \text{p}<.05, \quad r &= 0.938
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significantly increasing the volume of distribution for the contrast agent and resulting in a “brighter” voxel of tissue on T1-weighted images. For practical implementation, FGRE imaging is preferable to FSE for cardiac ablation therapy, because imaging times are decreased significantly and quality images may be acquired without cardiac and respiratory gating.

Comparison With Other Imaging Modalities

Several studies have demonstrated the utility of intracardiac ultrasound for guiding cardiac ablation therapy and visualizing thermal lesions in vitro. A recent study by Epstein and colleagues compared intracardiac ultrasound to fluoroscopy guidance for creating linear right atrial lesions in a canine model and showed that intracardiac ultrasound significantly improved targeting, energy delivery, and lesion formation. Although these reports are promising, the limitations of this approach include relatively poor spatial resolution, only limited views of the left and right atrium, the inability to distinguish multiple intracardiac catheters, the need for complementary x-ray fluoroscopy, and the inability to accurately quantify the spatial extent of the thermal damage in vivo. Direct in vivo visualization of right atrial anatomy and RF lesions with fiberoptic probes, in which thermal damage is monitored on the basis of heat-induced myocardial color changes, has also been performed successfully. In addition to the relatively small field of view produced by the probe, this methodology is subjective and does not accurately represent irreversibly damaged tissue.

MRI is not subject to the aforementioned limitations, but it does have a number of technical challenges to overcome before widespread use can be realized. Specialized hardware required for MRI-guided interventional electrophysiology studies, such as nonmagnetic catheters, monitoring equipment, and electromagnetic filtering systems, is generally not commercially available. In addition, although new advances in scanner hardware have allowed for real-time MR imaging (20 frames per second), passive catheter tracking can be confounded by complex catheter movements that cause the catheter to leave the imaging plane. Finally, the delayed nature of lesion formation after the initial RF delivery may confound instantaneous online assessment of lesion size. Online assessment of lesion size is possible during MRI-guided ablation but would require 3- to 5-minute pauses between RF deliveries to allow the lesion to reach maximum size. Despite these limitations, MRI offers several unique advantages for guiding cardiac interventions and may improve both the efficacy and safety of cardiac ablation therapy.

Clinical Implications

Although the approach described in this report has application for all cardiac arrhythmias curable by RFA, it may be particularly well suited for more complex arrhythmias that require the accurate placement of multiple, linearly arranged lesions (eg, atrial flutter, ventricular tachycardia complicating coronary artery disease, and reentrant atrial tachycardia after surgery for congenital cardiac disease) rather than ablation of a single focus. The area of highest potential impact for MR-guided interventional electrophysiology, however, is in the management of atrial fibrillation. In addition to improved anatomic targeting of critical focal sites, the ability to directly visualize the spatial extent of atrial lesions with high spatial resolution may help facilitate the placement of linear transmural atrial lesions and allow for real-time interactive detection and elimination of skip lesions. This potential may have particular importance, because it has been shown that ablation lines with skip lesions are not only ineffective but possibly arrhythmogenic. In addition, the ability to characterize the temporal evolution of lesions can be used for therapy titration and avoidance of damage to tissue outside the ablation target volume (although the observed delayed biophysical response of the lesion may confound instantaneous assessment of lesion size). These combined advantages may reduce the number of lesions required for conduction block, procedure times, and the risk of perforation, all without ionizing radiation.

Conclusions

These studies have, for the first time, demonstrated that RF cardiac ablation can be performed under MRI guidance in vivo. Catheters are clearly defined and easily positioned in gradient-echo images, and the spatial and temporal extent of ventricular ablation lesions can be accurately visualized by T2-weighted FSE imaging and T1-weighted contrast-enhanced fast-gradient-echo imaging with a standard cardiac phased-array thoracic coil. In addition, lesion size by MRI agrees well with actual postmortem lesion size, and high-fidelity intracardiac electrophysiological signals can be acquired and monitored during imaging. MRI-guided cardiac ablation may be a useful technique to guide interventional electrophysiology studies that will eliminate ionizing radiation exposure; will help provide accurate therapy titration and facilitate the creation of linear, contiguous, and transmural lesions; and may lend insight into the physiological effects of novel ablation techniques and technologies.

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References


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