Magnetic resonance imaging of atrial fibrosis: redefining atrial fibrillation to a syndrome

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Atrial fibrillation (AF) is the most common sustained arrhythmia and its treatment continues to be a challenge. Recently, delayed enhancement (DE)-MRI was introduced in the diagnosis and treatment of AF by the assessment of atrial fibrosis, which is considered the hallmark of the arrhythmogenic substrate in AF. Atrial fibrosis was reported to be an independent predictor of arrhythmia recurrences. Post-ablation DE-MRI allows for assessment of the total scar burden, complete encirclement of pulmonary veins, and the assessment of residual fibrosis, which were all reported to be strong predictors of arrhythmia recurrences post-ablation. Current pathophysiological perspectives for AF are heavily based on the adagium AF begets AF. However, several recent observations, such as atrial fibrosis being present in non-AF patients, do introduce a new pathophysiological perspective for AF. Potentially, atrial fibrosis is a disease process that triggers the initiation and maintenance of the syndrome AF.

Keywords
DE-MRI • Delayed enhancement • Atrial fibrillation • Atrial fibrosis • Ablation • Substrate • Atrial cardiomyopathy • Stroke • Residual fibrosis

Introduction

Atrial fibrillation (AF) is an atrial arrhythmia characterized on the electrocardiogram by an irregular ventricular interval and the absence of distinct organized atrial activity. The prevalence of AF increases with age, it is very rare before the age of 40, but almost 25% of the general population older than 80 years suffers from episodes of AF. The current classification of AF is based on the arrhythmia’s temporal behaviour and AF is considered a progressive disease in patients with paroxysmal AF frequently develop persistent AF and ultimately chronic AF.

Current pathophysiological perspectives of AF suggest that the arrhythmia is induced by a focal electrical activation (trigger) and maintained by an atrial substrate. The trigger for AF can be found in the pulmonary veins (PVs) in the majority of patients, and Haisaguerre et al. are credited with the observation that an encircling ablation lesion around the PVs can suppress the arrhythmia. Almost 2 decades later, many changes have been implemented, improving procedure duration and safety, but still not all patients remain free of AF despite isolation of the PVs and suppression of AF triggers. Current pathophysiological perspectives suggest AF recurrences are, among others, associated with more extensive electrical and structural remodelling of the atria, termed the AF substrate.

Recently, atrial fibrotic changes and treatment-related tissue scarring detected using delayed enhancement-MRI (DE-MRI) were reported to improve assessment of atrial substrate and thereby management of AF. This review will summarize current and future significance of DE-MRI in managing AF and its related atrial myopathic changes, highlighting recent findings and publications.

Delayed enhancement-magnetic resonance imaging of atrial tissue

Previous studies described the acquisition of DE-MRI scans. Briefly, in both pre- and post-treatment patients, an atrial DE-MRI is performed 10–20 min after gadolinium infusion. The raw images are processed in custom software (CorView, Marrek Inc., Salt Lake City, UT, USA), which allows operators to manually segment the endo- and epicardial borders of the left atrium (LA), including the PVs and LA appendage. A pixel intensity cut-off of 2 standard deviations above the mean is used to discern fibrosis from healthy tissue and ultimately results in an atrial shell, where fibrosis is displayed as
white–green, and healthy tissue is displayed as blue (Figure 1). Assessing atrial fibrosis from MRI images can be performed with a high intra- and interobserver correlation (>0.93). Furthermore, the total volume of fibrotic tissue is calculated as a percentage of the LA wall volume, and subsequently categorized into Utah stage I (<10% fibrosis), Utah stage II (10–20% fibrosis), Utah stage III (20–30% fibrosis), and Utah stage IV (>30% fibrosis).

**Atrial fibrosis in atrial fibrillation**

Fibrosis is considered the hallmark of arrhythmogenic atrial tissue structural remodelling. In a dog model, atrial fibrosis caused regions of conduction slowing, thereby increasing conduction heterogeneity. This heterogeneity provides the basis for unidirectional conduction block and re-entry, which are essential for AF initiation and perpetuation.

A recently published multi-centre prospective trial (the DECAAF study) reported the association between amount of atrial fibrotic changes and arrhythmia recurrence after ablative treatment of AF. A total of 272 patients were categorized into Utah stages and after 475 days, arrhythmia recurrences were significantly associated with the degree of atrial fibrosis on presentation (stage I: 15%, stage II: 36%, stage III: 46%, and stage IV: 69%). Furthermore, in multivariate analysis, atrial fibrosis was the only variable that was found significantly associated with arrhythmia recurrence post-ablation. Another recently published study retrospectively analysed 426 patients with a follow-up of 1 year and emphasized the finding in DECAAF.

A recent analysis of DECAAF focused on the architecture of atrial fibrosis, and demonstrated that the size of the largest fibrosis patch was associated with arrhythmia recurrences post-ablation, independent from total atrial fibrosis. Particularly, identification of patients in Utah stages II and III with a low arrhythmia recurrence risk improved significantly with the assessment of the largest patch size. Of note, in DECAAF, <15% of patients underwent substrate ablation, thereby suggesting that fibrosis patch size assessment could allow operators to select Utah stages II and III patients that will only require AF trigger ablation. In a recent publication, a flow-chart for DE-MRI-guided identification of AF ablation patients was published. In summary, patients in Utah stages I and II, as well as patients with localized fibrosis in Utah stage III, were considered

![Figure 1](image-url) Assessment of atrial fibrosis. Delayed enhancement-magnetic resonance imaging is acquired (step 1) that allows identification of the atrial wall (step 2). By identifying the atrial wall in all axial views, a three-dimensional left atrial wall can be rendered. Fibrotic tissue is displayed as white–green, healthy tissue is displayed as blue.
eligible for AF ablation. Patients in Utah stage IV and in Utah stage III with diffuse fibrosis were not considered eligible for AF ablation.20 However, based on these recent observations, the flowchart can be amended with fibrosis patch size assessment in Utah stages II and III patients, as demonstrated in Figure 2.

### Atrial fibrosis during treatment of atrial fibrillation

The goal of an AF ablation procedure is to deliver appropriate lesions within the targeted sites leading to chronic, transmural atrial lesions. Delayed enhancement-MRI has been reported by various centres to be able to detect ablation scarring post-ablation.21–23 In 12 swines, researchers performed an atrial ablation lesion, but intentionally left a gap in the ablation lesion. Immediately after ablation, a DE-MRI was performed to assess the ablation lesion. Gaps down to 1 mm could be identified using DE-MRI.24 Another human study reported that the number of circumferentially ablated PVs 3 months after ablation was associated with arrhythmia recurrences, but only in Utah stage II patients. However, in Utah stage III patients, a lower percentage of atrial ablation-induced scarring was associated with arrhythmia recurrences.25

Furthermore, DE-MRI allows for the assessment of ablation scar 3 months post-ablation, allowing for assessment of residual fibrosis, i.e. pre-ablation fibrosis – ablation scar = residual fibrosis (Figure 3). A recent analysis of the DECAAF study reported that the recurrence-free survival was significantly associated with residual fibrosis (q1: 85.1%, q2: 74.4%, q3: 62.8%, q4: 36.4%).26 Another study compared the arrhythmia recurrence rate between patients with residual fibrosis < 10% and those with residual fibrosis >10%. Arrhythmia recurrence-free survival was 80% in patients with <10% residual fibrosis and 49% in patients with >10% residual fibrosis. In multivariate analysis, residual fibrosis was independently associated with recurrences.27

Furthermore, one study28 reported that the number of isolated PVs 3 months after ablation was significantly associated with the risk of arrhythmia recurrence (all PVs isolated: 11.5%, 3 isolated PVs: 15.7%, 2 isolated PVs: 26.7%, and no PVs isolated: 44.4%), as depicted in Figure 4. The percentage of peri-PV scar was significantly lower in arrhythmia recurrence patients compared with arrhythmia-free patients for both left- and right-sided PVs (77.9 vs. 63.2% and 63.4 vs. 39.4%, P < 0.01 for both).28

These results suggest that total scar burden and the scar location plays an important role in the development of arrhythmia recurrences post-ablation, and hypothetically, the recurrence-free

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**Figure 2** Fibrosis-guided treatment flow chart. Flowchart of delayed enhancement-magnetic resonance imaging-guided patient selection for atrial fibrillation trigger ablation. Utah stage I patients show a high chance of ablation success, as well as patients in Utah stages II and III with a limited fibrosis patch size. Conversely, patients with a larger patch size, as well as Utah stage IV patients, display a low chance of success. Potentially, these patients may be eligible for substrate ablation or no ablation at all. AF, atrial fibrillation; DE-MRI, delayed enhancement magnetic resonance imaging.
survival can be improved by the ablation and the homogenization of atrial fibrosis. We hypothesize that by homogenizing the fibrosis, the arrhythmogenicity of the atrial tissue can be modified and thereby AF ablation outcome can be improved. A retrospective study demonstrated the feasibility of fibrosis ablation, and prospective studies are being performed to study the effect of targeting DE-MRI-detected fibrosis in improving AF ablation outcome.

Progression of fibrosis after treatment of atrial fibrillation

The effect of ablation on improvements in echocardiographically assessed LA function parameters was recently reported. Only patients who were free of AF after ablation demonstrated a significant improvement in LA diameter, LA emptying fraction, LA strain, and strain rate. In accordance with this study, an unpublished analysis in our centre revealed that 70 patients who underwent multiple post-ablation DE-MRI scans only displayed a reduction in total DE surface area if they were free of AF. In the case of arrhythmia recurrence, the mean scar burden remained unchanged during the study period. This highlights the fact, that in a subgroup of patients, despite appropriate lesion delivery, the fibrotic atrial disease impacts the procedural outcome. Examples of the atrial scar in patients with and without AF are displayed in Figure 5. This group of patients should be evaluated carefully before being considered for redo procedures.

Clinical variables and atrial fibrosis

Several studies have reported on the association between clinical variables and atrial fibrosis. Overall, these results are conflicting. In the study by McGann et al., previous TIA/CVA, AF type, and LA volume were associated with atrial fibrosis. However, age, gender, hypertension, coronary artery disease, and left ventricular ejection fraction were not significantly associated with atrial fibrosis. However, one study reported a significant association between atrial fibrosis score and age, and a study by Akkaya et al. reported that the degree of atrial fibrosis was significantly higher in patients with a reduced left ventricular ejection fraction compared with those with a normal left ventricular ejection fraction (21.5 vs. 15.4%, P < 0.001) and atrial fibrosis score was higher in patients with left ventricular hypertrophy (19.4 vs. 15.3%, P < 0.01). In another study on 120 patients, age, hypertension, and AF type were not associated with atrial fibrosis. In the study by Kuppahally et al., patients with more diffuse and extended atrial fibrosis had a reduced LA strain and strain rate at both investigated sites: the midseptal and midlateral LA wall. These results were confirmed by a recent study from a different centre demonstrating that the
Atrial systolic function was associated with atrial fibrosis. The results of these studies demonstrate that predicting the degree of atrial remodelling with clinical characteristics is difficult, hampering the identification of patients with a low risk of arrhythmia recurrence post-ablation based on clinical characteristics and providing a patient-tailored ablation approach. In a recently published comprehensive study, 23% of variation in atrial fibrosis could be predicted with clinical variables, emphasizing previous observations.

**Atrial fibrosis and stroke**

Previous studies have also reported on the association between thromboembolic events and atrial fibrosis. In a study by Daccarett et al., atrial fibrosis was significantly higher in patients with a history of stroke compared with those without a history of stroke (24.4 vs. 16.2%, \( P < 0.01 \)). The authors also reported that this association was independent from age, AF type, and warfarin use.
Another study\(^\text{35}\) reported an association between atrial fibrosis score and LA appendage spontaneous contrast (23.3 vs. 16.7%, \(P = 0.01\)) and thrombus (26.9 vs. 16.7%, \(P < 0.01\)). The authors reported that a high atrial fibrosis score was independently associated with LA appendage abnormalities.\(^\text{35}\) These studies demonstrate that a higher grade of LA disease is associated with an increased risk of thromboembolic events.

The consensus document on AF ablation\(^\text{7}\) currently states that oral anticoagulants may be ceased after ablation if there is no evidence of arrhythmia recurrences. However, if atrial remodelling is the main driver for stroke, than hypothetically, anticoagulants may only be ceased in patients with a low atrial fibrosis score (Utah stages I and II).

Another interesting finding was published in the CRYSTAL AF study.\(^\text{38}\) In this study, non-AF patients with crypto genetic stroke were included. Patients were randomized to routine follow-up and internal loop recorder implantation. In the group that underwent internal loop recorder implantation, 12.4% had developed AF in the next 12 months, vs. 2% in the control group.\(^\text{38}\) Even though some of these patients may have suffered from asymptomatic AF episodes prior to inclusion, it is likely that most of these patients did not have AF before inclusion at the time of the stroke. Owing to the association between atrial fibrosis and stroke, we hypothesize that the degree of atrial remodelling in crypto genetic stroke patients is increased, even before they develop AF, resulting in the ‘cryptogenic stroke’.

### Atrial fibrillation begets atrial fibration and what we learned from atrial tissue imaging

Current pathophysiological perspectives for AF are heavily based on the adagium AF begets AF, first posed by Allessie and colleagues.\(^\text{39}\) The hypothesis states that AF as an arrhythmia induces electrophysiological changes in the atrial myocardial cell, resulting in a reduced effective refractory period. Furthermore, structural changes (i.e. remodelling) such as increased atrial fibrosis and LA dilatation occur with AF. The hypothesis has been confirmed in animal studies that reported that high-frequency cardiac pacing results in sustained AF and structural remodelling. However, several recent observations pave the way to a new pathophysiological perspective of AF. First, there is much variety on the clinical presentation and follow-up of AF patients.\(^\text{40–42}\) Where some patients develop paroxysmal AF and stay in paroxysmal AF for many years, other patients are in persistent AF in their first episode, and seem to have ‘skipped’ both the asymptomatic and the paroxysmal AF stages.

Furthermore, atrial remodelling also occurs in patients without AF.\(^\text{43}\) Patients with a mitral valve stenosis or atrial septal defects but without AF displayed a reduced biatrial voltage, conduction velocity, and effective refractory periods.\(^\text{44,45}\) Furthermore, patients with hypertension but without AF also displayed significantly reduced conduction velocities when compared with healthy controls.\(^\text{46}\) Thirdly, before the onset of AF, hypertension,\(^\text{47}\) heart failure,\(^\text{12,48}\) and valvular heart disease\(^\text{12,49}\) already result in atrial fibrosis, potentially by increasing atrial stretch. Lastly, in a study by our own group,\(^\text{11}\) we observed a mean atrial fibrosis score of 3.1% in healthy subjects, and in another recently reported analysis, atrial fibrosis was 11.1% in non-AF patients.\(^\text{12}\)

These results demonstrate that structural remodelling is also present in non-AF patients. Hypothetically, structural remodelling in the atria is the central disease process, with AF as a mere consequence of the remodelling. However, as the atria are sufficiently remodelled to allow initiation and perpetuation of AF, than the arrhythmia may potentially accelerate the remodelling, in accordance with the ‘AF begets AF’ adagium. Thus, both hypotheses may be present in the same patient. Therefore, in order to provide a patient-tailed approach, patients should be treated both based on the cause of their atrial remodelling and for their arrhythmia.

Why a selected group of patients develops AF, but most patients remain AF free is still open to future research. Potentially, the architecture of the fibrosis plays an important role in the degree of disruption of normal electrophysiological propagation of electrical wavefronts of the atrial myocardial cells.

### Limitations

While various centres have been reporting success with fibrosis and scar imaging,\(^\text{36,50,51}\) others have attempted to reproduce the assessment of atrial fibrosis and ablation lesions using different sequences and image processing protocols\(^\text{52}\) and ablation scar,\(^\text{53}\) but have failed to do so, most likely due to inadequate image processing tools, considering the high intra- and interobserver correlation.\(^\text{17}\) It is important to note that the CARMA centre relies on highly trained and experienced professionals, who are fully committed to performing these image analyses. Major efforts by us and others are succeeding in scaling the use and helping with adoption of the DECAAF-study fibrosis and scar detection MRI imaging protocols across the world.

### Conclusion

Recent observations have paved the way for a new AF hypothesis, potentially defining AF as a syndrome perpetuating on an atrial myopathy. Potentially, atrial fibrosis is the disease allowing AF to sustain on this cardiac structural pathology. Delayed enhancement-MRI is an important imaging modality for assessing the degree of atrial fibrosis, improving AF ablation patient selection by improving post-ablation arrhythmia recurrence risk assessment, as well as patients at high risk of stroke.

### Conflict of interest

N.F.M. holds stock options in Marrek, Inc.

### References


Atrophic atrial fibrillation (AF) and AF


