Acute Pulmonary Vein Isolation Is Achieved by a Combination of Reversible and Irreversible Atrial Injury After Catheter Ablation Evidence From Magnetic Resonance Imaging

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**Background**—Pulmonary vein reconnection after pulmonary vein isolation is common and is usually associated with recurrences of atrial fibrillation. We used cardiac magnetic resonance imaging after radiofrequency ablation to investigate the hypothesis that acute pulmonary vein isolation results from a combination of irreversible and reversible atrial injury.

**Methods and Results**—Delayed enhancement (DE; representing areas of acute tissue injury/necrosis) and T2-weighted (representing tissue water content, including edema) cardiac magnetic resonance scans were performed before, immediately after (acute), and later than 3 months (late) after pulmonary vein isolation in 25 patients with paroxysmal atrial fibrillation undergoing wide-area circumferential ablation. Images were analyzed as pairs of pulmonary veins to quantify the percentage of circumferential antral encirclement composed of DE, T2, and combined DE+T2 signal. Fourteen of 25 patients were atrial fibrillation free at 11-month follow-up (interquartile range, 8–16 months). These patients had higher DE (71±6.0%) and lower T2 signal (72±7.8%) encirclement on the acute scans compared with recurrences (DE, 55±9.1%; T2, 85±6.3%; P<0.05). Patients maintaining sinus rhythm had a lesser decline in DE between acute and chronic scans compared with recurrences (71±6.0% and 60±5.8% versus 55±9.1% and 34±7.3%, respectively). The percentage of encirclement by a combination of DE+T2 was almost similar in both groups on the acute scans (atrial fibrillation free, 89±5.4%; recurrences, 92±4.8%) but different on the chronic scans (60±5.7% versus 34±7.3%).

**Conclusions**—The higher T2 signal on acute scans and greater decline in DE on chronic imaging in patients with recurrences suggest that they have more reversible tissue injury, providing a potential mechanism for pulmonary vein reconnection, resulting in arrhythmia recurrence. (Circ Arrhythm Electrophysiol. 2012;5:691-700.)

**Key Words:** ablation ■ atrial fibrillation ■ magnetic resonance imaging ■ pulmonary vein reconnection ■ reversible tissue injury
diffuses into the intracellular space after the loss of cell membrane integrity associated with acute tissue destruction, it can also accumulate acutely in the increased extracellular space created by myocardial edema, which may represent a reversible form of cardiac injury and is, therefore, not specific to necrotic tissue. An alternative method to visualize myocardial edema uses the linear relationship between T2 relaxation time and myocardial water content and may be a more sensitive in vivo marker of myocardial edema than DE MRI.

The aim of the study was to use DE+T2-weighted CMRI to characterize the tissue effect of left atrial ablation and to relate the pattern of acute atrial injury to clinical outcome. We hypothesize that acute PVI is caused by a combination of irreversible tissue destruction and reversible tissue injury at the LA-PV junction.

Methods

Patient Population
Twenty-five patients (17 men; mean age, 55±11 years) with symptomatic, drug-refractory paroxysmal AF undergoing their first PVI completed the study. Twenty-nine patients agreed to the study, but 4 were excluded (3 because of claustrophobia with failure to complete scan and 1 because of an ineffective respiratory navigator). All scans used for the purposes of data analysis were deemed of adequate quality for analysis by an experienced CMR operator. Therapeutic anticoagulation with an international normalized ratio >2 for at least 4 weeks before the procedure was mandated. The study was approved by Guy’s and St Thomas’ Hospitals Research Ethics Committee.

Ablation Procedure

Acute procedural success was defined as PVI confirmed using a circumferential mapping catheter. Clinical outcomes are reported at 6-month follow-up. Patients were followed up in a clinic to assess symptoms. Twenty-four-hour Holter monitors were used at 6 months. Every effort was made to obtain ECG recordings of symptomatic recurrences. Recurrences were defined on the basis of (1) symptoms with ECG evidence of the presence of AF/flutter/tachycardia; or (2) the presence of symptomatic or asymptomatic episodes of atrial arrhythmia lasting for >30 seconds on ambulatory cardiac monitoring.

MRI Acquisition

All participants underwent MRI in a 1.5-Tesla Philips Achieva MR system (Philips Healthcare, Best, the Netherlands), using either a 32-channel surface coil (Invivo, Orlando, FL) or a large 2-channel feed coil.

T2-weighted images were acquired using a multislice turbo spin echo technique, with a double inversion recovery prepulse for black-blood imaging. Spatial presaturation with inversion recovery fat suppression was applied. The echo time used was set at 120 ms, with linear profile ordering. This enabled the image resolution to be set at 1.5x1.5 mm², with a slice thickness of 5 mm. The number of slices was set to provide complete coverage of the left atrium (20–25 slices). Diaphragmatic motion was tracked, and respiratory motion correction was applied to minimize motion blurring and differences in respiratory phase between slices during image acquisition.

To visualize DE, a 3-dimensional ECG-triggered, free-breathing inversion recovery turbo field echo scan with respiratory navigator motion correction was performed with a pixel resolution of 1.3x1.3x4 mm³, which was then reconstructed to 1.3x1.3x2 mm³. Data were acquired at mid-diastole, with a 150-ms acquisition window and a low-high k-space ordering, as well as spatial presaturation with inversion recovery fat suppression. The inversion recovery delay time was determined from a Look-Locker sequence and was set at a TI intermediate between the optimal TIs to null myocardium and blood. Previous work has validated this method for reproducible visualization of the late enhancement signal from necrotic tissue. DE scans were performed 20 minutes after contrast agent administration. The number of slices was set for complete atrial coverage (30–40 slices).

Follow-up times are reported as the median and interquartile range. Categorical variables were compared between recurrence and non-recurrence groups using a χ² test. The percentage of circumferential encirclement by DE, T2, and DE+T2 was determined independently by both readers, and a consensus was reached. High degree of interobserver agreement was seen on a Bland Altman test, with a maximum observed difference of 10% seen. The mean±SD interobserver error for DE, T2, and DE+T2 was 1.5±2.5%, 1.5±3.5%, and 0.8±2.2%, respectively, which was acceptable for the purposes of data analysis.

Statistical Analysis

Summaries for continuous variables are expressed as mean±CI. Follow-up times are reported as the median and interquartile range. Categorical variables were compared between recurrence and non-recurrence groups using a χ² test. The percentage of circumferential encirclement by DE, T2, and DE+T2 groups was compared to test for differences between group means. Statistical analyses were performed using Stata (StataCorp 2009). A linear regression model with
predictor (code 1 for nonrecurrence and 0 for recurrence) and outcome T2, DE, T2 and DE, DE/(T2 and DE), respectively, was applied and run in Stata. We used the vce (cluster subject) option in Stata12 to allow for intersubject dependence (left PV [LPV] and right PV [RPV] measurements from the same patient). Analyses for acute and chronic PV findings on CMRI were performed separately. *P* < 0.05 was considered statistically significant.

**Results**

**Patient and Procedural Data**

The Table outlines the baseline study population demographics. Successful PV isolation was achieved in all patients. Median follow-up time was 11 (interquartile range, 8–16) months. A 3-month blanking period was observed, during which arrhythmia recurrences were treated with antiarrhythmic drugs or direct current cardioversion. No repeat ablation was performed within the blanking period. Clinical recurrence of AF was documented in 11 (46%) patients, with a median time to recurrence of 94 (interquartile range, 45–166) days. Patients with recurrences had significantly larger LA size and longer duration of AF. Seven of 11 patients with recurrences underwent a redo procedure; 2 patients are awaiting a redo procedure, and 2 declined further intervention. Procedural complications include 2 femoral venous hematomas, which did not require intervention. No stroke, tamponade, or esophageal fistula occurred in this study. The absence of both turbulence on MR angiography and luminal narrowing in comparison with the prescans confirmed no PV stenosis on follow-up MRI scans.

**Preablation MRI**

The circumferential burden of DE+T2-weighted signal detected before any ablation was low in comparison with acute postablation imaging (Figure 2) and did not occupy >5% of the PV circumference. The median time of image acquisition in relation to the procedure was 3 (interquartile range, 1–10) days. Preablation DE signal localized to the mitral annulus, a common finding because of the fibroelastic nature of cardiac tissue at this site. T2 signal was largely observed around the atrial roof, and this is likely explained by the imperfections arising from the MR sequence. In black-blood sequence, residual bright blood signal is observed in areas of slow through-plane flow (eg, in the apex of the ventricles). This problem has been reported in acute edema assessment in the ventricles after acute myocardial infarction.13 Overall, the amount of T2 signal preablation was very small.

**Postablation MRI**

All acute imagings were performed between 18 and 24 hours after catheter ablation. Figure 2 demonstrates the typical T2-weighted (Figure 2A) and DE (Figure 2B) appearances in 2 patients before and after catheter ablation. The left atrial burden of DE+T2-weighted signal was significantly increased after catheter ablation in comparison with baseline (Figure 2). On the acute scans, DE signal was concentrated in the PV...
antral region, whereas T2 signal was more widely distributed in the atrium, remote from sites of ablation.

Individual analysis of the circumferential extent of both signal types revealed that the T2-weighted signal occupied 100% of the antral circumference in 5 of 50 PV pairs, whereas the DE signal did not achieve complete encirclement of any vein pair. There was no significant difference between the circumferential extent of the DE signal around the LPVs (mean, 65%; CI, 56.4–73.6%) and the RPVs (63%; 55.4–70.6%; P=0.67).

Similarly, although the circumferential extent of the T2 signal was greater, there was no significant difference between LPVs (75%; 66.6–83.4%) and RPVs (80%; 73.0–87.0%; P=0.31).

Combined analysis of DE+T2 signals, using reconstructed shells codisplaying both signal types, revealed areas of T2 enhancement to overlap and interdigitate with those areas of high DE signal intensity (Figure 3). Hence, the sum of DE+T2 is ≤100%. For the LPVs, the circumferential extent of the DE signal, T2 signal, and the combination of both
Figure 3. A and B. A series of reconstructed 3-dimensional left atrial shells to visualize T2 and the delayed enhancement (DE) signal in patients shown in Figure 2. The 3 columns represent the 3 time points: preprocedure scans (prescans; column 1), acute postprocedure scans performed within 18 to 24 hours (column 2), and the late scans performed later than 3 months (column 3). Quantification of these enhancements was performed as percentage encirclements of the left and right pulmonary vein antra. Row A depicts the raw intensities mapped on to the shells from the T2 and DE magnetic resonance scans. Row B shows the corresponding T2 and DE 3-dimensional shells that have been thresholded semiautomatically. Red areas signify delayed enhancement, and blue areas signify T2 signal intensity. In row C, the combined enhancement of T2 and DE is seen together. On the acute scans seen in column 2, gaps present within areas of red (DE) are filled in by areas of blue (T2). In column 3, the blue (T2) and red (DE) signals resolve, with a greater effect seen for T2 versus DE signal. C. The electroanatomical maps in relation to the corresponding acute and late postprocedure 3-dimensional left atrial shell for the 2 patients.
signal types was 65% (56.4–73.6%), 75% (66.6–83.4%), and 90% (86.1–94.9%), respectively. For the RPVs, the circumferential extent of the DE signal, T2 signal, and the combination of both signal types was 63% (55.4–70.6%), 80% (73.0–87.0%), and 92% (86.4–97.6%), respectively. Compared with DE alone, the combined DE+T2 signal was significantly greater for both LPV ($P=0.009$) and RPV ($P=0.027$). Complete antral encirclement with combined DE+T2-weighted signals was seen in 17 of 50 (34%) PV pairs at the acute scan.

As seen on the chronic follow-up scans, the T2 signal had largely resolved (Figure 4), whereas a decline in the extent of the DE signal was seen. For the LPVs, the circumferential extent of the DE signal decreased from 65% (56.4–73.6%) to 51% (42.8–59.2%; $P=0.016$); for the RPVs, the circumferential extent of DE decreased from 63% (55.4–70.6%) to 46% (37.5–54.5%; $P=0.002$). Discontinuities in areas of the DE signal could be seen.

Recurrences of AF: Relationship to MR Assessment
Both acute and late scan data were divided into 2 groups according to the respective clinical outcome—those with and without AF recurrences. One hundred pairs of PVs (50 acute, 50 late) analyzed previously were divided into 2 groups according to the presence or absence of a clinical recurrence of AF. Figure 5 summarizes the percentage of circumferential encirclement of DE, T2-weighted signal, and the combination of DE+T2 around the LPV and RPV pairs by clinical outcome for both the acute and late scans.

### Table. Patient Demographics Categorized Into No Recurrences and Recurrences at 6-Month Clinical Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (n=25)</th>
<th>No AF Recurrence (n=14)</th>
<th>AF Recurrence (n=11)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58±10.7</td>
<td>49±12.4</td>
<td>55±10.8</td>
<td>0.46</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>17 (67)</td>
<td>11 (78)</td>
<td>6 (55)</td>
<td>0.60</td>
</tr>
<tr>
<td>Female (%)</td>
<td>8 (33)</td>
<td>3 (22)</td>
<td>5 (45)</td>
<td>0.68</td>
</tr>
<tr>
<td>Duration of AF, mo</td>
<td>28±16</td>
<td>18±10</td>
<td>30±11</td>
<td>0.04</td>
</tr>
<tr>
<td>(12–60)</td>
<td>(12–48)</td>
<td>(18–60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA size, cm</td>
<td>3.7±0.5</td>
<td>3.4±0.2</td>
<td>4.2±0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>55±5</td>
<td>60</td>
<td>50</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Valve disease</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>History of smoking</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Thyroid disease (%)</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (9)</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Previous ablation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial flutter (%)</td>
<td>5 (20)</td>
<td>2 (14)</td>
<td>3 (27)</td>
<td>&gt;0.10</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction.

Figure 4. This scatter boxplot shows a comparison of pre-, acute, and late T2, delayed enhancement (DE), and combined T2 and DE for both left and right pulmonary vein (PV) antrum. Each individual scatter plot represents the raw data for that specific group. The dots within each group have been dispersed horizontally to optimize visualization and clarity. The boxplots on the other hand represent median (red line), 95% CIs (yellow box), and 1 SD (blue box). An overall higher enhancement is seen in all 6 groups on the acute scans compared with the 6 groups on the chronic scans. The percentage of encirclement by T2 signal diminishes from >75% to <5% in keeping with reversible injury. The percentage of encirclement by DE signal diminishes to a much lesser extent. Using a combination of DE+T2 signal, the percentage of encirclement decreases from 90% at the acute scans to <50% at the follow-up scan. The categories on the X axis are composed of 3 elements: The first corresponds to the measure on the MRI scan (T2 or DE), the second is the time of the scan (P indicates pre; A, acute scan after ablation; L, late scan after ablation). The third represents left-sided veins (L) or right sided veins (R).
On the acute scans, there was no difference in the combined DE+T2 signal between both groups, with a mean percentage encirclement of 89% (83.6–94.4%) in the nonrecurrence group and 92% (87.2–96.8%) in the recurrence group. When the DE signal was analyzed, a significantly higher mean percentage encirclement was noted in the AF-free group (mean, 71%; CI, 65.0–77.0% versus 55%; 45.9–64.1%, respectively; P=0.016). Conversely, the T2 signal was noticeably lower in the AF-free group compared with the recurrence group (mean, 72%; CI, 64.2–79.8% versus 85%; 78.7–91.3%, respectively; P=0.038). With the combined areas of DE+T2 forming almost complete rings around the PVs, ratios of DE to (DE+T2) were calculated. Patients with no recurrences had a higher mean DE/(DE+T2) ratio compared with the recurrence group (0.82±0.12 versus 0.58±0.20; P=0.0001).

On the late scans, DE was the predominant signal type seen and was significantly greater in the AF-free group compared with the recurrence group (mean, 60%; CI, 54.3–65.7% versus 34%; 26.7–41.3%, respectively; P<0.0001). A comparison of the acute and late scan DE data in both groups showed a lower regression of this signal type in the AF-free group (from mean, 71%; CI, 65.0–77.0% to 60%; 54.3–65.7%; P=0.03) relative to the group with arrhythmia recurrences (from mean, 55%; CI, 45.9–64.1% to 34%; 26.7–41.3%; P=0.01).

Discussion

The findings of this article are as follows: (1) acute PV isolation is not associated with complete circumferential injury as determined by CMRI performed at a median of 20 hours after ablation; (2) increased DE+T2-weighted signals are both seen within 24 hours of left atrial catheter ablation; (3) the T2-weighted signal has largely resolved by 3 months of follow-up, supporting its use as a marker of acute, reversible atrial injury; and (4) in patients with clinical recurrences, a greater proportion of the acute circumferential atrial injury is accounted for by the T2-weighted signal than in arrhythmia-free patients.

Previous works evaluating the role of CMRI in LA assessment after catheter ablation has focused on delayed enhancement imaging delineating areas of scar before and after ablation. However, MRI of acute, reversible atrial injury after catheter ablation has only been recently reported. There is evidence from animal studies that tissue edema causes right atrial wall thickening after linear ablation in the right atrium. Left atrial edema most likely occurs during and immediately after AF ablation, as evidenced by an increase in atrial wall thickness, and resolves within 1 month. During late-gadolinium MRI performed immediately after ablation, both nonenhancing and hyperenhancing tissue types are seen, the former being a poor predictor of scar visualized at 3-month follow-up. This is likely to reflect ablated but not necessarily necrotic tissue confirming previous work, including that from our own laboratory, that DE MRI overestimates the acute...
extent of tissue injury after left atrial catheter intervention by virtue of the accumulation of gadolinium in extravascular water associated with acute inflammation. Although there is a good correlation between endocardial voltage-defined scar and T2-weighted signal immediately after ablation, there is a poor correlation with the DE MRI–defined scar at 3-month follow-up, further supporting the transient nature of at least part of the ablation injury process.

T2 signal was found in the acute CMR scans, remote from the ablation sites. Similar observations have previously been described. This is most likely related to a cytokine (interleukin-6)-mediated inflammatory response after RF ablation. Another possible mechanism giving rise to this observation may be related to sheer/rotational force of the catheters against the atrial wall during catheter manipulation.

Acute PVI and Atrial Ablation Injury
The data presented in this article demonstrate a high circumferential extent of each T2 and DE signal within 24 hours of ablation. Although this is consistent with a high degree of overlap of the 2 imaging signal types, there are also some areas where the T2 signal can be detected in the absence of the DE signal and vice versa (Figure 3). By overlaying DE+T2-weighted images on the same anatomical shell, we have demonstrated that the circumferential extent of ablation injury is greater when both signal types are summated, reaching ~90% (Figure 4). Although 100% circumferential extent of combined T2 and DE signals was seen in only 17 of 50 PV pairs, it is well known that acute PV isolation can be achieved using a segmental, electrogram-guided approach, rather than a circumferential ablation approach, the former not necessarily resulting in ablation of the entire PV circumference. This may explain the finding that PV isolation can be readily achieved without circumferential MR evidence of ablation injury.

Atrial Scar and Arrhythmia Recurrence
The MR data at the follow-up scan demonstrate near abolition of the T2 signal, whereas the DE signal is reduced and continues to occupy only 60% of the circumferential extent of both pairs of PVs. This is in keeping with the finding that chronic PV reconnection is ubiquitous after conventional wide-area circumferential ablation and, indeed, was seen in all AF recurrences in this article. In the present study, a greater extent of circumferential DE signal at the 24-hour scan was predictive of freedom from AF (Figures 4 and 5), whereas the extent of T2 signal was greater in the arrhythmia recurrence group. Although there is a lack of clarity of what DE+T2 signals truly represent in the immediate aftermath of a catheter ablation procedure, the presence of a DE signal beyond 3-month follow-up is likely to represent permanent atrial scarring.

The formation of scar after ablation and its representation by DE+T2 sequences are not completely understood. However, there are some similarities with findings of a DE signal observed in serial CMRI (acute and late) after acute myocardial infarction, with regression of delayed enhancement areas over time. From this small sample of 25 patients, we can qualitatively say that DE regions generally become more distinct and smaller with time but that T2 regions did not predictably become regions of DE, although there is some overlap. Recognizing this as a hiatus in our knowledge of atrial characterization by MR, an animal study is underway...
to investigate further the temporal course of atrial injury/scar after catheter ablation.

The decline in circumferential extent of DE signal between acute and follow-up scans was less in patients with no AF recurrence than in those with AF recurrence. This supports our hypothesis that the greater the contribution of T2 signal, representing reversible injury to acute PV1, the higher the likelihood of PV reconnection after resolution of tissue edema. Although preliminary work has demonstrated a qualitative correlation between discontinuities in areas of high DE signal and conduction gaps on electrophysiology study,8,25 PV reconnection also occurs in patients without clinical arrhythmia recurrence,26 and therefore, caution must be exercised in relying on the use of MR-defined scar as a surrogate for electrophysiological reconnection.

**Potential Clinical Significance**

It has been previously shown that durable RF lesion formation is dependent on parameters, including catheter tip electrode size, power, catheter tip temperature, and contact force. The presented data suggest that there is an element of reversible myocardial injury during ablation. Ablation strategies and techniques that favorably alter the necrosis/edema ratio, such as alternative energy sources, contact pressure sensing, and improved catheter stability, may minimize reversible myocardial injury.

**Study Limitations**

There are significant limitations to MRI of the left atrium after catheter ablation, with no widely accepted standardization of technique between laboratories. Although there is evidence from animal studies that gadolinium is predominantly a marker for tissue necrosis, by virtue of its kinetics, it also accumulates in extracellular water that is seen in acute inflammation. In addition, although T2 MRI can preferentially represent myocardial edema, there is currently no robust histological evidence corroborating this in the atria after RF ablation.

Although the DE+T2 signals recorded acutely after ablation almost certainly include some double counting of edema and necrosis by both techniques, the near-complete resolution of T2 signal at follow-up indicates that, at the very least, T2 predominantly represents some form of reversible atrial injury.

The annotation of lesions on an electroanatomic map is subjective and likely does not accurately reflect the site of atrial injury, which may explain, in part, the unanticipated MR finding of PV encirclement in only 36% of PV pairs. We attempted to mitigate this by using a point-by-point technique, with RF applications of 30 seconds and 1 tag per application.

Detection of asymptomatic recurrences of AF without the use of continuous monitoring is impossible. Because of the frequency of monitoring, it is likely that the incidence of asymptomatic AF is underreported in the current study.

This is a small, hypothesis-generating study, and the use of necrosis and edema imaging as a predictor of long-term clinical outcome would require a larger study for validation.

**Conclusion**

Acute PV isolation is achieved by a combination of reversible and irreversible circumferential tissue injury at the PV-LA junction. The greater the ablation extent accounted for by reversible injury, the higher is the incidence of AF recurrence.

**Sources of Funding**

This work was supported, in part, by the Technology Strategy Board under grant 17352, in part, by the Philips Healthcare, Best, The Netherlands, and, in part, by the EPSRC under grant EP/D061474/1. Dr Arujuna was supported by St. Jude Medical and Dr Caulfield by an EU Heart Grant. We acknowledge support from the UK Department of Health via the National Institute for Health Research Centre award to Guy’s and St. Thomas’ NHS Foundation Trust in partnership with King’s College London and King’s College Hospital NHS Foundation Trust.

**Disclosures**

None.

**References**


Single ablative therapy for paroxysmal atrial fibrillation has moderate success, and many patients present with recurrent arrhythmia. We proposed that the structure of the radiofrequency lesion applied during ablation is important in determining recurrences. The nature of the radiofrequency lesion was studied using magnetic resonance imaging with delayed enhancement (DE) and T2 at 3 time points: before ablation, within 24 hours, and 6 months after ablation. Patients were divided into those with (n=11) and without (n=14) recurrent arrhythmia. Levels of DE+T2 were compared SSFP improves diagnostic confidence in edema imaging in acute myocardial infarction compared to turbo spin echo. *Magn Reson Med.* 2007;57:891–897.

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**CLINICAL PERSPECTIVE**

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_Circ Arrhythm Electrophysiol_. 2012;5:691-700; originally published online May 31, 2012; doi: 10.1161/CIRCEP.111.966523

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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