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ATRIAL FIBRILLATION

Cardiac MRI assessment of atrial fibrosis in atrial fibrillation: implications for diagnosis and therapy

Koji Higuchi, Mehmet Akkaya, Nazem Akoum, Nassir F Marrouche

Atrial fibrillation (AF) is the most commonly encountered cardiac arrhythmia in clinical practice, with a prevalence of 0.4–1% in the US population. AF is a potent risk factor, increasing the risk of stroke fivefold and accounting for approximately 15% of all strokes in the USA. AF also significantly increases the risk of mortality from heart failure. Many therapies, including pharmacological approaches and direct current cardioversion, have been tried to treat this malignant arrhythmia, but were not found to be that effective.

Catheter ablation of AF has provided better outcomes compared with other treatments, especially by applying pulmonary vein (PV) isolation in patients with paroxysmal AF. However, other procedures modifying the substrate of AF, such as complex fractionated atrial electrogram ablation or posterior wall debulking, are required to obtain satisfying results for persistent AF patients with massive left atrial structural remodeling (LASRM) caused by massive atrial fibrosis.

Since atrial fibrosis is one of the main factors determining AF relapse after catheter ablation, evaluating atrial fibrosis in AF subjects is now of increasing importance for AF ablation strategies. Nowadays echocardiography is the mainstream technique for detecting LASRM which may cause left atrial (LA) volume expansion and atrial conduction slowing and heterogeneity. Late gadolinium enhancement (LGE) MRI has the greatest predictive value for atrial fibrosis in AF.

DEVELOPMENT OF ATRIAL FIBROSIS

Electrical remodelling: ‘AF begets AF’

Recognising that AF alters atrial electrophysiological properties and promotes AF induction and maintenance—that is, ‘AF begets AF’—is a breakthrough in AF pathophysiology. AF induces electrical remodelling primarily due to a very rapid atrial rate and associated tachycardia induced atrial remodelling. Action potential duration (APD) decreases during AF due to disruption of ion channel functions such as L-type Ca2+ currents, inward-rectifier K+ currents, and transient outward K+ currents. Diminished APD shortens atrial refractoriness and reduces the wavelength, which allows for smaller and more atrial re-entry circuits, thus making AF unlikely to terminate.

Replacement by fibrotic tissue

The perpetuation of AF and continuous electrophysiological disturbance (electrical remodelling) in atrial myocytes ultimately cause cell apoptosis, and then fibrotic tissue replaces the dead atrial myocytes. Underlying mechanisms developing interstitial fibrotic tissue into atria are not fully understood and may vary in different structural heart disease. However, several hormonal factors are known to be profibrotic factors such as transforming growth factor (TGF)-β1, platelet derived growth factor, connective tissue growth factor, and angiotensin II. These profibrotic factors are involved in signal transduction for activating fibroblasts and replace dead myocytes with fibrotic tissue. As fibrotic tissue penetrates into the atria, AF is not likely to stop spontaneously as fibrotic tissue develops more substrate of AF. The question still remains, however: Is it fair to implement the findings from an experimental AF model into human AF, or are we dealing with two different AF models?

EVALUATING LASRM USING LGE-MRI

LGE-MRI enables us to distinguish diseased myocardium from normal myocardium by utilising slow washout kinetics of gadolinium in diseased tissue. For some time, LGE-MRI has been used for detecting fibrosis in the left ventricle in conditions such as myocardial infarction, dilated cardiomyopathy, and hypertrophic cardiomyopathy. Detecting fibrosis in the LA wall using LGE-MRI was first applied by our group at the CARMA Center, and enabled us to visualise the location, extent, and amount of atrial fibrotic changes. In this study the LA was scanned using LGE-MRI to evaluate the extent of enhancement in the LA before AF ablation, and correlated with low voltage area in three dimensional (3D) electroanatomical mapping (CARTO; Biosense Webster, Diamond Bar, California, USA) during AF ablation (figure 1). Low voltage areas in electroanatomical mapping demonstrated a significant association with the area of LGE on the LA (figure 1); also the amount of LGE had an excellent correlation with the amount of low voltage tissue in electroanatomical mapping (figure 2). In this study, the extent of LA wall enhancement had the greatest predictive value for AF recurrence after ablation with the greatest odds ratio after multivariate analysis including LA volume. This study paved the way to establish LGE-MRI as an atrial disease (fibrotic tissue) detection and quantification tool.

Standard LGE-MRI sequence for LA

Studies are currently being performed with 1.5 or 3 Tesla clinical MR scanners (Siemens Medical

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Solutions, Erlangen, Germany) 35±15 days before ablation using phased array receiver coils. Each scan is acquired about 15 min following contrast agent injection (0.1 mmol/kg, Multihance (Bracco Diagnostic Inc, Princeton, New Jersey, USA)) using a 3D inversion recovery, respiration navigated, ECG gated, gradient echo pulse sequence. Typical acquisition parameters are: 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), and inversion time (TI)=270–320 ms. The other imaging parameters are optimised for respective field strength of scanner to improve fibrosis visibility and simultaneously keep scan duration acceptable for patients (<15 min). For scans performed on a 1.5 Tesla scanner the parameters are: TR=5.4 ms, TE=2.3 ms, and flip angle=20°. For scans performed on a 3 Tesla scanner the parameters are: TR=3.1 ms, TE=1.4 ms, and flip angle=14°. ECG gating is 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 is defined using the cine images of the LA. Fat saturation is used to suppress fat signal. The TI value for the LGE-MRI scan is identified using a TI scout scan.

Quantification of LASRM from LGE-MRI

After image acquisition, the LA wall is manually segmented from an LGE-MRI image by expert observers using Corview image processing software (MARREK Inc, Salt Lake City, Utah, USA). The protocol for segmentation is processed as follows. First, the endocardial border of the LA is defined, including the extent of PV sleeves, by manually tracing the LA-PV blood pool in each slice of the LGE-MRI. Next, the endocardial segmentation is morphologically dilated and then manually adjusted to create an assessment of the boundary of the epicardial LA surface. Finally, the endocardial segmentation is subtracted from the epicardial segmentation to define a wall segmentation, which is manually edited to exclude the mitral valve and PVs. Thus, the resulting LA wall segmentation includes the 3D extent of both the LA wall and the antral regions of the PVs.

Quantification of the LASRM is as follows. To delineate regions of LASRM in pre-ablation LGE-MRI, we define the enhancement through an intensity threshold that is determined by expert inspections. To assist this process, initial visualisation uses a volume rendering tool in Corview that allows the operator to visualise the distribution of enhancement in 3D. A custom transfer function allows the operator to define gradations of

Figure 1 Late gadolinium enhancement (LGE) MRI and electroanatomical mapping in patients with mild, moderate and severe left atrial (LA) structural remodelling. (A) Two dimensional slice from LGE-MRI scan. (B) Three dimensional (3D) LGE-MRI (maximum intensity projection) scans show LGE on the LA wall. (C) Colour map of 3D LGE-MRI scan. Area of structural remodelling (fibrosis) is displayed in green and healthy myocardium in blue. (D) Low voltage areas in electroanatomical mapping show good correlation with the area of LGE on the LA. EA, electroanatomical; LASRM, left atrial structural remodelling; MIP, maximum intensity projection; PA, posterior anterior.

Figure 2 Correlation between enhancement on late gadolinium enhancement (LGE) MRI and low voltage regions on electroanatomic (EA) map, which represents structural remodelling. Linear regression between the extent of enhancement seen on 18 segmented left atrial models of LGE-MRI and the amount of low voltage tissue seen on 18 segmented electroanatomic map graded by blinded reviewers.
enhancements, while suppressing blood and normal tissue with a transfer function.

Inter-observer and intra-observer differences were evaluated for the validation of this quantification process in the study by Oaks et al.\textsuperscript{9} Inter-observer difference was calculated using two independent observers, and the average difference was 0.9%. Intra-observer difference was 0.49%.

**Correlation of LGE-MRI with human tissue sample from the LA**

Tissue samples from the LA of a human autopsied heart were obtained at the University of Utah and examined for fibrosis penetrating into the LA wall. Masson’s trichrome staining showed that the region with high gadolinium enhancement expressed a massive penetration of fibrosis (figure 3-1), whereas minimal penetration of fibrosis was detected in the region with low gadolinium enhancement (figure 3-2).

**STAGING OF LASRM AND ITS IMPLICATION**

Although several studies have been conducted to determine predictors of AF recurrences following catheter ablations, identifying the ideal candidate for catheter ablation of AF remains a significant challenge. Akoum et al\textsuperscript{10} reported important data which can be utilised for personalising the strategy of AF ablation. Based on the amount of pre-ablation delayed enhancement in the LA wall, patients are divided into four stages of LASRM. Utah stage I is defined as $\leq 5\%$ enhancement (minimal), Utah stage II as $>5\%$ and $\leq 20\%$ enhancement (mild), Utah stage III as $>20\%$ and $\leq 35\%$ enhancement (moderate), and Utah stage IV as $>35\%$ enhancement (extensive) (figure 4). Patients with minimal LASRM (Utah stage I) had excellent results after AF ablation, whereas poor results were obtained in patients with extensive LASRM (Utah stage IV) (figure 5). Interestingly, they also demonstrated in this study, using the Cox multivariate regression model, that creating an ablation scar on the LA posterior wall becomes more important than PV isolation as LASRM advances.\textsuperscript{10}

These results have an important impact on clinical decision making, both for AF patients and physicians managing the arrhythmia. For patients, expectations on the outcome of the AF ablation procedure can be satisfactorily estimated and the patient can then weigh the risks of undergoing the ablation procedure against the benefits of maintaining sinus rhythm. For electrophysiology (EP) cardiologists, quantification of LASRM (fibrosis) can be used effectively for counselling patients about the expected outcomes after catheter ablation. Moreover, the operator can plan the procedure better with the knowledge that patients with advanced LASRM will have an improved outcome with a more extensive ablation on the posterior LA wall, rather than with only PV isolation.

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![Figure 3](image)

**Figure 3** Tissue samples corresponding to the red squares in three dimensional (3D) late gadolinium enhancement (LGE) MRI of the left atrium. The degree of fibrotic tissue penetration correlated fairly with the degree of enhancement in 3D LGE-MRI. AP, anteroposterior; ENDO, endocardium; EPI, epicardium; MVR, mitral valve regurgitation; PA, posteroanterior.

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Based on the results described above, we have developed a treatment algorithm to individualise AF ablation strategies. Ablation therapy (PV isolation and posterior wall debulking) would be applied for all patients in Utah stage I and II, and also for patients with localised fibrosis in Utah stage III. For Utah stage III patients with diffuse fibrosis, however, pharmacotherapy including anticoagulants would be given instead of ablation therapy. All patients in Utah stage IV would be treated only by medication (Figure 6).

**LASRM DETECTED BY LGE-MRI AND RISK OF STROKE**

The CHADS₂ score is a simple and thus widely used risk stratification model for predicting the risk of stroke. Risk factors included in the CHADS₂ score are congestive heart failure, hypertension, age, diabetes, and prior stroke. However, this score does not include some common risk factors and thus it still has a poor ability to predict strokes.²⁵ In addition, the CHADS₂ score has been shown to have a poor predictive power for patients with moderate risk, who comprise the majority of patients with AF.²⁶ Claire et al also evaluated the predictive value of the CHADS₂ score in a systematic review and meta-analysis, in which modest C-statistic values were indicated (0.63, 95% CI 0.52 to 0.75).²⁷ Recently, the CHA₂DS₂-VASc score has been proposed as an alternative to the CHADS₂ score and has been incorporated into the 2010 European Society of Cardiology guidelines. The CHA₂DS₂-VASc score is a new scoring system, and the risk factors are congestive heart failure, hypertension, age, diabetes, prior stroke, vascular disease, and sex. Friberg et al¹¹ have evaluated risk factors and risk classification schemes for ischaemic stroke and bleeding in 182 678 patients with AF from the Swedish National Hospital Discharge Registry. The authors found that discrimination for stroke events was minimally improved by the CHA₂DS₂-VASc score compared with the CHADS₂ score (C-statistic 0.67 vs 0.66).¹¹ w²⁸ However, the CHA₂DS₂-VASc score did help identify a very low risk group of patients.²⁹

In the study by Daccarett et al,¹² the association of LASRM evaluated by LGE-MRI with stroke risk and also with the CHADS₂ score was investigated. Patients who experienced a prior stroke had a significantly higher percentage of LASRM than those without a history of previous stroke (24.4±12.4% vs 16.1±9.8%, p<0.001). Patients with minimal remodelling (quartile 1: <8.5% LGE) experienced very low rates of thromboembolism (1%).

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Figure 4  Left atrial three dimensional late gadolinium enhancement (LGE) MRI displayed in the posteroanterior view illustrating areas of structural remodelling (fibrosis, bright green; blue, healthy myocardium) across the four stages of structural remodelling. Images of two representative patients in each stage are displayed. Utah stage I ≤5% enhancement (minimal), Utah stage II >5% and ≤20% enhancement (mild), Utah stage III >20% and ≤35% enhancement (moderate), Utah stage IV >35% enhancement (extensive).

Figure 5  Kaplan–Meier survival curve depicting atrial fibrillation recurrence stratified over the different stages of structural remodelling. Utah stage I ≤5% enhancement (minimal), Utah stage II >5% and ≤20% enhancement (mild), Utah stage III >20% and ≤35% enhancement (moderate), Utah stage IV >35% enhancement (extensive).

In comparison, 19.6% of patients with extensive remodelling (quartile 4: >21% LGE) experienced an ischaemic event (figure 7). In addition, LASRM had a significant correlation with stroke prevalence and the CHADS² score. Using multivariate regression analysis, LASRM evaluated by LGE-MRI was independently associated with stroke.

Furthermore, LASRM evaluated by LGE-MRI was found to have a strong association with left atrial appendage (LAA) thrombus which was found during transoesophageal echocardiography examination. The C-statistics for the predictive value of LGE-MRI for thrombus detection in LAA indicated 0.87, which showed a very strong predictive value (figure 8), whereas the CHADS² and CHA²DS²-VASc scores conveyed moderate C-statistics between 0.6 and 0.7.

**CLINICAL IMPLICATION OF LGE-MRI EVALUATION OF LA**

Catheter ablation for AF has emerged as a promising therapeutic option which can successfully emancipate patients from this malignant arrhythmia. In fact, many studies have demonstrated the AF-free survival rate to be between 30–60% at 5 years follow-up. Even after multiple procedures, the arrhythmia-free survival rate was around 60% at 5 years post-ablation if persistent AF patients (probably with massive fibrosis in the LA) were included in studies. Since we still cannot exactly predict the outcome after AF ablation procedures in each patient, we need to include potential non-responders for AF ablation.

Although comorbidities associated with AF, such as hypertension, diabetes, valvular disease, age, etc, might be similar in the majority of the AF population, we have shown that the atrial disease detected using MRI is widely different (figure 4), and conclude that following comorbidities as a tool to predict procedural outcome and plan treatment is not satisfactory.

LGE-MRI seems to be able to individualise AF treatment based on the quality and quantity of the atrial fibrotic disease. As shown in this article, LGE-MRI is an established tool not only to predict procedural outcome and define the best ablation approach, but also to predict the risk of stroke and thrombus formation associated with AF.

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**Figure 6** The algorithm of individualised treatment for patients with atrial fibrillation based on Utah classification. Utah stage I ≤5% enhancement (minimal), Utah stage II >5% and ≤20% enhancement (mild), Utah stage III >20% and ≤35% enhancement (moderate), Utah stage IV >35% enhancement (extensive). LGE, late gadolinium enhancement.

**Figure 7** Stroke prevalence in patients with different degrees of left atrial structural remodelling. Quartile 1 (n=97), <8.5%; quartile 2 (n=97), 8.6–16%; quartile 3 (n=97), 16.1–21%; quartile 4 (n=96), >21%. LA, left atrial; LGE, late gadolinium enhancement.
LIMITATION OF LGE-MRI ASSESSMENT OF ATRIAL FIBROSIS

In the study by Oakes et al., even though the extent of LASRM detected by LGE-MRI was an independent and the strongest predictor of AF recurrence after ablation, LA volume was also an independent predictor of AF recurrence. Therefore, both LGE-MRI assessment and echocardiogram evaluation should be considered to assess LASRM, since both parameters definitely have a strong correlation.

There are inherent limitations of image quality in cardiac MRI, especially when scanning the thin LA wall compared with the left ventricular wall. The poor image quality is due in part to the lack of technician education, the uncontrolled heart rate, and the obesity of patients. Despite this, in the past few years major progress has enabled us and other facilities to obtain higher quality images and decrease the rate of poor quality images to <4%.

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