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LGE-MRI Characterization of Left Atrial Fibrosis: a Tool to Establish Prognosis and Guide Atrial Fibrillation Ablation

Eva M. Benito [1,2,3] · Francisco Alarcon [1,2,3] · Lluís Mont [1,2,3,4]

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Abstract

Purpose of Review Atrial fibrillation (AF) is the most frequent arrhythmia and also an important cause of morbidity, hospitalization, and mortality. Pulmonary vein isolation (PVI) is often the preferred therapy, but the incidence of recurrences is still significant. This review summarizes the contribution of atrial substrate identification using late gadolinium enhancement magnetic resonance imaging (LGE-MRI) to establish prognosis and to guide AF ablation.

Recent Findings Left atrial (LA) fibrosis is thought to create the necessary substrate to sustain AF. The accuracy of LGE-MRI to identify areas of atrial fibrosis remains controversial. However, the amount of LA fibrosis visible in the 3D reconstruction of LGE-MRI has been identified as a sign for AF progression and poor outcome after ablation. Additionally, the scar created by radiofrequency and cryoablation lesions can be visualized after the procedures. Discontinuities in PVI ablation lines have been related to recurrence and can be used to identify electrical reconnections. Ongoing research is directed toward validating fibrosis ablation as a new target to improve ablation outcomes.

Summary Atrial fibrosis assessment by LGE-MRI may show the severity of atrial disease and could be used to select patients likely to benefit the most from AF ablation. Usefulness of an individually tailored LGE-MRI-guided ablation approach is still under evaluation.

Keywords Atrial fibrosis · Atrial fibrillation · Catheter ablation · Late gadolinium enhancement magnetic resonance · Substrate

Abbreviations

AF	Atrial fibrillation
IIR	Image intensity ratio
LGE-MRI	Late gadolinium enhancement magnetic resonance
LA	Left atrium
PVI	Pulmonary vein isolation
SI	Signal intensity

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✉ Lluís Mont
lmont@clinic.cat

Eva M. Benito
Benitom@clinic.cat

Francisco Alarcon
Falarcon@clinic.cat

[1] Institut Clínic Cardiovascular, Hospital Clinic, Universitat de Barcelona, Barcelona, Catalonia, Spain

[2] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain

[3] Cardiology Department, Hospital Clinic, C/Villarroel, 170, 08036 Barcelona, Spain

[4] CIBERCV, Instituto de Salud Carlos III, Madrid, Spain

Introduction

Characterization of left atrial (LA) fibrosis using late gadolinium enhancement magnetic resonance imaging (LGE-MRI) has emerged as a promising technique to identify and quantify fibrotic tissue [1, 2•, 3•]. The amount and location of atrial fibrosis may have clinical implications in prognosis and treatment of atrial fibrillation (AF) [4, 5, 6••]. This review aims to summarize the currently available trials focused on atrial substrate identification by LGE-MRI directed to establish prognosis and to guide atrial fibrillation procedures.

Left Atrial Remodeling: Atrial Fibrosis

Structural remodeling of the left atrium can be evidenced by collagen deposition in the interstitial space of myocardial fibers.

The presence and degree of fibrotic tissue are related to the etiology and progression of atrial fibrillation [7, 8]. Atrial fibrosis increases with age and is more frequent in patients with cardiomyopathies or hypertension [9], but also has been reported in patients with AF but no structural heart disease (*lone AF*) [4].

LGE-MRI: a Non-Invasive Tool for the Assessment of Atrial Fibrosis

LGE-MRI detects myocardial fibrosis. The paramagnetic metal present in gadolinium-based contrast agents has the ability to accumulate in the extracellular space, modifying the magnetic properties of water. As fibrotic tissue has a greater proportion of extracellular space, compared to healthy myocardium [10], gadolinium accumulates in this expanded extracellular space after infusion of contrast. The resulting delay in the contrast wash in and wash out leads to higher signal intensity (SI) in T1-weighted MRI scans [11].

Although fibrosis visualization in LGE-MRI has been widely adopted at the ventricular myocardium level [12], the limited spatial resolution of MRI scanning results in a challenge for accuracy in fibrosis discrimination in the narrower atrium walls. Several acquisition protocols and post-processing software approaches are being used, mainly as a research tool [13•]; their use in clinical practice remains limited. Table 1 summarizes the different approaches reported to date in native atrium [1, 2•, 3•, 6••, 26] and in post-ablation patients [17••, 20••, 22, 28, 29].

Image Post-Processing Algorithms and Thresholds to Identify Atrial Fibrosis

Acquisition image protocols, either in 1.5 T or 3 T MRI scanners, are similar between groups. The main differences are related to the algorithms used for post-processing and the method for choosing the SI threshold to define fibrosis. The Utah group uses the Corview image processing and analysis software (Marrek, Sal Lake City, Utah) with a dynamic threshold based on a histological validation [5]. This method was also used in the largest prospective multicenter study of outcomes in atrial fibrillation ablation to date [6••]. We consider that the main limitation of this approach is the need for an expert eye to define thresholds, making external validation and reproducibility difficult.

Khurram et al. normalized SI with blood pool intensity (image intensity ratio (IIR)) l [2•], establishing a threshold validated by low-voltage areas, considered as a voltage below 0.5 mV. Our group established a fixed threshold of 1.20 mV, based on two standard deviations from SI in young healthy subjects. More recently, Khurram et al. adjusted their threshold to 0.3 mV and reported better correlation with histology specimens having chronic scar [21•]; the IIR threshold obtained was similar to that later reported by our group [15, 30].

Table 1 Differences between centers in LGE-MRI acquisition and post-processed protocols for fibrosis assessment

Methodology by center	Scan magnet strength	Voxel size	IT (ms)	Scan time (min)	Fibrosis visualization methodology	Threshold
CARMA/DECAAF centers. Salt Lake City, Utah [1, 4, 6••, 14]	1.25 × 1.25 × 2.5	1.5 T/3 T	nr	15	SD above ref. histogram	Mean SI of normal tissue + 2/4 SD
J. Hopkins Baltimore [2•, 15, 16••]	1.3 × 1.3 × 2.0	1.5 T	240–290	15–25	IIR	Voltage validation set at 0.5–0.1 V; IIR: 0.97–1.6
Clinic H Barcelona ([3•, 17••, 18•, 19••]	1.25 × 1.25 × 2.5	3 T	280–380	11–18	Maximum scar density %/IIR	40–60% MPI Mean IIR + 2 SD healthy population (1.20)
King's College London [20••, 21•]	1.3 × 1.3 × 4.0	1.5 T	nr	20	SD above ref. blood pool	Mean SI blood pool + 2.3 to 3.3 SD (acute and chronic post-ablation)
Beth Israel Boston [22, 23]	1.3 × 1.3 × 4.0	1.5 T	280	15–25	Visual assessment	Expert characterization
CHU Bourdeaux [24]	1.25 × 1.25 × 2.5	1.5 T	260–320	5–10	SD above ref. histogram	Mean SI of normal tissue 2/4 SD
Imperial College London [25]	1.5 × 1.5 × 4.0	1.5 T	nr	12–20	SD above ref. blood pool	Voltage validation set at 3 SD above blood pool
Prague [26]	1.6 × 1.6	1.5 T	270	11 4	SD above ref. histogram FWHM	Mean SI of nulled myocardium + 6 SD SI mitral valve-SI min/2
Korea [27]	1.5 × 1.5	3 T	230–270	15–25	SD above nulled myocardium FWHM	Mean SI of normal tissue + 3–5 SD Th SI max-SI min/2

IIR, image intensity ratio; *MPI*, maximum pixel intensity; *ms*, milliseconds; *min*, minutes; *nr*, not reported; *SD*, standard deviations; *SI*, signal intensity

Karim et al. [31] provide the only study that compares some of these algorithms of post-processed LGE-MRI obtained in the same population with AF. They found wide discrepancies but observed the best correlation in patients with a previous ablation procedure. Induced dense scarring is more visible and better discriminates between scar and non-scar tissue. Detection of native fibrosis will continue to be challenging, as atrial collagen deposition is a continuous variable with an unknown degree of overlap between healthy individuals and patients with AF. The desire to establish a threshold and transform it into a qualitative variable is understandable, but this certainly represents an oversimplification of actual histological changes.

LGE-MRI in the Prediction of Outcomes After Atrial Fibrillation Ablation

Catheter ablation is the therapy of choice in symptomatic AF patients' refractory to antiarrhythmic drugs [32]. However, the post-ablation success rate is still limited, particularly in persistent AF [33]. Better protocols for selection of ablation

Table 2 Available trials about the usefulness of atrial fibrosis identified in LGE-MRI in atrial fibrillation ablation procedures

Study	Year	Study type	*N*	MRI performed	Results
LGE-MRI: atrial fibrosis as a predictor of outcomes in atrial fibrillation ablation					
Peters et al. [23]	2009	Observational Single center	35	Post-ablation	Lesser atrial scarring after PVI is associated with recurrence
Akoum et al. [14]	2011	Observational Single center	144	Pre-ablation Post-ablation	In mild/moderate UTAH stages, post-ablation scarring predicts recurrences
Malcolme-Lawes et al. [25]	2013	Observational Bi-center	50	Pre-ablation	Greater pre-ablation percentage of LA scar is associated with recurrences
Marrouche et al. (DECAAF trial) [6••]	2014	Observational Multicenter	329	Pre-ablation	Atrial fibrosis is independently associated with recurrence
Mcgann et al. [5]	2014	Observational Single center	426	Pre-ablation	Extensive atrial fibrosis (> 30% LA) is a predictor of poor response to catheter ablation
Sramko et al. [26]	2015	Observational Single center	95	Pre-ablation	Extent of LGE does not predict recurrences.
Akoum et al. [38•]	2015	Observational Multicenter	172	Pre-ablation Post-ablation	Baseline and residual fibrosis are predictors of recurrences A number of pulmonary veins completely encircled is not related to outcomes.
Khurram et al. [16••]	2016	Observational Single center	165	Pre-ablation	Advanced stages of fibrosis (LGE > 35%) are associated with poor outcomes.
Den Uijl et al. [18•]	2018	Observational Single center	83	Pre-ablation	No significant relationship between absolute fibrosis degree and recurrence UTAH stage IV tended to show a higher risk of recurrence.
Linhart et al. [19••]	2018	Observational Single center	94	Post-ablation	Total relative gap length is associated with AF recurrence.
Guided substrate ablation assessed by MRI					
Bisbal et al. [17••]	2014	Experimental (non-randomized) Single center	15	Post-ablation (Redo-procedures)	LGE-MRI is useful to guide redo-procedures, reducing procedural and RF time.
Harrison et al. [20••]	2015	Observational Single center	22	Post-ablation (Redo-procedures)	LGE-MRI is unable to predict sites of electrical reconnections.
Utah, DECAAF II [39••]	Recruiting	Experimental Randomized Multicenter	888 (expected)	Pre-ablation	NR
Barcelona ALICIA [40]	Recruiting	Experimental Randomized Bi-center	154 (expected)	Pre-ablation Post-ablation	NR

AF, atrial fibrillation; *LA*, left atrium; *LGE-MRI*, late gadolinium enhancement magnetic resonance; *NR*, no results; *PVI*, pulmonary vein isolation

candidates may avoid risks and multiple unsuccessful interventions in patients with little chance of response.

Advanced atrial disease is related to poor outcomes after ablation [34]. Several parameters have been used to identify the severity of atrial remodeling, and LA diameter [35], LA volume [18•], atrial fibrosis [34], and sphericity [36, 37] have been described as predictors of success. On the other hand, a number of studies have tested the accuracy of LGE-MRI detection of atrial fibrosis in predicting outcomes after AF ablation, with conflicting results (Table 2).

The Utah group proposed a classification based in LGE percentage in LA as a powerful independent predictor of outcomes [5, 6••, 38•]. Reported recurrences increased progressively with the severity of fibrosis, and ablation had a very low success rate in advanced stages of fibrosis (classified as UTAH-IV). In the multicenter DECAAF study, probabilities of recurrence increased up to 6% per 1% increase in global atrial fibrosis [6••]. Khurram et al. reported similar results, with a 1.5-fold increased hazard of AF recurrence for each 10% increment in LGE. More than a 35% LGE extension predicted less than 50% success at 1-year follow-up [16••]. However, other studies have not found LA fibrosis assessment to have predictive value [18•, 26]. Using the same methodology as Khurram et al. but a more restrictive threshold for fibrosis, Den Uijl et al. found a higher recurrence rate in patients classified as stage UTAH-IV, compared to I-III UTAH stages [18•].

LGE-MRI is also useful to detect lesions induced by catheter ablation [14, 21•, 22] and may localize the potential discontinuities in ablation lines [17••, 19••]. Peters et al. reported that the total amount of post-ablation scar was related to recurrences [23]. Although Akoum et al. confirmed those results; they found no predictive value for patients with advanced stages of fibrosis pre-ablation [14]. In an earlier study, researchers found that, in most cases, recurrences are related to PVI reconnections [41]. According to Linhart el al, recurrences are not related to the number of discontinuities or complete PVIs, but are powerfully related to the total relative gap length; for each 10% of the increase in relative length, recurrences increased 16% [19••].

Substrate Atrial Fibrosis as a New Target for Ablation Procedures

Improving the results of AF ablation remains challenging. Although PVI is well established as the standard procedure for treating paroxysmal AF [42], its success rate in non-paroxysmal AF is modest despite additional linear ablation or the elimination of complex fractionated atrial electrograms [43, 44]. Targeting the fibrotic atrial substrate is reportedly useful, but has not been validated in large randomized trials [45]. Furthermore, the AF phenotype is not always correlated with the degree of remodeling [46].

Appropriate selection of patients who could benefit from an extensive LA substrate-based ablation approach could be the key to obtain better results. Atrial substrate modification based on voltage criteria has recently been evaluated with promising results [47–49]. Use of LA characterization by LGE-MRI to define areas with significant native fibrosis as an ablation target is being tested in a small randomized trial (ALICIA) [40] and in a multicenter trial (DECAAF II) [39••]. In patients undergoing a first ablation procedure, the fibrotic areas identified by LGE-MRI are isolated or ablated. The ALICIA study is also evaluating the utility of LGE-MRI to guide re-ablation procedures [40], as illustrated in Fig. 1. Bisbal et al. reported redo-ablation guided only by LGE-MRI and blinded to electrical voltage reconnections. Although concordance between the electrical site of reconnections and cardiac MRI was observed in 79% of cases, the ablation of LGE-MRI gaps achieved isolation in 95.6% of veins [17••]. Harrison et al. reported that LGE-MRI was not sufficiently accurate to detect gaps when voltage comparison was performed, although the lack of a blinded design was a limitation of the study [20••].

Finally, evaluation of electrical gaps by circular catheter may have pitfalls that could explain discrepancies between LGE-MRI and electrical mapping [50]. New multipolar electrodes have the potential to better identify the location of functional gaps and show improved correlation with LGE-MRI [51].

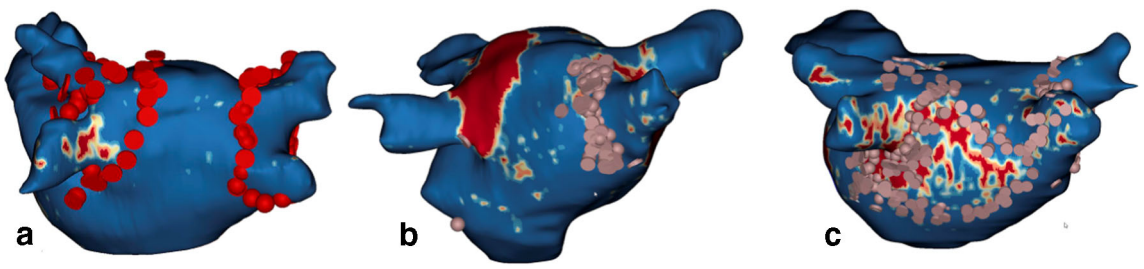

Fig. 1 Individually tailored ablation guided by LGE-MRI. Panel **a** shows conventional first ablation procedure: PVI in a patient with minimal fibrosis around the veins. Panel **b** shows individually tailored re-ablation of anatomical "gaps" guided by LGE-MRI. Panel **c** shows individually tailored first ablation procedure guided by LGE-MRI: PVI + isolation of areas with significant fibrosis. (PVI, pulmonary vein isolation; LGE-MRI, late gadolinium enhancement magnetic resonance)

Conclusions

Use of LGE-MRI has been shown to accurately detect, quantify, and characterize atrial fibrosis, and also to predict patient outcomes after AF ablation. Although this makes it a promising tool for appropriate patient selection, its use in clinical practice remains limited by the lack of standardized acquisition protocols and SI thresholds. Furthermore, the potential benefit of substrate-guided ablation is still being evaluated. As research continues, future improvements in image technology, software, and clinical guidelines may help to translate the acquired knowledge to daily clinical practice.

Compliance with Ethical Standards

Conflict of Interest L Mont is a shareholder of Galgo Medical Company. The other authors declare that they have no conflicts.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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17.•• Bisbal F, Guiu E, Cabanas-Grandio P, Berruezo A, Prat-Gonzalez S, Vidal B, et al. CMR-guided approach to localize and ablate gaps in repeat AF ablation procedure. JACC Cardiovasc Imaging. 2014;7(7):653–63. https://doi.org/10.1016/j.jcmg.2014.01.014 **This was the first study to evaluated the feasability of a guided MRI ablation approach in redo procedures targeting the anatomical gaps detected by LGE-MRI compared with**

conventional approach. LGE-guided ablation led to reisolation of 95.6% of reconnected PVs.

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