The association of baseline left atrial structure and function measured with cardiac magnetic resonance and pulmonary vein isolation outcome in patients with drug-refractory atrial fibrillation

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BACKGROUND Prognostic significance of left atrial (LA) function in patients with atrial fibrillation (AF) is poorly defined.

OBJECTIVE To examine the association of LA function measured with cardiac magnetic resonance (CMR) feature-tracking and AF recurrence following catheter ablation.

METHODS One hundred and twenty-one AF patients (72% paroxysmal, mean age 59 ± 10 years) were enrolled. Baseline LA function was measured by calculating passive, active, and total emptying fractions (LAEF) and analysis of global longitudinal strain and strain rates. Patients were followed up for recurrence of AF or atrial tachycardia (AT). Hazard ratios for recurrence were calculated using Cox proportional models adjusted for potential clinical confounders, type of AF, left ventricular ejection fraction, AF duration, LA volume, and late gadolinium enhancement (LGE).

RESULTS During a mean follow-up of 18 ± 9 months, 52 patients (43%) experienced recurrent AF/AT. Patients with recurrent AF/AT had higher baseline LA volume index and lower LA passive, and total LAEF (P < .05 for all). The baseline peak LA strain and strain rates in all phases of LA function were lower in the AF/AT recurrence group (P < .01 for all). In multivariable analysis total LAEF, peak LA strain, and systolic and late diastolic strain rates were associated with recurrence. Both peak LA strain and total LAEF improved prediction of recurrent AT/AF compared to the baseline clinical model, including LA LGE (C statistic 0.82 vs 0.77, P < .05 for both total LAEF and peak LA strain).

CONCLUSIONS LA reservoir function was independently associated with recurrent AF/AT after PVI and can additionally improve risk stratification in patients undergoing PVI.

KEYWORDS Pulmonary vein isolation; Cardiac MRI; Left atrial fibrosis

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Introduction

Percutaneous catheter ablation of the left atrium (LA) to encircle the pulmonary veins (pulmonary vein isolation; PVI) is an established method to maintain sinus rhythm in patients with symptomatic atrial fibrillation (AF). Despite advances in ablation techniques, the recurrence rate remains substantial.¹,² Therefore identifying methods to risk-stratify AF patients undergoing catheter ablation is of great clinical value.

Several clinical parameters have been shown to predict arrhythmia recurrence after PVI. These include age, sex, left ventricular ejection fraction (LVEF), hypertension, diabetes mellitus, obstructive sleep apnea, nonparoxysmal AF, and LA size.³–⁶ Additionally, LA function has been used to identify patients at higher risk of recurrence.⁷–⁹ In the majority of recent studies, speckle-tracking echocardiography has been used for the assessment of LA function. However, given the anatomic location and the thin wall of
LA, echocardiographic assessment of LA function can be challenging. On the other hand, cardiac magnetic resonance (CMR) with a higher spatial resolution is the gold-standard modality for the assessment of myocardial motion. More recently, feature-tracking magnetic resonance imaging (MRI) has been successfully used to assess LA functional parameters with high reproducibility. In this study we sought to examine the association of phasic LA function measured with the novel technique of feature-tracking CMR and AF recurrence after PVI. We hypothesized that poor LA function at baseline would be associated with AF recurrence after PVI.

**Methods**

**Study population**

The Johns Hopkins Institutional Review Board approved the study and all patients provided written informed consent. Between January 2011 and September 2013 all consecutive patients with drug-refractory symptomatic AF undergoing CMR at Johns Hopkins Hospital for definition of pulmonary vein anatomy prior to AF ablation who agreed to participate in our registry were enrolled. The study cohort included patients undergoing first-time radiofrequency ablation who were in sinus rhythm at the time of CMR. In order to assess both LA passive and active functions, patients who were in AF at the time of MRI were excluded.

**CMR protocol**

Images were acquired using 1.5 Tesla scanners (Avanto and Aera; Siemens, Erlangen, Germany), a 6-channel–phased array body coil in combination with a 6-channel spine matrix coil. Cine CMR images were obtained in standard horizontal (4-chamber) and vertical (2-chamber) long axis planes using a retrospective electrocardiogram (ECG)-gated steady-state free precession sequence with the following parameters: typical repetition time/echo time of 3.0/1.5 msec, slice thickness 8 mm, spacing 2 mm, flip angle 78º, field of view 36–40 cm, and typical in-plane resolution and temporal resolution of 1.5 × 1.5 mm and 30–40 msec, respectively. Late gadolinium enhancement CMR (LGE-CMR) images were acquired within a range of 15–25 minutes (mean 18.8 ± 2.4 minutes) after a gadolinium injection (0.2 mmol/kg; gadopentetate dimeglumine; Bayer Healthcare Pharmaceuticals, Montville, NJ) using a fat-saturated 3-dimensional inversion recovery prepared fast spoiled gradient recalled echo sequence with respiratory navigation and ECG gating, echo time of 1.52 ms, repetition time of 3.8 ms, in-plane resolution of 1.3 × 1.3 mm, slice thickness of 2.0 mm, and flip angle of 10º. Trigger time for 3-dimensional LGE-CMR images was optimized to acquire imaging data during diastole of LA as observed from the cine images. The optimal inversion time was identified with an inversion time scout scan (median 270 ms; range 240–290 ms) to maximize nulling of the LA myocardium.

**LA functional analysis**

Multimodality Tissue Tracking software (version 6.0; MTT, Toshiba, Japan) was used to measure phasic LA volumes, strain, and strain rate from 4-chamber and 2-chamber cine CMR images, which were obtained before catheter ablation. The methods have been described and validated previously with excellent reproducibility. An experienced operator, blinded to the outcome status of the patients, contoured endocardial and epicardial LA borders in 2- and 4-chamber cine CMR images. Once contouring is complete in one phase, the software automatically tracks on screen pixels during the cardiac cycle (Video 1; supplemental material available online). Using the volume/time curves, measurements for maximum LA volume (LAV_max), LA volume before LA contraction (LAV pre-a), and minimum LA volume (LAV_min) were extracted (Figure 1). LA total, passive, and active emptying fractions were then calculated as follows:

- Passive LA emptying fraction (Passive LAEF): 100 × (LAV_max – LAV pre-a)/LAV_max
- Active LA emptying fraction (Active LAEF): 100 × (LAV_pre-a – LAV_min)/LAV pre-a
- Total LA emptying fraction (Total LAEF): 100 × (LAV max – LAV min)/LAV max

Global longitudinal strain and strain rate curves were generated by averaging longitudinal strain and strain rate measurements in all LA segments, as shown in Figure 1.

**Quantification of LA enhancement**

Our method of LA delayed enhancement measurement has been described in detail previously. In summary, we used the image intensity ratio, defined as the mean pixel intensity of each sector divided by the mean pixel intensity of the entire LA blood pool. A threshold of 0.97, which previously was shown to be correlated to a bipolar voltage of <0.5 mV, was used for LA enhancement determination.

**PVI protocol**

Details of the PVI techniques at our institution have been described previously. An endocardial map of the LA was created with an electroanatomic mapping system (CARTO; Biosense Webster, Diamond Bar, CA) and superimposed upon the pre-existing CMR image of the chamber. Radiofrequency catheter ablation using the PVI strategy was performed with a 3.5-mm open-irrigation tip (Navistar Thermocool; Biosense Webster) in all cases. The electrical isolation was confirmed by a circular multipolar electrode mapping catheter (Lasso; Biosense Webster). Acute PVI was achieved in all subjects. In persistent AF cases, the ablation procedure also included a linear LA roofline. The cavo-tricuspid isthmus was ablated if atrial flutter could be induced or was previously documented. Patients who were still in AF at the end of the procedure were electrically cardioverted.
Patients were observed in hospital for 24 hours following the procedure.

**Follow-up**

The first 3 months following the procedure were considered as a blanking period. The primary outcome of interest was >30 seconds AF recurrence or atrial tachycardia (AT) occurrence after the blanking period. The diagnosis of AF or AT was confirmed by either routine or symptom-promoted ECG or Holter/event monitoring. Follow-up also consisted of a combination of outpatient visits and phone interviews every 3 months after the procedure using a standard checklist and a follow-up questionnaire. If symptoms were suggestive of arrhythmia occurrence, patients were asked to undergo a 24-hour Holter monitoring or 30-day event monitoring based on their symptom frequency. In the absence of reported symptoms, patients were evaluated for asymptomatic recurrence using ECG and/or 1- to 7-day monitoring at 3, 6, and 12 months. Patients without recurrence were censored at the time of their last available follow-up. To prevent short-term recurrences of AF, patients were continued on the antiarrhythmic drug they presented with at the time of referral for catheter ablation. The drug was discontinued if the patient was AF free at the 3-month visit. A redo procedure was offered to those with symptomatic AT/AF recurrence after the blanking period. In patients with arrhythmia recurrence that underwent a redo procedure, pulmonary veins were assessed for reconnection.

**Statistical analysis**

Continuous variables are presented as mean ± standard deviation. Categorical data are presented as numbers and percentages. The baseline characteristics and CMR-measured LA parameters were compared among patients with and without AF/AT recurrence using the χ² test and Student t test where appropriate. Multivariable Cox proportional-hazards models were used to determine the association with late recurrence of AF/AT. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). In model 1, the association was adjusted for age and sex. Model 2 was additionally adjusted for other known clinical covariates of AF recurrence, including body mass index, hypertension, diabetes mellitus, heart failure, LVEF, type of AF (paroxysmal or persistent), AF duration, and LA volume. In model 3 the extent of LA LGE was added to model 2. To provide detailed analyses of the dose–response relationship of LA function variables with AF recurrence, we modeled the variables with restricted quadratic splines with knots at the 1st, 10th, and 99th percentiles of their distribution. In spline analyses, we used the 50th percentile of the variable as the reference value. Receiver operating characteristic (ROC) curves were generated to assess the overall performance of addition of LA functional parameters to clinical parameters in predicting arrhythmia recurrence. Areas under the curve (AUC) derived from ROC.

![Figure 1](image-url)

Figure 1  Left atrial (LA) volume and function during reservoir, conduit, and booster pump phases. A: Changes in LA volume during cardiac cycle, maximum LA volume (V<sub>max</sub>), minimum LA volume (V<sub>min</sub>), and LA volume before atrial contraction (V<sub>prea</sub>) are shown. B: LA longitudinal strain in different segments of LA are depicted by colored lines; the dotted line shows the average of LA longitudinal strain in all segments. C: LA longitudinal strain rates in different LA segments are depicted by colored lines. The dotted line shows the average of the strain rate in all segments. The points for systolic strain rate, early diastolic strain rate, and late diastolic strain rate are shown.
curve analysis were calculated and compared using a method previously described by DeLong et al. Statistical analyses were performed using STATA software (Version 11.2; StataCorp, College Station, Texas).

**Results**

The CMR image sets of 208 patients were evaluated for inclusion in the study. Sixty-nine patients (33%) were excluded because of the absence of sinus rhythm at the time of MRI. Four patients were excluded owing to the presence of severe cine image artifacts, and 3 patients were excluded because of lack of follow-up data. To make the study population homogeneous, we also excluded 11 patients who underwent cryoablation. Therefore, the final study cohort included 121 patients. Among all patients in the cohort, 25 were female (20.6%), and the average age was 59.5 ± 10 years (range, 20–83 years). During a mean follow-up of 18 months, 52 patients (42.9%) experienced AF/AT recurrence. One patient died during the follow-up period. Baseline characteristics of the patients, stratified by their outcome, are summarized in Table 1. Patients with arrhythmia recurrence had comparable baseline characteristics with patients without recurrent AF/AT except for history of heart failure, which was more common in patients with arrhythmia recurrence (19.2% vs 7.2%, respectively, \(P = .048\)).

**Left atrial structure, function, and outcome of catheter ablation**

Measurements of LA volume, function, and delayed enhancement are summarized in Table 2. Both maximum and minimum LA volumes were higher in patients with arrhythmia recurrence (LAVI\(_{\text{max}}\): 54.1 ± 12.6 mL/m\(^2\) vs 48.9 ± 17.5 mL/m\(^2\), \(P = .045\) and LAVI\(_{\text{min}}\): 32.9 ± 10.9 mL/m\(^2\) vs 26.2 ± 10.7 mL/m\(^2\), \(P < .001\)). Except active LAEF, all phasic measurements of LA function (including total LAEF, passive LAEF, peak LA strain, and strain rates) were, on average, from 19% (for passive LAEF) to 29% (for late diastolic SR) lower in patients with recurrence (\(P < .05\) for all). Patients with recurrence also had a higher extent of LA enhancement (36.9 ± 13.1 vs 29.5 ± 12.9, \(P = .009\)).

The HRs of measured LA parameters for arrhythmia recurrence are shown in Table 3. In multivariable analysis, after adjusting for age, sex, body mass index, hypertension, heart failure, diabetes mellitus, nonparoxysmal AF, AF duration, and LAVI\(_{\text{max}}\), all measured functional parameters except active LAEF had statistically significant associations with arrhythmia recurrence. When additionally adjusted for the extent of LA LGE, the association was attenuated for passive LAEF and early diastolic strain rate. Figure 2 illustrates the association of AF recurrence with LA functional parameters based on the cubic spline model after controlling for the covariates in model 2.

To further explore the additional value of LA function in predicting arrhythmia recurrence, we generated ROC curves representing each model in Table 4. The additional value of each measured LA parameter with significant association with AF/AT recurrence to the baseline model (including age, sex, body mass index, heart failure, diabetes mellitus, LVEF, AF duration, LAVI\(_{\text{max}}\), and LA LGE) was measured. As shown in Table 4, the base model including age, sex, hypertension, diabetes mellitus, nonparoxysmal AF, LVEF, LA volume, and extent of LA LGE had an AUC of 0.77 for predicting AF/AT recurrence. However, further addition of peak LA strain or total LAEF improved the AUC to 0.82 (\(P < .05\)).

Out of 54 patients with AF/AT recurrence, 21 (38%) underwent a repeat PVI. Out of 82 pulmonary veins in 21 patients, 63 were reconnected pulmonary veins, with at least 1 reconnected pulmonary vein in each patient.

**Discussion**

Here we report a strong association between CMR-measured phasic LA function and arrhythmia recurrence following PVI. The association was independent of clinical predictors of recurrence, LA size, and LGE, emphasizing the potential role of LA function in risk stratification of patients undergoing PVI.

The reported long-term recurrence rate of AF/AT after PVI in patients with AF varies widely, ranging between 25% and 60%.\(^{1,4,12}\) Several studies have shown many predictors of late recurrent AF including hypertension, nonparoxysmal AF, LA volume, and obstructive sleep apnea.\(^{3–6}\) However, these associations have been generally weak and are not confirmed in all studies. In contrast to several older studies that showed an association between LA size and the outcome of AF ablation, an independent association between LA size and outcome has not been confirmed in recent studies.\(^{7–9}\)

In our study, unadjusted models revealed an association between LA size and AF recurrence following ablation. However, after we adjusted for clinical and imaging parameters, LA volume was no longer associated with AF...
recurrence. Recently there has been emerging evidence supporting the role of LA structure and function, both as predictors of incident AF in the general population and as prognostic markers in patients with AF. Therefore, assessment of LA structure and function has been proposed as a noninvasive risk stratification method for AF patients undergoing PVI. In the ENGAGE AF_TIMI 48 cohort, 19% of 1120 subjects with AF had impaired total LAEF despite undergoing PVI. In our study, passive but not active LAEF was associated with recurrent AF/AT. To the best of our knowledge there is no similar study to investigate the association of passive LAEF and PVI outcome independent of LA LGE. One possible hypothesis for explaining why total LAEF is the only volumetric measurement that is independently associated with PVI outcome could be the stronger association of total LAEF with left ventricular end diastolic pressure compared to passive or active LAEF. LA strain analysis using echocardiography has also been used to risk-stratify AF patients. In 2 different studies decreased baseline global atrial strain measured with speckle-tracking echocardiography was associated with more AF recurrence following PVI. In these studies global peak LA strain has been superior to other echocardiographic parameters of LA deformation, such as regional strain and LAEF. However, in none of the prior studies have these associations been evaluated independent of LA fibrosis, whereas in our study lower peak LA strain and systolic and late diastolic strain rates were associated with worse outcome following PVI, independent of LA LGE.

<table>
<thead>
<tr>
<th>Measured LA parameters</th>
<th>With recurrence N = 52</th>
<th>Without recurrence N = 69</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum LA volume, mm³</td>
<td>112.8 ± 29.3</td>
<td>99.5 ± 30.2</td>
<td>.017</td>
</tr>
<tr>
<td>Maximum LA volume index, mm³/m²</td>
<td>54.1 ± 12.6</td>
<td>48.9 ± 17.5</td>
<td>.045</td>
</tr>
<tr>
<td>Minimum LA volume, mm³</td>
<td>68.8 ± 25.6</td>
<td>53.3 ± 21.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Minimum LA volume index, mm³/m²</td>
<td>32.9 ± 10.9</td>
<td>26.2 ± 10.7</td>
<td>.001</td>
</tr>
<tr>
<td>Total LAEF, %</td>
<td>40.1 ± 0.6</td>
<td>47.6 ± 8.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Passive LAEF, %</td>
<td>17.5 ± 5.7</td>
<td>21.5 ± 7.1</td>
<td>.001</td>
</tr>
<tr>
<td>Active LAEF, %</td>
<td>25.5 ± 6.9</td>
<td>23.2 ± 8.0</td>
<td>.087</td>
</tr>
<tr>
<td>Peak LA strain, %</td>
<td>21.1 ± 7.2</td>
<td>27.0 ± 7.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic SR</td>
<td>0.85 ± 0.36</td>
<td>1.09 ± 0.34</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Early diastolic SR</td>
<td>0.76 ± 0.34</td>
<td>0.99 ± 0.41</td>
<td>.001</td>
</tr>
<tr>
<td>Late diastolic SR</td>
<td>0.93 ± 0.56</td>
<td>1.32 ± 0.51</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LA LGE extent (% of LA myocardium)</td>
<td>36.9 ± 13.1</td>
<td>29.5 ± 12.9</td>
<td>.009</td>
</tr>
</tbody>
</table>

LA = left atrial; LAEF = left atrial emptying fraction; LGE = late gadolinium enhancement; SR = strain rate.

*Absolute values.

### Structural and functional LA changes in AF patients
LA mechanical and structural changes are present in patients with and without AF. It is hypothesized that these changes are adaptive responses to stressors such as hypertension, ischemia, systolic dysfunction, valvular disease, pressure and/or volume overload, and systemic inflammation. In addition, structural remodeling and LA fibrosis in response to atrial arrhythmias have been demonstrated. Studies have shown that LA remodeling is present before AF development and that remodeling progresses with increased duration of sustained AF. However, given the wide variety of adaptive responses, predicting the degree of LA remodeling using only clinical characteristics is difficult. Additionally, despite the presence of LA remodeling, many patients may not develop AF, some may develop paroxysmal AF and remain paroxysmal, and some patients are in persistent AF after their first episode of AF. We believe that in most
patients worsening LA function and extensive LA LGE could be markers of prolonged exposure to the stressors. In our previous study on 90 patients with AF, worsening LA function was associated with more extensive LA LGE. Also, LA remodeling was more prominent in persistent compared to paroxysmal AF patients and in patients undergoing a repeat ablation compared to those without prior AF ablation. In contrast, the structural and functional changes were minimal in healthy volunteers. Given the association of CMR-measured LA function and extent of LA LGE, in our previous study we hypothesized that parameters of LA function could be used as a surrogate for LA fibrosis to risk-stratify patients undergoing AF ablation. We found an

Table 4 Comparison of area under the receiver operator characteristic curves of clinical predictors and phasic left atrial function measurements for atrial tachycardia/fibrillation recurrence

<table>
<thead>
<tr>
<th>Measure</th>
<th>AUC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base model + LA LGE</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Base model + total LAEF</td>
<td>0.82</td>
<td>.048</td>
</tr>
<tr>
<td>Base model + peak LA strain</td>
<td>0.82</td>
<td>.049</td>
</tr>
<tr>
<td>Base model + systolic SR</td>
<td>0.80</td>
<td>.051</td>
</tr>
<tr>
<td>Base model + late diastolic SR</td>
<td>0.79</td>
<td>.051</td>
</tr>
</tbody>
</table>

The base model includes age, sex, hypertension, diabetes mellitus, nonparoxysmal AF, LVEF, LA volume. P values are for comparisons of each model with the base model. AUC = area under the curve; other abbreviations are the same as in Table 2.
independent association between LA functional parameters and AF recurrence following ablation. Total LAEF and peak LA strain, representatives of LA reservoir function, also provided incremental predictive values over clinical features including age, sex, hypertension, diabetes mellitus, non-paroxysmal AF, LVEF, AF duration, LA volume, and LA LGE.

**Challenges in the assessment of LA function**

Phasic LA function can be assessed using both volumetric and deformational analysis methods. Measurement of the volume during the cardiac cycle enables calculation of passive, active, and total LAEF representatives of conduit, contractile, and global/reservoir functions, respectively. On the other hand, the deformational analysis focuses on the global or regional phasic strain or strain rate. In most current studies, assessment of LA function has been performed using tissue Doppler imaging or speckle-tracking echocardiography. However, because of the posterior location and thin wall of the LA, and the complex atrial geometry with presence of pulmonary veins and atrial appendage, accurate assessment of LA function using echocardiography could be challenging. To the best of our knowledge, there are no studies comparing LA functional parameters measured by echocardiography and CMR. However, there are multiple studies showing underestimation of echocardiography in the measurement of LA volume compared to CMR by 14%–37%. Also, both inter- and intra-observer reproducibility for LA volume measurement have been reported to be lower in 2-dimensional echocardiography compared to CMR. On the other hand, the higher spatial resolution of CMR, which is independent of the cardiac chamber’s anatomic location, makes it a more accurate modality in detection of the LA border. More recently, feature-tracking CMR has been proposed as an accurate modality for the assessment of LA function. The advantage of this semi-automated method is its ability to measure LA strain and strain rate, which has been shown in a previous study performed by echocardiography to be superior to volumetric measures in predicting success of PVI.

**Limitations**

This study is performed only on patients with available CMR prior to the procedure; therefore, patients with renal failure or those with cardiac implantable electronic devices are not included in our cohort, which limits the generalizability of our results to patients in these subgroups. Additionally, the assessment of phasic LA function precluded imaging during AF and restricts the generalizability of these results to patients in sinus rhythm at the time of CMR. This would be potentially more limiting for patients with persistent AF. However, patients with persistent AF accounted for 28% of our study population who were in sinus rhythm at the time of CMR. The AF duration in this study was determined by ECG documentation, which may have underestimated the actual duration of AF. No cardioversions were performed in this cohort within 2 weeks of CMR. Our study population, however, did not undergo routine pre-CMR rhythm monitoring. Therefore, having a depressed atrial function should be interpreted cautiously, given the possibility of atrial mechanical “stunning” as a result of a recent spontaneous conversion to sinus rhythm. Finally, implantable loop monitors were not used in this study. Additionally, while routinely performed, the duration of monitoring for asymptomatic AF varied from ECG to 7-day monitoring. Importantly, however, the duration of monitoring was not differential with respect to LA function, LGE, or AF recurrence.

**Conclusions**

We report a strong association between CMR-measured reservoir LA function and AF recurrence after catheter ablation. The association is independent of clinical predictors of recurrence and LA LGE. CMR imaging prior to AF ablation is often performed in many centers. In patients in sinus rhythm at the time of CMR, incorporating LA functional parameters alone or in addition to the LA enhancement may improve risk stratification of AF patients undergoing catheter ablation.

**Appendix**

**Supplementary data**

Supplementary material cited in this article is available online at [http://dx.doi.org/10.1016/j.hrthm.2016.01.016](http://dx.doi.org/10.1016/j.hrthm.2016.01.016).

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