Role of Magnetic Resonance Imaging of Atrial Fibrosis in Atrial Fibrillation Ablation

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Abstract

Atrial fibrillation (AF) likely involves a complex interplay between triggering activity, usually from pulmonary vein foci, and maintenance of the arrhythmia by an arrhythmogenic substrate. Both components of AF, triggers and substrate have been linked to atrial fibrosis and attendant changes in atrial electrophysiology. Recently, there has been a growing use of imaging modalities, particularly cardiac magnetic resonance (CMR), to quantify the burden of atrial fibrosis and scar in patients either undergoing AF ablation, or who have recently had the procedure. How to use the CMR derived data is still an open area of investigation. The aim of this article is to summarise what is known as atrial fibrosis, as assessed by traditional catheter-based techniques and newer imaging approaches, and to report on novel efforts from our group to advance the use of CMR in AF ablation patients.

Keywords

Atrial fibrillation, fibrosis, catheter ablation

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Atrial fibrillation (AF) is a remarkably common arrhythmia, affecting roughly 6 % of patients over 65 years of age, with an estimated US prevalence of over two million patients.¹ That prevalence is likely to increase as patients live longer, and will contribute to rising morbidity and mortality over time.^{2–4}

Efforts to treat AF remain imperfect. Rhythm control approaches typically consist either of antiarrhythmic drug use or, increasingly, catheter ablation of atrial targets. Over the last decade there has been general consensus among treating electrophysiologists that for most patients, isolation of triggering foci in the pulmonary vein (PV) ostia is the mainstay of ablative therapy.⁵ Recently, this paradigm has been challenged, in part because of better understanding of atrial fibrosis and ensuing abnormal patterns of atrial conduction that may serve to sustain AF once induced.⁶ Novel approaches targeting stable electrical rotors may represent a new approach to catheter ablation of AF. The purpose of this review is to summarise the state of knowledge about fibrosis as a contributor to AF, and how cardiac magnetic resonance (CMR) is increasingly utilised to assess for atrial fibrosis and inform clinical decision-making.

Basic Mechanisms

Decades ago Gordon Moe reported that AF was due to the functional reentry of several wandering wavelets coursing through atrial tissue.^{7–9} The hypothesis was based largely on modeling work. Allesie and colleagues performing cardiac mapping studies further investigated this hypothesis years later. Pacing-induced AF was shown by Allesie to shorten atrial refractory periods, thus increasing the potential for reentry and the perpetuation of AF.^{10–12} Subsequent investigators have

found that in addition to the fundamental changes in refractoriness of atrial tissue, conduction velocity is significantly reduced in diseased atria that are prone to fibrillation.¹³

Changes in atrial conduction are likely the result of altered myocyte connectivity, due both to changes in gap junction-mediated electrical coupling and to the formation of interstitial fibrosis and scarring.^{14–17} This combination of deranged conduction (with likely areas of frank conduction block), reduced refractoriness and triggering foci conspire to create a perfect substrate for initiation and maintenance of reentry. Triggered beats arrive at areas of unidirectional block, and are conducted slowly through fibrotic tissue. Shortened refractory periods allow for rapid electrical recovery of diseased tissue and the perpetuation of the arrhythmia.

The role of fibrosis in this process has been investigated in experimental models and in patients. Forced generation of fibrosis in a variety of investigational constructs, by gene overexpression in mice,¹⁸ by tachycardia-induced myopathies,^{19,20} in ageing models,^{21,22} and in models of valvular heart disease,²³ all are linked with the development of sustained AF. In humans, AF is typically seen in conditions known to cause increased burdens of atrial scar, including congestive heart failure (CHF), valvular disease and coronary disease.^{24–27} While there appears to be a clear association between conditions linked with increased atrial fibrosis and AF, how fibrosis may contribute to AF is more speculative. As discussed above, one plausible mechanism is through alterations in atrial conduction properties. A second mechanism may be that fibrotic regions, like the PV ostia, give rise to triggering beats that initiate AF from non-PV foci.

Scar Mapping

Catheter ablation strategies have evolved significantly over the last 15 years. Early ablation approaches emulated the long lesions created by the surgical maze procedure of Dr James Cox, and were designed to compartmentalise atrial tissue into discreet regions incapable of sustaining AF.^{28–31} With Haïssaguerre's observation that PV foci serve as triggering sites that frequently initiate AF,³² ablation strategies quickly evolved towards those designed to isolate or eliminate PV triggers. Focal and segmental ablation has largely given way to wide area circumferential ablation approaches, with adjunctive therapy (linear lesions, ablation of ganglia, mapping and ablation of rotors) performed occasionally for persistent AF.⁵

Catheter ablation has allowed for direct, voltage-based assessment of left atrial (LA) fibrosis in humans with AF. Natale and colleagues have reported on perhaps the largest series of patients (700) undergoing initial pulmonary vein isolation (PVI).³³ They describe that areas of frank scar, as determined by catheter-based assessment of electrogram amplitude, were present in 6 % of patients, and that scar appeared to correlate with large LA size, low ejection fraction (EF) and elevated C-reactive protein (CRP) levels. Patients with scar had an AF recurrence rate of 57 %, compared with 19 % recurrence in those free of scar. The investigators concluded that scarred regions likely contribute to AF both by providing regions of slow conduction and block, and also potentially by giving rise to ectopic, triggered beats.

Other investigators have also documented not only scar, but significant regional heterogeneity of scar distribution in patients with AF versus non-AF controls. AF patients appear to have an increased total burden of scar, with a concentration of fibrotic tissue particularly in the posterior LA wall.³⁴ More recently, investigators have turned to non-invasive scar assessment using CMR, and correlating those image-based measurements with catheter-based ones. A discussion of magnetic resonance (MR)-based scar quantification is provided below.

Cardiac Magnetic Resonance for Assessment of Left Atrial Scar

The use of late gadolinium enhanced (LGE) CMR to assess the overall burden and distribution of LA scar was first proposed by Dr Dana Peters. After the initial report by Peters, Marrouche and colleagues made significant strides in applying this technique to the management of patients with atrial arrhythmia. However, the technique requires significant expertise for proper implementation in scanners and for proper image analysis. Therefore, it has been slow to be adopted in routine practice. Our group has focused on methodologies to improve objective quantification of scar and generalizability of results to clinical practice.

How Does Late Gadolinium Enhanced Identify Scar Tissue?

The technique of LGE takes advantage of differential uptake and washout kinetics of gadolinium contrast in blood, healthy myocardium and myocardial scar. Contrast levels peak in the blood ahead of normal myocardium and scar. Therefore, imaging immediately after contrast injection results in enhancement of the blood pool and cardiac chambers thus providing optimal images for segmentation of the LA. Contrast perfuses into normal myocardium and scar later than the cardiac chambers. However, due to poor perfusion of scar tissue, contrast washout from scar is delayed compared with normal myocardium. At the time of late imaging, contrast has washed out of normal myocardium, and has high concentrations in scar

myocardium. Therefore, LGE imaging highlights scar myocardium. The technique has been used for two principal aims in AF patients:

- to characterise the pre-existing LA scar burden prior to AF ablation for prognostic purposes; and
- to characterise the post-ablation scar burden and distribution, both for prognosis and for potential planning of redo ablation procedures.

Pre-ablation Assessment of Left Atrial Scar

The first report that applied LGE imaging to LA scar was performed in patients who had undergone AF catheter ablation. Peters and colleagues obtained high-spatial-resolution free-breathing LGE images in 23 patients with AF. They examined the LA in 15 patients before ablation and in 18 patients at least 30 days after ablation. The presence of LGE on images and circumferential completeness of scar around the pulmonary veins was assessed. Contrary to later results, the investigators found no pre-ablation LGE in any participants. However, post-ablation LGE was seen in all patients. Only 62 % of patients images revealed greater than 90 % circumferential LGE of the pulmonary veins.³⁵ Following this work, Marrouche and colleagues reported on a series of 46 patients that underwent LGE CMR prior to and after AF ablation. Pre-procedure CMR detected LA fibrosis in 8.7 % of patients.³⁶

Two years following this initial study, Marrouche and colleagues refined their image analysis methodology for assessment of LGE burden, and introduced the Utah scoring system. In this study, which focused on patients with lone AF,³⁷ the Utah system categorised patients by the extent of enhanced LA area, dividing patients into four groups: 1 (<5 %), 2 (5–20 %), 3 (20–35 %) and 4 (>35 %). In this cohort of patients, procedural outcomes were predicted by baseline LA scar burden. After a mean follow-up of 324 days all patients in the group 1 were free of AF, in contrast with only 4 % of patients in group 4, which remained free of AF. The authors concluded that CMR is a powerful tool for pre-procedural patient selection for catheter ablation of AF. Subsequently, Marrouche and colleagues have proposed that the strategy used during AF ablation, such as stand-alone PVI versus coupling of PVI with linear ablations or debulking, be informed by scar burden as assessed by LGE CMR.^{38,39} The outcomes of patient-specific ablation strategies tailored based upon the pre-procedural scar burden remain unknown.

T1 Mapping of Left Atrial Myocardium

The technique of CMR T1 mapping is an emerging tool for objective quantification of myocardial fibrosis, previously applied to non-invasively quantitate the degree of ventricular global diffuse (rather than cohesive) fibrosis. We recently performed a study to examine the feasibility of LA myocardial T1 mapping in 51 patients before AF ablation and in 16 healthy volunteers. The T1 relaxation time is shorter in tissues that contain diffuse fibrosis. We found that the median LA T1 relaxation time was shorter in patients with AF compared with healthy volunteers, and was shorter in patients with AF with prior ablation compared with patients without prior ablation. In a generalised estimating equations model, adjusting for data clusters per participant, age, prior ablation, AF type, hypertension and diabetes, each 100 milliseconds (ms) increase in T1 relaxation time was associated with 0.1 millivolt (mV) increase in intracardiac bipolar LA voltage ($P=0.025$). This novel methodology, which provides an objective and easy to measure estimate of diffuse fibrosis, may improve the quantification of fibrotic changes in thin-walled myocardial tissues.⁴⁰

The Assessment of Left Atrial Scar After Ablation

A number of studies have focused on assessing the utility of LGE imaging of LA scar after ablation. The burden of scar visualised by LGE after ablation includes not only endogenous atrial fibrosis, but also the ablation lesion set. Scar burden prior to ablation is negatively associated with post-ablation outcome. However, after AF ablation the implications of high scar burden on LGE images are different. It has been reported that increased density of LA scar after AF ablation associates with improved procedural outcomes. Marrouche and colleagues reported that in 144 patients that had undergone AF ablation, the LA total LGE burden and the degree of circumferential isolation of pulmonary vein ostia were directly proportional with freedom from AF after the procedure.⁴¹ Completely circumferential scar surrounding all four pulmonary veins was seen in only 7 % of patients. It has been proposed that post-procedure CMR can be used to assess the adequacy ablation,⁴² that ablated regions on CMR correlate well with ablation sets recorded on electroanatomical mapping systems,⁴³ and that repeat ablation can be guided by LGE CMR images obtained after the initial procedure.⁴¹

The resolution of CMR, as performed at Johns Hopkins Hospital, remains suboptimal for identification of conduction gaps in lesion sets. In a recent study, we enrolled 10 patients undergoing repeat ablation for AF recurrence to undergo pre-procedural LGE-CMR of the LA in conjunction with high-density voltage mapping of the LA during the ablation procedure. LA wall regions with hyperenhancement were segmented from LGE-CMR images and retrospectively co-registered with the electroanatomic LA map. Of 37 pulmonary veins, 30 had regained electrical continuity with the LA. At the end of the repeat procedure, all patients underwent successful re-isolation of all pulmonary veins using standard ablation techniques. In this cohort of patients we noted a significant association between scar identified by LGE and low-voltage regions of the LA. However, there was no association between scar gaps and PV reconnection sites.⁴⁴

Other Potential Uses for Left Atrial Scar Images

Non-invasive assessment of LA scar burden using LGE CMR may also prove helpful for stroke risk stratification in the setting of

AF,⁴⁵ for assessment of LA pump function post-ablation,⁴⁶ and for evaluation of collateral damage to structures abutting the LA during AF ablation.⁴⁷ It is likely that with improving techniques for higher spatial and contrast resolution, the utility of CMR imaging for pre-, peri- and post-procedural guidance of AF ablation will continue to increase.

Potential Limitations of the Technique

The CMR technique of LGE for imaging LA scar requires significant expertise for image acquisition and image analysis. Therefore, the generalizability of results is not optimal. Additionally, image artifacts due to arrhythmia, patient movement and breathing, and poor myocardium or fat signal suppression, result in inadequate image quality in a significant proportion of cases even at the most experienced centres. However, new techniques for image acquisition and analysis may soon improve the quality and reproducibility of images, as well as the generalizability of results to routine clinical practice. Further improvements in image resolution and contrast-to-noise ratio by using higher field strength scanners, equilibrium contrast imaging by continuous infusion of contrast, endogenous contrast mechanisms, and/or reducing the sensitivity of images to motion artifacts with prolonged scan-time using free breathing acquisitions combined with temporal filtering or parallel reconstruction are likely. Adoption of image analysis techniques that standardise measurements of scar across all patients will also improve the inter-patient and longitudinal intra-patient comparability of LA fibrosis.

Conclusions

The presence of LA scar likely contributes to AF initiation and maintenance, the response to ablation, LA function post-ablation, and the risk of stroke over time. The CMR techniques of LGE and T1 mapping will likely improve our understanding of the atrial arrhythmia substrate. Patient-specific strategies for AF ablation based upon such pre-procedural images have the potential to revolutionise our current strategies, especially for treatment of persistent AF. However, significant challenges remain due to the thin profile of the LA wall, which is near the limit of CMR image resolution. Improved techniques for optimal image resolution and reproducible image analysis are necessary. ■

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