Echocardiographic left atrial reverse remodeling after catheter ablation of atrial fibrillation is predicted by preablation delayed enhancement of left atrium by magnetic resonance imaging

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Background Atrial fibrosis is a hallmark of atrial structural remodeling (SRM) and leads to structural and functional impairment of left atrial (LA) and persistence of atrial fibrillation (AF). This study was conducted to assess LA reverse remodeling after catheter ablation of AF in mild and moderate-severe LA SRM.

Methods Catheter ablation was performed in 68 patients (age 62 ± 14 years, 68% males) with paroxysmal (n = 26) and persistent (n = 42) AF. The patients were divided into group 1 with mild LA SRM (<10%, n = 31) and group 2 with moderate-severe LA SRM (>10%, n = 37) by delayed enhancement magnetic resonance imaging (DEMRI). Two-dimensional echocardiography, LA strain, and strain rate during left ventricular systole by velocity vector imaging were performed pre and at 6 ± 3 months postablation. The long-term outcome was monitored for 12 months.

Results Patients in group 1 were younger (57 ± 15 vs 66 ± 13 years, \( P = .009 \)) with a male predominance (80% vs 57%, \( P < .05 \)) as compared to group 2. Postablation, group 1 had significant increase in average LA strain (\( \Delta \uparrow: 14\% \text{ vs } 4\% \), \( P < .05 \)) and strain rate (\( \Delta \uparrow: 0.5 \text{ vs } 0.1 \text{ cm/s}, P < .05 \)) as compared to group 2. There was a trend toward more patients with persistent AF in group 2 (68% vs 55%, \( P = .2 \)), but it was not statistically significant. Group 2 had more AF recurrences (41% vs 16%, \( P = .02 \)) at 12 months after ablation.

Conclusion Mild preablation LA SRM by DEMRI predicts favorable LA structural and functional reverse remodeling and long-term success after catheter ablation of AF, irrespective of the paroxysmal or persistent nature of AF. (Am Heart J 2010;160:877-84.)

The substrate for atrial fibrillation (AF) is atrial fibrosis, the hallmark of structural remodeling (SRM).1,2 Atrial fibrillation begets AF, and increasing AF burden leads to structural and functional remodeling, creating a substrate that is favorable for sustaining AF propagation,3 and paroxysmal AF eventually becomes persistent or permanent AF. Catheter ablation of AF results in improvement of symptoms and quality of life, in addition to significantly lowering recurrence rate of AF.4,5 The goal of ablation is to identify and eliminate the AF trigger(s) and modify the substrate of AF to halt the vicious cycle of arrhythmia and remodeling.

Identification of the arrhythmic substrate and assessment of the structural and functional changes in the atria by noninvasive modalities can be useful in selecting patients for rhythm control therapy, including catheter ablation, early in the disease process. It can also help in monitoring the effects of therapies over time. Delayed enhancement magnetic resonance imaging (DEMRI) to characterize fibrotic or scarred tissue has been used extensively to study ventricular myocardium. The research at our center has shown that DEMRI can accurately quantify the extent of left atrial (LA) SRM and can predict procedural outcome in different stages of SRM.6,7 However, the degree of reverse remodeling of LA after ablation in various stages of SRM is unknown.

The LA function by strain and strain rate is an emerging technology.8,9 It is feasible and overcomes the limitations of tissue Doppler imaging.10,11 The extent of SRM by DEMRI inversely correlates with LA strain as reported earlier by our group.9
We conducted this study to compare echocardiographic measures of structural and functional reverse remodeling after catheter ablation of AF in patients with preablation mild versus moderate-severe LA SRM by DEMRI. In addition, we evaluated the preablation echocardiographic and MRI remodeling parameters and their relationship to procedural outcome.

Methods

We conducted a single-center, prospective, cross-sectional study at the University Of Utah Hospital. The study was approved by the investigational review board at University of Utah and was compliant with the Health Insurance Portability and Accountability Act of 1996. No extramural funding was used to support this work. We enrolled 76 patients referred to the AF clinic who were considered for catheter ablation. Before ablation, they were evaluated with 3-dimensional (3D) DEMRI to define the pulmonary veins (PVs), location of the esophagus, LA anatomy, and characterization of the LA wall tissue. Two-dimensional (2D) transthoracic echocardiography was performed before catheter ablation and repeated ≥3 months after ablation. Exclusion criteria were patients with suboptimal echocardiographic and/or MRI images and mechanical cardiac valves.

Atrial fibrillation ablation procedure

Pulmonary vein antrum isolation, in addition to LA posterior and septal debulking was performed under intracardiac echocardiographic guidance. The procedure has been described elsewhere.6 Briefly, a 10F, 64-element, phased-array ultrasound catheter (AcuNav, Siemens, Mountain View, CA) was used to visualize the interatrial septum and to guide the transeptal puncture. A circular mapping catheter (Lasso; Biosense Webster, Diamond Bar, CA) and an irrigated tip ablation catheter (Thermocool; Biosense Webster) were inserted into the LA. Intracardiac echocardiogram was used to define the PV ostia and their antra and to help position the circular mapping catheter and ablation catheter at the desired sites. Temperature and power were set to maximum of 50° and 50 W (pump flow rate at 30 mL/min), respectively.

Follow-up after catheter ablation

After the procedure, all patients were monitored overnight in a telemetry unit. Warfarin was continued to maintain an international normalized ratio of 2.0:3.0 for 3 months in paroxysmal and 6 months in persistent AF. Event monitors were placed for a minimum of 2 months after their pulmonary vein antrum isolation. Patients were instructed to activate the monitors any time they felt symptomatic. Patients were assessed every 3 months to determine the success of the ablation procedure by clinical examination and Holter monitoring for 8 days at the 3, 6, and 12 months follow-up, in addition to 2D echocardiography. Recurrences were determined from patient reporting, electrocardiogram, event monitoring, and Holter monitoring. Success was defined as a lack of any atrial arrhythmias (atrial tachycardia, AF/flutter) lasting for >30 seconds while off antiarrhythmic medications, after a blanking period of 8 weeks as per Heart Rhythm Society consensus document guidelines.8,9 Patients with recurrence during the blanking period were offered electrical cardioversion and/or antiarrhythmic drugs.

DEMRI

As previously described,6 DEMRI studies were performed on a 1.5 Tesla MR system (Avanto Siemens Healthcare, Erlangen, Germany). High-resolution DE images of LA were acquired in 15 minutes after contrast agent injection (0.1 mmol/kg, Multihance; Bracco Diagnostic Inc, Princeton, NJ) using a 3D respiration-navigated, inversion-recovery gradient echo pulse sequence (Repetition time/Echo time (TR/TE) = 2.38/5.4 milliseconds, flip angle of 20°, bandwidth of 220 Hz/pixel, Field of View (FOV) of 360 × 360 × 100 mm, matrix size of 288 × 288 × 40, and voxel size of 1.25 × 1.25 × 2.5 mm). The inversion pulse was applied every heartbeat, and fat saturation was applied immediately before data acquisition (23 views per heartbeat) during LA diastole. To preserve magnetization preparation in image volume, navigator was acquired immediately after data acquisition block. Typical scan time for DEMRI study was 5 to 10 minutes depending on patient heart rate and respiration pattern.

For this study, we included only good quality images, and 41 (60%) patients were in sinus rhythm and 27 (40%) patients were in AF during preablation MRI and echocardiographic studies. Only 3 patients (4%) were in AF during postablation follow-up studies. Also, those in AF had good heart rate control with average heart rate of 70 ± 20 beats per minute. To quantify the extent of baseline LA wall SRM, the LA epicardial and endocardial borders on DEMRI images were traced and isolated from the remaining structures. A computerized algorithm generated a histogram of pixel intensities, and at 3 SD from the mean, it was defined as significant SRM. The degree of enhancement or SRM was reported as percentage of the total LA wall volume.

Transthoracic echocardiography

Echocardiography was performed using standard views and harmonic imaging (Sequoia, Siemens, Mountain View, CA). Patients with AF had echocardiographic acquisition over 2-second duration or for 2 heartbeats. In the parasternal long-axis views, LA maximum anteroposterior (AP) diameter was measured. In the apical 4-chamber view, we measured left ventricular (LV) end-diastolic and end-systolic volumes, LV stroke volume index, and LVEF calculated by Simpson’s method. In the same view, LA maximum and minimum volumes were measured, and LA emptying fraction was calculated as maximum volume – minimum volume/maximum volume. The LA maximum volume was also measured by biplane area-length method (0.85 × area 1 × 2 divided by the length) indexed to body surface area.13 The LA superior-inferior diameter was measured from the mitral annular plane to the posterior wall of the LA. Pulsed-wave Doppler at the tips of mitral valve leaflets allowed us to measure diastolic parameters that included transmitral early (E) and late (A) diastolic filling velocities, E/A ratio, and E deceleration time (DT). The LV early diastolic tissue velocity (E) was measured by tissue Doppler imaging of the medial mitral annulus. E/E’ was calculated, and a value >15 was considered to represent elevated LV filling pressure.14 In AF, E/E’ was averaged with 5 cardiac cycles. Mitral regurgitation was semiquantitatively assessed by color Doppler across mitral valve and graded as none/trace (0), mild (1), moderate (2), moderately severe (3), and severe (4).15
Velocity vector imaging

Offline analysis of the gray scale images obtained by 2D echocardiography was done by using velocity vector imaging software (Siemens Medical Solutions USA). The endocardium of LA wall was manually traced starting from the medial to the lateral mitral annulus and was automatically tracked along the border throughout ≥1 cardiac cycles.

In the apical 4-chamber view, the regional analysis consisted of placing the sample in the midseptal and midlateral LA walls in the same cardiac cycle. In the midseptal wall, sample was placed 1 to 2 cm proximal to the medial mitral annulus, and the fossa of ovalis was avoided for optimal tracking of the endocardium. In the lateral wall, sample was placed 1 to 2 cm proximal to the lateral mitral annulus and the point of entry of the pulmonary veins was avoided. Thus, strain versus time and strain rate versus time curves were generated from these regions of interest. The strains and strain rates from the 2 regions were averaged to give average LA strain and strain rate. The velocity vector imaging software averaged the strain and strain rate for at least 2 cardiac cycles in AF. Speckle tracking has been reported to be a feasible and reproducible method to assess LA longitudinal deformation properties and reference values in healthy individuals have been reported by Cameli et al.11 We assessed the strain and strain rate in 25 normal controls and found the average LA strain of 68% ± 20% and average strain rate of 2.5 ± 0.5 U/s.9

The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

Statistical analysis

Continuous variables are presented as mean ± SD, and dichotomous data are presented as numbers and percentages. The echocardiographic parameters in groups 1 and 2 at baseline, and at 6 ± 3 months after catheter ablation are compared using Student paired and unpaired t tests, respectively. Pearson’s correlation and χ² are reported for comparison between dichotomous variables. A *P* value of ≤ 0.05 was considered statistically significant. Univariate and multivariate linear regression analysis were done to assess the correlation between different variables. Univariate and multivariate Cox regression analysis for recurrence of AF were done to evaluate the predictive value of several pre and postablation clinical and echocardiographic parameters.

Results

After excluding patients with suboptimal echocardiographic images (n = 6/76, 8%) and mechanical valves (n = 2, 3%), 68 patients were divided them into 2 groups based on the degree of delayed enhancement of LA wall by MRI as group 1 with mild LA SRM (≤10%, n = 31) and group 2 with moderate-severe LA SRM (>10%, n = 37). Figure 1

![Figure 1](image-url) Preablation DEMRI images of the left atrium in 2 patients with AF, (A) patient in group 1 with mild (7%) SRM and (B) patient in group 2 with moderate-severe SRM (34%) SRM. The blue areas represent normal myocardium, and the green areas are hyperenhanced areas that represent pathologic myocardium, presumed to be fibrosis.

![Figure 2](image-url) Improvement in left atrial superior-inferior diameter by transthoracic echocardiography before and 6 ± 3 months after catheter ablation of AF.
demonstrates DEMRI examples of 2 patients in different stages of LA SRM. The average degree of SRM was 6.8% ± 2.5% in group 1 and 26.0% ± 13.6% in group 2 (P < .005).

In all, 26 patients (38%) had paroxysmal AF and 42 patients (62%) had persistent AF as defined by the Heart Rhythm Society consensus document on AF ablation. Group 2 showed a trend toward more patients with persistent AF than group 1, but it was not statistically significant (68% vs 55%, P = .2). There were no significant differences in the number of patients with hypertension (42% vs 43%), coronary artery disease (10% vs 19%), on statin therapy (26% vs 43%), or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (29% vs 43%) between the 2 groups. There were no major complications from ablation in either group, and follow-up was similar in both groups. After the blanking period, AF recurrence was documented in 20 patients. Of these, 16 patients underwent repeat ablation.

The patients in group 1 were younger (57 ± 15 vs 66 ± 13 years, P = .009) and had a male preponderance (80% vs 59%, P = .07) as compared to group 2. Overall, females were older than males (69 ± 13 vs 59 ± 14 years, P = .007) and

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: left atrial wall fibrosis &lt;10% (n = 31)</th>
<th>Group 2: left atrial wall fibrosis &gt;10% (n = 37)</th>
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<tbody>
<tr>
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<td>After ablation</td>
<td>Before ablation</td>
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<tr>
<td>LA anterior-posterior diameter (cm)</td>
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<td>3.7 ± 0.6*</td>
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<td>LA superior-inferior diameter (cm)</td>
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<td>LA emptying fraction (%)</td>
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<td>LA average strain (%)</td>
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<td>LA average strain rate (U/s)</td>
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<td>LV end-systolic volume index (mL/m²)</td>
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<tr>
<td>LV filling pressure (E/E')</td>
<td>9.2 ± 3.3</td>
<td>10.8 ± 5.3</td>
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</table>

* P value in the same group.

Figure 3

Vector velocity imaging (VVI) of left atrium: strain (%) and strain rate (SR, U/s) versus time (milliseconds) curves obtained by VVI, before and 6 ± 3 months after catheter ablation of AF. Patient in group 1 with mild (≤10%) LA SRM by DEMRI had significant improvement in midseptal and midlateral strain and strain rate (A, preablation and B, postablation) as compared to the patient in group 2 with moderate-severe LA SRM (>10%) (C, preablation and D, postablation). The red and blue curves represent the midseptal and midlateral left atrial samples, respectively.
had significantly more LA SRM (25 ± 16 vs 14 ± 12, P = .003) and higher E/E’ (15 ± 9 vs 10 ± 5, P = .02) than males.

Structural reverse remodeling of LA in mild versus moderate/severe stages of SRM after catheter ablation

At 6 ± 3 months after ablation, patients in group 1 showed a significant reduction in LA biplane volume index, LA AP diameter and superior-inferior diameter. Patients in group 2 had reduction in LA biplane volume index and in AP diameter but not in superior-inferior diameter (Figure 2) (Table I).

Functional reverse remodeling of LA in mild versus moderate/severe stages of SRM after catheter ablation

At 6 ± 3 months after ablation, patients in group 1 showed a significant improvement in the average LA strain and strain rate as compared to the strain and strain rate in group 2 (Figure 3 shows pre and postablation strain and strain rate imaging; A and B for a patient in group 1, and C and D for a patient in group 2). The average (Δ↑) postablation increase in LA strain in groups 1 and 2 was 14% versus 4% (P < .05) and increase in strain rate was 0.56 U/s versus 0.15 U/s (P = .04) (Figure 4).

Overall, there was a significant increase in LA emptying fraction (44% ± 16% to 47% ± 13%, P = .05) and in LVEF (53% ± 11% to 56% ± 11%, P = .05) postablation (Table I).

Subgroup analysis of patients with persistent AF and paroxysmal AF showed significant improvement in average LA strain and strain rate in those with mild LA SRM of ≤10% as compared to those with moderate-severe SRM of >10%, similar to the entire group.

Predictors of successful ablation of AF

At 12 months follow-up postablation, 48 patients (71%) remained free of AF with significantly more recurrences in group 2 compared to group 1 (41% vs 16%, P = .02). A Kaplan-Meier curve shows the difference in long-term recurrence-free days after ablation in the 2 groups (Figure 5). Patients with recurrence had more LA SRM at baseline (25% ± 18% vs 14% ± 11%, P < .05) as compared to those without recurrence but had no significant difference in LA and LV parameters before ablation. Without recurrence, the average LA strain and strain rate, LA emptying fraction, LA superior-inferior diameter, biplane maximum volume index, and LVEF improved significantly as compared to those who had recurrence of AF (Table II). In the patients with recurrence, there was
no significant difference in the number of patient with paroxysmal (29% vs 44%) versus persistent AF (71% vs 55%) as compared to those without recurrence.

Preablation predictors of recurrence of AF: Using Cox multivariate stepwise regression analysis, preablation LA wall fibrosis predicted recurrence after adjusting for, paroxysmal versus persistent AF, preablation LA AP diameter, superior-inferior diameter, LA maximum biplane volume index, LA emptying fraction, average LA strain, and LVEF ($P < .02$, hazard ratio 1.04, 95% CI 1.01-1.08).

Postablation predictors of recurrence of AF: Using Cox multivariate stepwise regression analysis, early postablation LA emptying fraction predicted long-term recurrence at 12 months, after adjusting for paroxysmal versus persistent AF, postablation LA AP diameter, superior-inferior diameter, LA maximum biplane volume index, average LA strain, and LVEF ($P < .02$, hazard ratio 1.04, 95% CI 1.01-1.08).

Postablation predictors of recurrence of AF: Using Cox multivariate stepwise regression analysis, early postablation LA emptying fraction predicted long-term recurrence at 12 months, after adjusting for paroxysmal versus persistent AF, postablation LA AP diameter, superior-inferior diameter, LA maximum biplane volume index, average LA strain, and LVEF ($P < .02$, hazard ratio 1.04, 95% CI 1.01-1.08).

Discussion

In this study, we demonstrated significant structural and functional reverse remodeling of the LA by 2D echocardiography and strain and strain rate imaging when catheter ablation of AF was performed in LA with mild SRM by DEMRI. It is also associated with less recurrence of AF. The benefits of ablation of AF seem to be dependent on the stage of LA SRM and not on paroxysmal or persistent nature of AF. Advanced age and female gender had a predisposition for more advanced LA SRM. To our knowledge, this is the first study reporting the degree of reverse remodeling of LA after catheter ablation of AF in various stages of LA SRM quantified by DEMRI.

Structural and functional remodeling of the left atrium in AF

The hallmark of SRM is LA myocardial fibrosis that leads to progressive LA dilation. Longer duration of AF is known to cause progressive remodeling and increased LA size and volume,\textsuperscript{13,16,17} and persistent AF is considered to be an advanced stage of arrhythmia as compared to paroxysmal AF. The patients in our study with persistent AF had larger LA size and volume and reduced strain as compared to patients with paroxysmal AF before ablation.

An interesting finding in our study was the lack of difference in the number of patients with paroxysmal and persistent AF when they were classified as mild and moderate-severe LA SRM by DEMRI. This raises an intriguing question about the mechanisms of AF initiation and persistence. Some patients diagnosed as paroxysmal AF may have more progressive LA SRM and resistance to rhythm control therapies, whereas other patients with persistent AF may have mild LA SRM and good response to rhythm control therapies. Identifying the exact pathogenesis of AF in a patient may facilitate individualizing rhythm control therapies. With catheter ablation, areas of LA SRM visualized on DEMRI may be targeted to potentially cure the arrhythmia. Of note, detection of diffuse LA SRM by DEMRI does not serve as an absolute marker. It simply shows the severity of LA pathologic condition. Focal areas of SRM can be targeted as absolute markers for ablation.

The older patients with AF, especially females, had more LA SRM by DEMRI in our study. Females also had elevated LV filling pressure, measured by $E/E'$. Cardiac fibrosis is a diffuse process occurring in both the ventricles and the atria and is triggered by higher filling pressure and vice versa.\textsuperscript{18} With increasing age, the degree of atrial fibrosis increases as shown by Gramley et al.\textsuperscript{19} With DEMRI, we can demonstrate the AF substrate in high-risk patients.

Reverse remodeling of left atrium after catheter ablation of AF

In the structurally remodeled LA, we measured both AP and superior-inferior diameter as LA enlarges in an
asymmetric fashion. The extensively remodeled atria can take a longer time to recovery of atrial contractile dysfunction after conversion to sinus rhythm.

The type of AF did not predict the recurrence in our study. Mild LA SRM by DEMRI. The benefits of ablation of AF and long-term success seem to be dependent on the stage of LA SRM and not on paroxysmal or persistent nature of AF, as traditionally defined. The degree of LA wall SRM preablation and improvement in LA emptying fraction early postablation predict success of ablation at 1 year follow-up. Longer duration of follow-up is necessary to evaluate other identifiable characteristics that lead to recurrence after successful ablation. Moreover, this also has important clinical implications such as continuing anticoagulation and antiarrhythmic medications after ablation.

Predictors of long-term success of catheter ablation of AF

Successful ablation was achieved in 71% of our patients at 1 year follow-up. In other studies, the recurrence of AF after ablation has been variable between 40% and 86%.

The ability to predict recurrence before rhythm control therapies in AF can be helpful in deciding long-term anticoagulation and antiarrhythmic therapy. The type of AF did not predict the recurrence in our study. Mild LA SRM preablation and improvement in LA emptying fraction early postablation were found to be the only predictors of long-term successful ablation. Neither pre or postablation LA strain and strain rate nor other echocardiographic parameters were useful in predicting success. This is in contrast to the findings by Di Salvo et al and Wang et al who reported that patients with higher LA strain before cardioversion were less likely to have recurrence. Higher postablation strain and strain rate predicted success after ablation in the study by Schneider et al.

By DEMRI, the LA SRM is quantified in 3D view and gives a complete assessment of the LA pathologic condition. Probably that was the reason why the 3D LA SRM predicted recurrence, whereas 2D LA dimension did not.

Limitations

The main limitation of our study was a short duration of follow-up by echocardiography. The success of ablation at long-term follow-up needs to be assessed to see how many need repeat ablation for better outcome. It is also important to see if the degree of LA and LV reverse remodeling seen at medium-term follow-up is maintained and progressive at longer duration. The LA strain and strain rate were assessed in only the septal and lateral walls of the LA because those walls were consistently imaged without significant dropout. Strain data from ablated regions, mainly the posterior wall, could not be obtained because of imaging limitations. The average strain may reflect the overall function of the LA and can be reliably measured in the same location. There are limitations inherent to imaging when patients are in AF that can be fairly overcome by imaging with good heart rate control as done in our patients. Quantification of LA wall fibrosis in thin-walled LA by DEMRI is limited by the inadequate spatial resolution from partial volume effects and cannot give accurate information on the transmurality of fibrosis.

Conclusion

The reverse remodeling of the LA structure and function after catheter ablation of AF is significantly better when performed in the early stage of arrhythmia with mild LA SRM by DEMRI. The benefits of ablation of AF and long-term success seem to be dependent on the stage of LA SRM and not on paroxysmal or persistent nature of AF, as traditionally defined. The degree of LA wall SRM preablation and improvement in LA emptying fraction early postablation predict success of ablation at 1 year follow-up. Longer duration of follow-up is necessary to evaluate other identifiable characteristics that lead to recurrence after successful ablation. Moreover, this also has important clinical implications such as continuing anticoagulation and antiarrhythmic medications after ablation.

Disclosures

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