Temporal left atrial lesion formation after ablation of atrial fibrillation

Troy J. Badger, MD,* Robert S. Oakes, BS,* Marcos Daccarett, MD,* Nathan S. Burgon, BS,* Nazem Akoum, MD,* Eric N. Fish,* Joshua J. E. Blauer, BS,*† Swati N. Rao,* Yaw Adjei-Poku, BS,* Eugene G. Kholmovski, PhD,‡ Sathya Vijayakumar, MS,‡ Edward V. R. Di Bella, PhD,‡ Rob S. MacLeod, PhD,† Nassir F. Marrouche, MD, FHRS*

*From the *Atrial Fibrillation Program, Division of Cardiology, University of Utah School of Medicine, and the †Scientific Computing Institute and ‡Utah Center for Advanced Radiology Research, University of Utah. Salt Lake City, Utah.*

BACKGROUND Atrial fibrillation (AF) ablation uses radiofrequency (RF) energy to induce thermal damage to the left atrium (LA) in an attempt to isolate AF circuits. This injury can be seen using delayed enhancement magnetic resonance imaging (DE-MRI).

OBJECTIVE The purpose of this study was to describe DE-MRI findings of the LA in the acute and chronic stages postablation.

METHODS Twenty-five patients were scanned at two time points postablation. The first group (n = 10) underwent DE-MRI at 24 hours and at 3 months. The second group (n = 16) was scanned at 3 months and at 6 or 9 months. One patient had three scans (24 hours, 3 months, 9 months) and was included in both groups. The location and extent of enhancement were then analyzed between both groups.

RESULTS The median change in LA wall injury between 24 hours and 3 months was −6.38% (range −11.7% to 12.58%). The median change in LA wall injury between 3 months and later follow-up was +2.0% (range −4.0% to 6.58%). There appears to be little relationship between the enhancement at 24 hours and 3 months (R^2 = 0.004). In contrast, a strong correlation is seen at 3 months and later follow-up (R^2 = 0.966). Qualitative comparison revealed a stronger qualitative relationship between MRI findings at 3 months and later follow-up than at 24 hours and 3 months.

CONCLUSION RF-induced scar appears to have formed by 3 months postablation. At 24 hours postablation, DE-MRI enhancement appears consistent with a transient inflammatory response rather than stable LA scar formation.

KEYWORDS Atrial fibrillation; Pulmonary vein antrum isolation; Left atrial scar; Delayed enhancement MRI; Catheter ablation; Radiofrequency energy

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Introduction

Catheter ablation has emerged as an interventional treatment for atrial fibrillation (AF) patients who have failed antiarrhythmic or rate-control therapy.[1–4] Many current ablation techniques, including pulmonary vein antrum isolation (PVAI), use radiofrequency (RF) energy to induce thermal damage to the left atrial (LA) substrate in attempt to electrically disconnect and isolate arrhythmogenic foci originating from the pulmonary veins (PVs).[5–7] Energy delivery causes myocardial necrosis followed by inflammatory infiltrates that result in fibrotic scarring of the LA wall and disruption of the LA-PV conduction pathways.[8–12]

Delayed enhancement magnetic resonance imaging (DE-MRI) recently has been introduced as a means to visualize this RF-induced scarring postablation.[13,14] DE-MRI uses the poor washout kinetics of the contrast agent gadolinium in injured tissue to enhance regions of nonviable myocardium. These scans can be rendered into three-dimensional (3D) recreations of the LA showing the anatomical location and size of postablation scars.[14,15] These models can be used to analyze how LA lesions appear in size, intensity, and location in the acute and chronic postablation stages and the manner in which their morphology changes over time. Understanding the temporal process of scar formation and whether scar significantly reduces or expands over time may be valuable in determining whether certain patients are more susceptible to recovery of electrical conduction and a subsequent recurrence of AF.

In this study, we examine ablation-induced scar and how it responds over time. We evaluated LA lesions in two separate groups of AF patients: The first group had scans acquired at 24 hours postprocedure and 3 months postprocedure. The second had scans acquired at 3 months postprocedure and at 6 or 9 months postprocedure. The results presented here provide important insights into the healing

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process after ablation of the LA and its subsequent remodeling.

Methods

Patients

Between November 2006 and January 2008, 25 patients who presented for PVAI were enrolled in this study. The protocol was approved by the Institutional Review Board at the University of Utah and was Health Insurance Portability and Accountability Act compliant. Patients were eligible if they underwent DE-MRI at two different time points (24 hours, 3 months, 6 months, or 9 months) after PVAI. Patients were then separated into one of two groups. Group 1 (10 patients) included patient with scans acquired at 24 hours and 3 months postablation. Group 2 (16 patients) included patients with scans acquired at 3 months and 6 or 9 months postablation. Of the 25 patients, one patient underwent DE-MRI at 24 hours, 3 months, and 9 months postablation and was included in both groups for a total of 26 sets of scans analyzed (see Table 1 for the patient characteristics).

Before the PVAI procedure, all patients underwent transesophageal echocardiogram to rule out LA appendage thrombus. Patients then underwent MRI to define LA anatomy, LA area, and LA wall thickness for electroanatomical mapping during the ablation procedure. Of the 25 patients included in the study, 20 (80%) received quality delayed enhancement scans before the ablation; however, these were not included in the analysis.

DE-MRI acquisition

All patents underwent MRI studies on a 1.5 Tesla Avanto clinical scanner (Siemens Medical Solutions, Erlangen, Germany) using a DE-MRI method as described elsewhere.[14] Briefly, DE-MRI was acquired about 15 minutes after injection of the contrast agent using a 3D inversion recovery, respiration navigated, electrocardiogram (ECG)-gated, gradient echo pulse sequence. Typical acquisition parameters were free breathing using navigator gating, a transverse imaging volume with voxel size = 1.25 × 1.25 × 2.5 mm (reconstructed to 0.625 × 0.625 × 1.25 mm), [TR (Repetition Time) TE (Echo Time)] TR/TE = 6.3/2.3 ms, inversion time (TI) = 230 − 270 ms, GRAPPA with R = 2, and 32 reference lines. ECG gating was used to acquire a small subset of phase-encoding views during the diastolic phase of the LA cardiac cycle. The time interval between the R-peak of the ECG and the start of data acquisition was defined using the cine images of the LA. Fat saturation was used to suppress fat signal. The TE of the scan (2.3 ms) was chosen such that fat and water are out of phase, and the signal intensity of partial volume fat tissue voxels was reduced to allow improved delineation of the LA wall boundary. The TI value for the DE-MRI scan was identified using a scout scan. The typical scan time for the DE-MRI study was 5–10 minutes depending on subject respiration and heart rate. If the first acquisition of 3D DE-MRI did not have an optimal TI or had suboptimal image quality, the scan was repeated.

PVAI and posterior wall debulking

The methods for PVAI have been described elsewhere.[4,15] We have modified this procedure to include isolation and debulking of the posterior wall. The technique is briefly summarized below.

After venous access, a 14-pole coronary sinus catheter was placed into the coronary sinus via the right internal jugular access (TZ Medical Inc., Portland, OR) for use as a mapping reference. A phased-array ultrasound catheter was

Table 1 Patient demographics

	Overall (n = 25)*	Group 1 (n = 10)	Group 2 (n = 16)	$P^{\dagger}$
Age, years	63.01 ± 11.9	58.48 ± 14.6	66.33 ± 8.59	
Type of AF:				.320
Paroxysmal	16 (64.0)	5 (50.0)	12 (75.0)	
Persistent	8 (32.0)	5 (50.0)	3 (18.8)	
Long-standing persistent	1 (4.0)	—	1 (6.2)	
Gender:				
Female	12 (48.0)	7 (70.0)	5 (31.3)	.025
Male	13 (52.0)	3 (30.0)	11 (68.7)	
Hypertension	10 (40.0)	5 (50.0)	6 (37.5)	.412
Diabetes	3 (12.0)	1 (10.0)	2 (12.5)	.677
Coronary artery disease	—	—	—	—
History of smoking	6 (24.0)	3 (30.0)	3 (18.8)	.420
Valve surgery	1 (4.0)	—	1 (6.3)	.615
Myocardial infarct	—	—	—	—
Congestive heart failure	1 (4.0)	—	1 (6.3)	.640
Recurrence	7 (28.0)	3 (30.0)	4 (25.0)	.490
LA volume	93.75 ± 34.6	83.83 ± 36.5	100.34 ± 8.59	.250‡

Data in parentheses are percentages.

*One patient received scans at 24 hours and 3 and 6 months postablation. As a result, the patient data have been included in both groups 1 and 2.

†Fisher exact test between groups 1 and 2. Comparison included 26 cases.

‡Independent-samples *t*-test.

positioned in the midright atrium (Siemens AG Inc., Malvern, PA) and used to guide a double transseptal puncture, through which was placed a 10-pole Lasso catheter and an F-curve, Thermocool 3.5-mm irrigated-tip ablation catheter (Biosense Webster Inc. Diamond Bar, CA).

Using fluoroscopy and electroanatomic mapping (CARTOMERGE, Biosense Webster, Inc.) for catheter navigation, intracardiac potentials in the PV antra and on the posterior wall were mapped during sinus rhythm and were targeted for ablation if fractionation was seen distinct from far-field atrial potentials. Lasso-guided RF delivery was performed, using Lasso electrogram artifacts to confirm ablation catheter tip location relative to the substrate of interest. Lesions were delivered using 50 W with a 50°C temperature limit, for a duration of 10–15 seconds, with the endpoint being elimination of all high-frequency electrogram components. When all antral and posterior wall targets had been ablated, this entire region was resurveyed for any return of electrical activity, and any such regions were retreated. In addition, entry block in all four PVs was confirmed with the ablation catheter after debulking was accomplished.

Postablation management

After the procedure, all patients were observed on a telemetry unit for 24 hours. Patients underwent 8 weeks of patient-triggered and autodetected cardiac event monitoring. Persistent AF patients were discharged on a 2-month course of antiarrhythmic medications. Eight-day Holter recordings were obtained at 3 and 6 months. Patients were seen in clinic at 3 and 6 months to receive an ECG and to assess for symptoms. Procedure success was defined as a lack of symptoms and absence of AF or atrial flutter on all ECG, Holter, and cardiac event monitoring according to published guidelines.[16]

Image analysis

Three-dimensional MRI models

All MR images were processed into 3D models of the LA and processed using the MRI DICOM formatted data sets in Osirix. LA data from 3D DE-MRI acquisitions were evaluated slice by slice using volume-rendering tools. Smooth table opacity and application of a color lookout table were applied to better illuminate hyperenhanced regions for visualization purposes.

Percent enhancement of LA wall

The relative percent of LA wall enhancement was measured using a threshold-based lesion detection algorithm. In all images, the epicardial and endocardial borders were manually contoured using custom image display and then analyzed by software written in Matlab (The Mathworks Inc., Natick, MA). Normal and injured tissue were defined based on a bimodal distribution of pixel intensities within the LA wall. The first mode of lower pixel intensities was chosen as normal tissue. Injured tissue was defined at 3 standard deviations above the normal tissue mean pixel intensity. Regions defined as lesion were visualized independently to ensure appropriateness of lesion detection. In one case in which the degree of enhancement detected by the automated algorithm was determined to be inaccurate by an expert trained in DE-MRI, the cutoff value was adjusted by 1 standard deviation. The number of voxels corresponding to scar was determined for each slice and then summed for the entire scan. The degree of enhancement was reported as a ratio of lesion volume to total LA wall volume.

Comparison of enhancement patterns at different time points

A 3D panel was created for all time points with image views of the posterior wall, septum, and free wall. Two independent experts in cardiac imaging assessed the correlation between the panels of time point 1 with time point 2 in a fashion blinded to the date of the scan. The relationship of enhancement patterns based on the size, location, and intensity of the enhancement between the two time points was then rated on a 0–4 scale, where 0 was coded as "no relationship," 1 as "poor," 2 as "moderate," 3 as "good," and 4 as "excellent." Both reviewers assessed all image sets 4 times, and both the interobserver and intraobserver variability were then calculated.

Statistical analysis

Continuous variables are presented as median and the range. Continuous data were analyzed by the Wilcoxon rank sum test to measure for statistically significant differences. Fisher's exact tests were used to test for differences in categorical measurements due to the small size of the cohort. $P < .05$ was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago).

Results

Patient group 1—DE-MRI

After ablation, all patients showed detectable LA enhancement. There were substantial qualitative differences between the types of enhancement seen in patients at 24 hours when compared with all other time points. At 24 hours, DE-MRI patterns appeared less intense and more diffuse in nature, encompassing regions not targeted during the ablation procedure. Figure 1 shows the enhancement patterns in patients at 24 hours and 3 months post-PVAI. The characteristic pattern of diffuse, patchy enhancement at 24 hours (top) is clearly visible. Further, the overall intensity of the enhancement is less. In contrast, scans at 3 months (bottom) show well-connected, well-defined regions of intense enhancement in areas targeted during the ablation. PV isolation can be noted, which cannot be completely identified at 24 hours.

Patient group 2—DE-MRI

MRI scans taken at 6 or 9 months show enhancement patterns similar to those acquired at 3 months. Figure 2 shows an example of enhancement patterns in three patients at 3 and 6 months post-PVAI. At 3 months, MRI shows scar

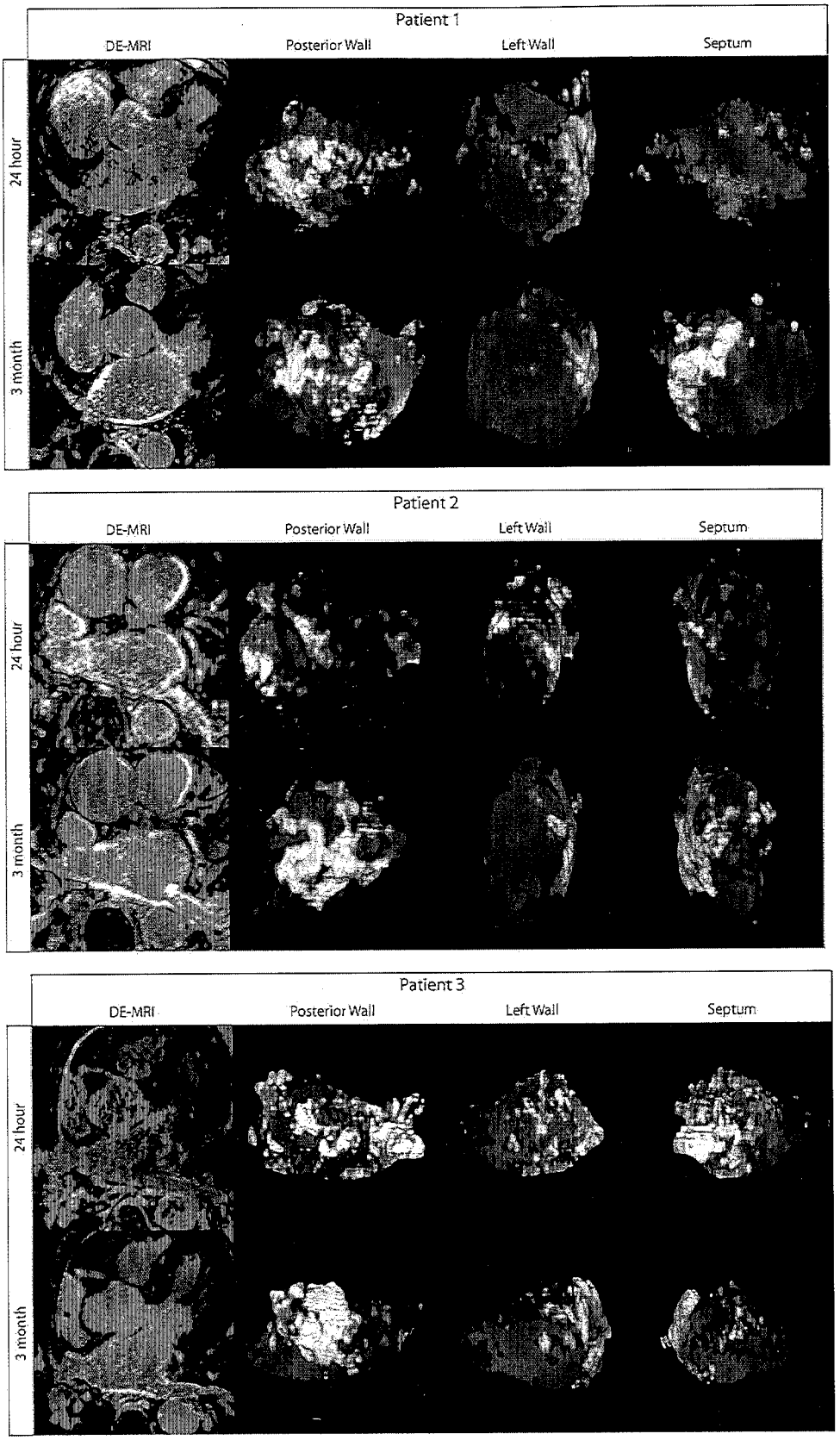

Figure 1 Three-dimensional DE-MRI analysis of scar patterns of three patients at 24 hours (*top row*) and 3 months (*bottom row*) post-PVAI. Twenty-four hour MRI shows diffuse and less intense enhancement patterns with a substantial reduction in algorithm-detected scar at 3 months. There is also substantial enhancement in regions not targeted during the ablation such as the anterior wall (*top right*) that appears to resolve by 3 months. Also at 3 months, LA scar patterns appear to be in well-demarcated scar borders along the posterior wall and around the PV antrum.

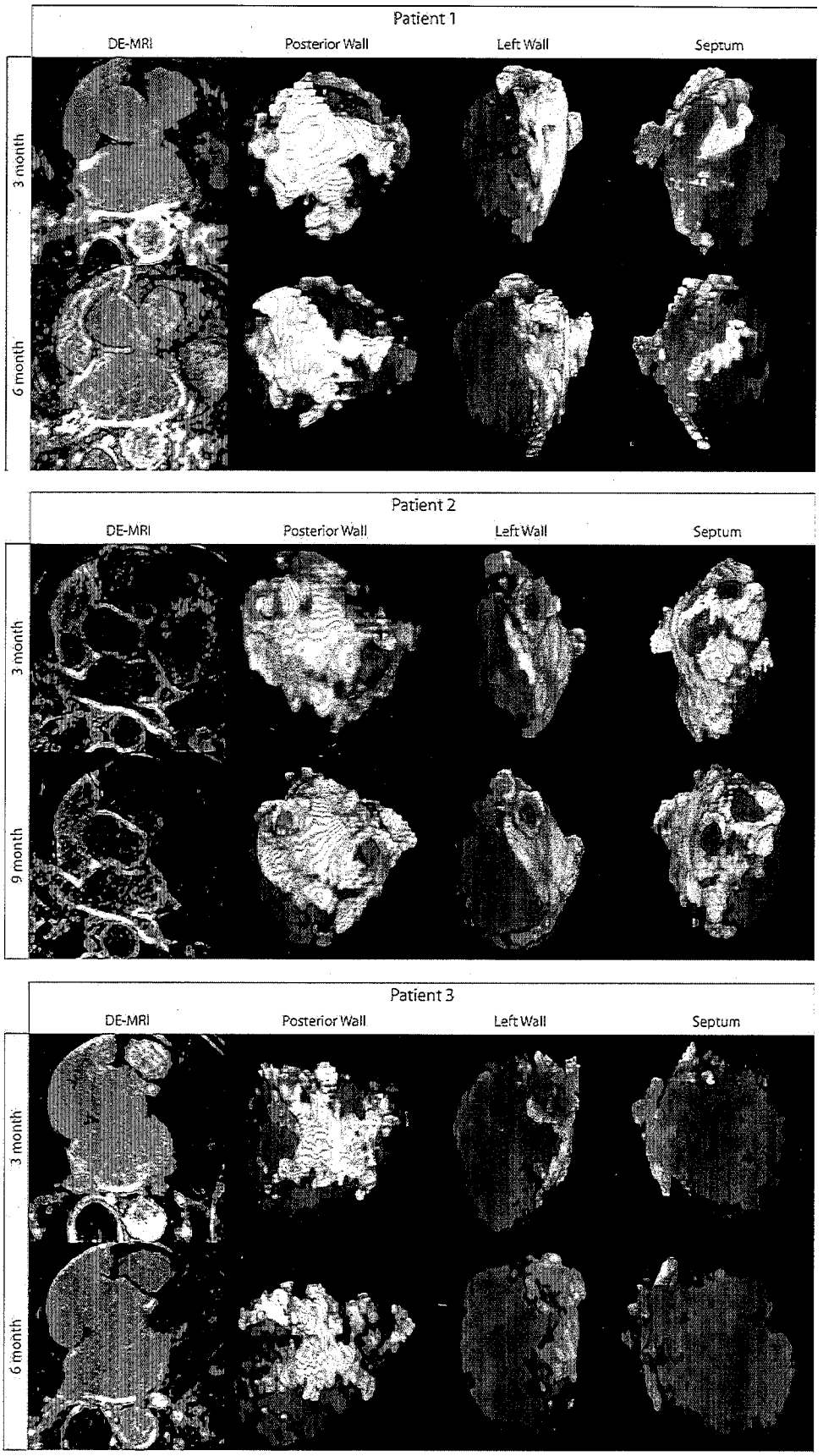

Figure 2 MRI scans acquired at 3 months (*top*) and 6 months (*bottom*) in three patients. Enhancement intensity and location are similar in the two-dimensional MRI slices (*left*) at both time points. Three-dimensional reconstructions in three views (posterior, left lateral, and right lateral) show scarring that is consistent between the 3- (*top*) and 6-month (*bottom*) scans, indicating minimal changes in enhancement between these two time points.

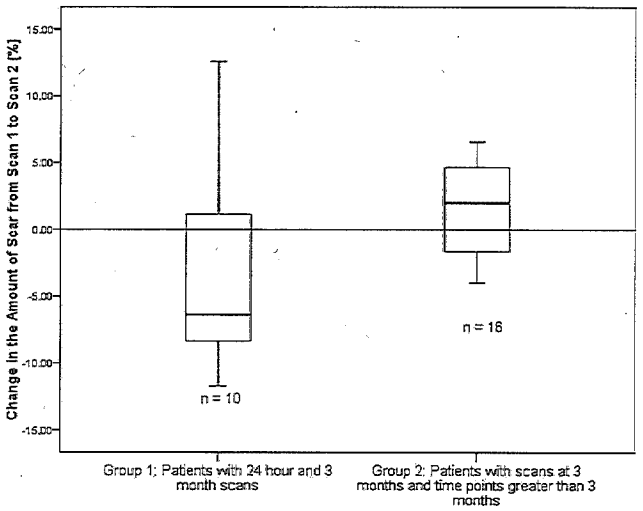

Figure 3 Change in scar in patients from 24 hours to 3 months (group 1) and from 3 months to 6 or 9 months (group 2). An overall reduction is seen in patients from 24 hours to 3 months, while a small increase is seen in patients from 3 months to the time of latest follow-up. The difference between the two groups was statistically significant (P = 0.048, Wilcoxon rank sum test).

patterns consistent with scar seen at 9 months. As evident in the 3D LA reconstructions, the overall intensity, location, and extent of ablation scarring are similar between the two MRI scans.

DE-MRI quantification and qualitative assessment

At 24 hours postablation, the median LA wall injury was 9.9% of the LA myocardium (range 7.20%–19.80%). At 3 months (in groups 1 and 2) the median LA wall injury was 13.6% (range 1.58%–64.5%). The median patient change in LA wall injury between 24 hours and 3 months (group 1) was −6.4% (range −11.7% to 12.6%). The median patient change in LA wall injury between 3 months and later follow-up (group 2) was 2.0% (range −4.0% to 6.6%). Figure 3 shows the range and interquartile range of both groups. The difference between group 1 and group 2 was statistically significant (P = .048, Wilcoxon rank sum test).

Qualitative comparison of LA scar patterns between group 1 and group 2 revealed a stronger qualitative relationship among MRI scans acquired from 3 months to later time points. Figure 4 shows the distribution for the qualitative assessment score. The relationship between MRI scans in group 1 was significantly lower than between those in group 2 (P <.001, Wilcoxon rank sum). The interobserver variability of the qualitative comparison was ≤10%, and the intraobserver variability with repeat assessments was ≤5%. Figure 4 (patient 1) shows an example of a 24-hour scar pattern that is diffuse and patchy (left) and that reduces at 3 months. In contrast, patient 2 shows an example in which the LA posterior wall scar patterns remain consistent in size, intensity, and location from 3 months on.

Figure 5 shows the results of pairwise regression analysis between the detected scar formation in group 1 and in group 2. There appears to be no relationship between the overall scar extent at 24 hours and that detected later at 3 months (R^2 = 0.0004). In contrast, a strong correlation is seen between injury detected at 3 months and injury detected at later follow-up (R^2 = 0.966).

Discussion

Our study is the first analysis to detail the morphological changes of RF-induced tissue injury after AF ablation. We demonstrate that in the acute stages postablation, patients showed decreased LA wall enhancement from 24 hours to 3 months, with qualitatively distinct enhancement patterns between those two time points. We also found that RF-

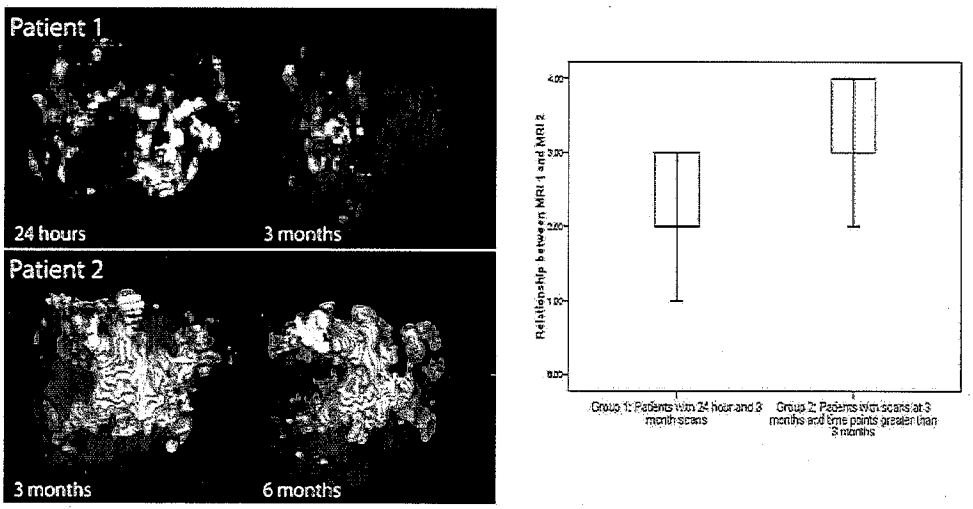

Figure 4 Qualitative comparison of LA posterior wall scar patterns between 24 hours and 3 months (patient 1) and 3 and 6 months (patient 2). In patient 1 (*top row*), the 24-hour scar pattern (*top left*) appears diffuse and less intense compared with the scan at 3 months (*top right*). In patient 2, scar patterns are consistent in size and location between 3 and 6 months, showing little apparent change or recovery. The graph at the right illustrates the statistical significance (P<.001, Wilcoxon rank sum test) of similar LA scar patterns in the acute versus chronic stages after PVAI. The qualitative relationship between scars at chronic time points is much greater than that seen during acute time points.

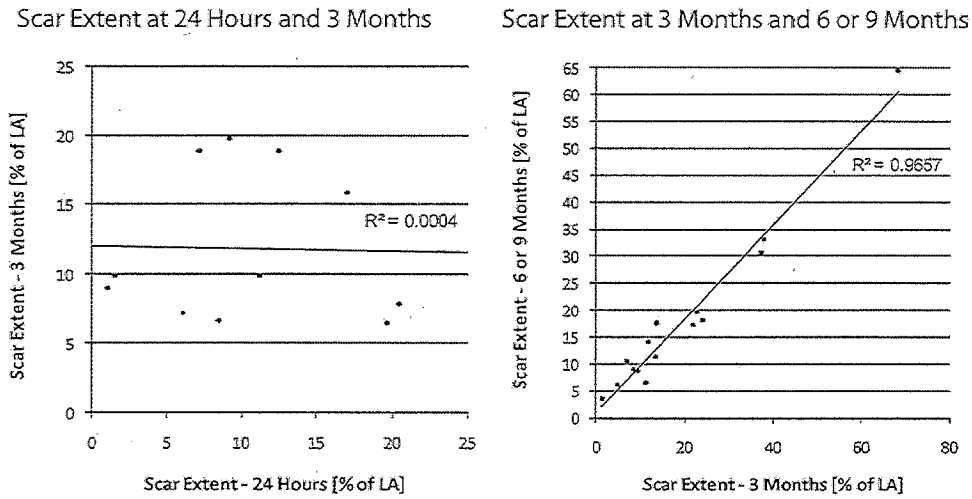

Figure 5 Relationship between detected scar formations at 24 hours and 3 months (*left*) or 3 months and later follow-up (6 or 9 months; *right*). No correlation is seen between the extent of detected injury at 24 hours and 3 months, while a strong correlation is seen between detected injury at 3 months and later follow-up.

induced scar appears to form by 3 months postablation with no recovery or reduction of scar after that time point.

Acute response

Our results indicate that AF patients experience significant total LA wall enhancement in the acute stages postablation, with the majority of patients showing decreased enhancement at 3 months. Analysis of 3D MRI models of the LA showed distinctly unique enhancement patterns between these two time points. Acute scans showed a less intense but more diffuse and scattered enhancement pattern encompassing not only the posterior wall but also the anterior and left lateral wall. Some LA enhancement, particularly in the anterior wall, had resolved by 3 months.

We believe the overestimation of LA enhancement in the acute stage post-PVAI could be the result of an inflammatory process induced by RF energy delivery. A transient inflammatory process causing LA edema and hemorrhage has been described in numerous animal studies involving RF catheter ablation.[8,10,17] Deneke et al[17] described an acute tissue reaction post-RF catheter ablation (post-RFCA) with distinctly different atrial tissue reactions between the first week and month after RF ablation with detectable zones of fresh bleeding up to 22 days after the procedure. Oswald et al[18] also found elevated inflammatory markers immediately postablation. Okada et al[19] using electron beam X-ray computed tomography demonstrated significant LA wall edema after RF ablation that self-resolved by 1 month after the procedure. Other investigators have reported that severe LA edema may remain even 2 months after the ablation procedure.[20]

It has been shown that gadolinium accumulates in tissue with increased water content,[21] enhancing myocardial regions in which the extracellular volume is increased, such as in conditions of inflammation, edema, and/or necrosis. Our manuscript is the first to detail how this acute inflammatory response appears on DE-MRI and how LA enhancement differs in the acute and chronic stages postablation. The difficulty in distinguishing necrosis and inflammation with DE-MRI could explain why enhancement seen at 24 hours does not precisely correlate with enhancement at 3 months and why evaluation of scar location in the immediate postablation state might not be predictive of eventual lesion formation.[22–24]

Chronic response

In our study, we found that by 3 months postablation LA wall enhancement seen on MRI showed great consistency in size, location, and intensity with scans acquired at 6 or 9 months. This indicates that enhancement seen at 3 months likely represents permanent LA wall injury. In our analysis, most patients experienced only a minimal change in scar after 3 months, with some patients experiencing a slight expansion of relative LA scar percentage at later follow-up. This minimal increase in scar percentage could be related to the repeatability of the approach or could be secondary to volumetric changes associated with structural remodeling of the LA after restoration of sinus rhythm. The increase could also be the result of the physiologic properties of the bordering cardiomyocytes, similar to those of LV ischemic patients in whom hypertrophied cells outgrow the capillary network and undergo apoptosis.[25–27]

Currently, there is much debate and speculation regarding the mechanisms of AF recurrence after catheter ablation.[28] One theory is that recovery of LA scar occurs, allowing for resumption of electrical conduction in previously isolated PVs.[28–31] Our data appear to indicate that by 3 months postablation, there is no recovery or reduction in scar lesions. This may signify that any recovery of electrical isolation is likely the result of inadequate scarring from the procedure rather than resumption of electrical conduction in previously scarred atrial tissue.

Clinical implications

Our findings indicate that 3 months postablation is an appropriate time to acquire DE-MRI to evaluate the extent of LA wall scarring. Further research correlating LA wall scar patterns with successful procedure outcome may provide significant insights regarding proper techniques and strategies for catheter ablation in different subgroups of AF patients.

Study limitations

Although the trends noted are consistent among patients, the sample size of our study is small. In addition, 3D MRI this study was performed on a 1.5 Tesla Scanner. Significant improvements in LA wall imaging with greater spatial resolution, signal-to-noise ratio, and contrast-to-noise ratio are expected at higher magnetic fields (3 Tesla). A second limitation regards the limited number of time points for individual patients. Future work in this area should use a greater number of time points for acquisition of DE-MRI in individual patients.

Conclusion

RF-induced scar as measured by DE-MRI appears to have formed by 3 months postablation. Scar patterns remain consistent in extent, location, and intensity at later follow-up. At 24 hours postprocedure, DE-MRI enhancement patterns appear consistent with a transient inflammatory response that self-resolves before LA scar formation.

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