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ELECTROPHYSIOLOGY

# Late gadolinium enhancement-MRI determines definite lesion formation most accurately at 3 months post ablation compared to later time points

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## Abstract

**Aims:** Neither the long-term development of ablation lesions nor the capability of late gadolinium enhancement (LGE)-MRI to detect ablation-induced fibrosis at late stages of scar formation have been defined. We sought to assess the development of atrial ablation lesions over time using LGE-MRI and invasive electroanatomical mapping (EAM).

**Methods and Results:** Ablation lesions and total atrial fibrosis were assessed in serial LGE-MRI scans 3 months and >12 months post pulmonary vein (PV) isolation. High-density EAM performed in subsequent repeat ablation procedures served as a reference. Serial LGE-MRI of 22 patients were analyzed retrospectively. The PV encircling ablation lines displayed an average LGE, indicative of ablation-induced fibrosis, of 91.7% ± 7.0% of the circumference at 3 months, but only 62.8% ± 25.0% at a median of 28 months post ablation ($p < 0.0001$). EAM performed in 18 patients undergoing a subsequent repeat procedure revealed that the consistent decrease in LGE over time was owed to a reduced detectability of ablation-induced fibrosis by LGE-MRI at timepoints > 12 months post ablation. Accordingly, the agreement with EAM regarding detection of ablation-induced fibrosis and functional gaps was good for the LGE-MRI at 3 months ($\kappa$ .74; $p < .0001$), but only weak for the LGE-MRI at 28 months post-ablation ($\kappa$ .29; $p < .0001$).

**Conclusion:** While non-invasive lesion assessment with LGE-MRI 3 months post ablation provides accurate guidance for future redo-procedures, detectability of atrial ablation lesions appears to decrease over time. Thus, it should be considered to per-

**Abbreviations:** AF, atrial fibrillation; EAM, electroanatomical mapping; LA, left atrium; LGE-MRI, late gadolinium enhancement cardiac MRI; PV, pulmonary vein (s)

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form LGE-MRI 3 months post-ablation rather than at later time-points > 12 months post ablation, like for example, prior to a planned redo-ablation procedure.

KEYWORDS
ablation lesions, atrial fibrillation, atrial fibrosis, cardiac MRI, late gadolinium enhancement

## 1 | INTRODUCTION

Late gadolinium enhancement cardiac MRI (LGE-MRI) is increasingly used to detect atrial fibrosis in the context of atrial fibrillation (AF).[1] Atrial fibrosis is considered a hallmark of arrhythmogenic atrial tissue structural remodeling, and the extent of atrial fibrosis as determined by LGE-MRI has been established as independent predictor of AF recurrence after catheter ablation treatment.[2] While pulmonary vein isolation is still the cornerstone of AF ablation, approaches targeting LGE-MRI-detected atrial fibrosis are currently being investigated in the large randomized multicenter DECAAF II-trial (NCT02529319).[2] Of note, by exploiting the slow washout kinetics of gadolinium in extracellular space, LGE-MRI is not only capable of determining preexisting atrial fibrotic tissue, but also to detect ablation-induced scarring.[3–6] Moreover, several groups have reported localization of functional gaps in ablation lesions with high accuracy, even though data in this respect is somewhat conflicting.[3,4,7,8] Of note, time points for LGE-MRI performance were highly variable in those studies.

Against this background, several approaches of LGE-MRI-guided ablation in repeat procedures have been reported for atrial fibrillation or atrial tachycardia.[3,5,9,10] However, development of cardiac fibrosis has been shown to be a dynamic process characterized by sustained remodeling, and little is known about the ability of LGE-MRI to detect fibrotic tissue at late stages of scar formation and remodeling. Recent longitudinal LGE-MRI studies on ventricular post myocardial infarction scar are suggesting a long-term regression of fibrotic tissue over time.[11,12] However, unlike short-term observations in the acute setting, validation of these long-term data by histology or electroanatomical voltage mapping (EAM) is missing. Here we report on our observation of a decrease in LGE-MRI-detectable ablation-induced atrial fibrosis over time, as well as its validation by EAM.

## 2 | METHODS

This was an observational, retrospective analysis of a prospective patient registry conducted at the Arrhythmia Section of Hospital Clínic, University of Barcelona. Written informed consent was obtained from each patient and the protocol was reviewed and approved by the local research ethics committee. The study included consecutive patients over the age of 18 who had serial LGE-MRI for fibrosis quantification performed following AF ablation between December 2012 and June 2020. Selected were all cases with an LGE-MRI scan 3 months post ablation (3 months follow-up) and an additional LGE-MRI scan at least 12 months following the first LGE-MRI (late follow-up). In the majority of patients, the late follow-up LGE-MRI was performed in preparation of a repeat ablation, and the high density EAM acquired during those procedures were used as a reference to validate the LGE-MRI studies with respect to fibrosis detection and prediction of functional gaps in the ablation lesions.

### 2.1 | LGE-MRI image acquisition

LGE-MRI studies were performed in sinus rhythm, using two different 3-Tesla scanners (Magnetom Trio-Tim, Siemens Healthcare, Erlangen, Germany and GE Signa Architect, Chicago, Illinois, USA) and 32-channel phase array cardiovascular coils with electrocardiographic triggering. If AF was present before LGE-MRI, electrical cardioversion was performed. The acquisition protocol has been described previously.[3,13] Briefly, 3D-delayed gadolinium enhancement images were acquired 20 min after an intravenous bolus of 0.2 mmol/kg of gadobutrol (Gadovist, Bayer Hispania). A free-breathing 3D navigator and electrocardiographically gated inversion recovery gradient-echo sequence was applied in axial orientation. The acquired voxel size was $1.25 \times 1.25 \times 2.5$ mm. Other typical sequence parameters were as follows: repetition time 2.3 ms, echo time 1.4 ms, flip angle 11°, bandwidth 460 Hz/pixel and inversion time (TI) 280–380 ms. A TI scout sequence was used in order to determine the optimal TI that nullifies the left ventricular myocardial signal.

### 2.2 | LGE-MRI post-processing and fibrosis quantification

Post-processing of the LGE-MRI data was performed by two experienced observers, blinded to the LGE-MRI time point and the data from electroanatomical mapping, using the ADAS 3D software (ADAS 3D, Barcelona, Spain). The atrial wall was manually traced on each axial-plane slice and automatically adjusted to build a 3D shell. An image intensity ratio (IIR) was calculated as the ratio between the signal intensity of each voxel and the mean signal intensity of the blood pool in every patient. Each IIR value was color-coded and projected onto the 3D shell of the atrium to create an IIR map. Previously validated thresholds were applied to discriminate normal from fibrotic tissue (image intensity ratio, IIR > 1.2 and ≤1.32 for border zone fibrosis; IIR > 1.32 for dense fibrosis/scar).[14] Extent of fibrosis was quantified with pulmonary veins, left atrial appendage, and mitral valve excluded.

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### 2.3 | Qualitative assessment of regional fibrosis distribution

Regional distribution of fibrosis was analyzed in the 3D LA shell using 12 segments dividing the atrium into anatomically meaningful regions that have been defined by our group previously.[15] Presence of fibrosis was considered when more than 2.5% of the corresponding segment was involved.[14]

### 2.4 | Qualitative assessment of ablation-induced fibrosis and gaps

For the purpose of qualitative ablation lesion assessment and analysis of gaps, the ablation line encircling ipsilateral pulmonary vein antra was divided into eight segments according to the 2 × 8-segment model previously described.[16,17] A gap was defined as a discontinuation > 3 mm in the LGE projecting onto the ablation line.[4]

### 2.5 | Electroanatomical mapping

In most patients the late follow-up LGE-MRI was performed in preparation of a repeat ablation procedure. In those patients' electrophysiological studies and high density EAM acquired during the subsequent repeat ablation procedure was used as a reference for validation. EAM was performed with the CARTO 3 system (Biosense Webster Inc.) and multipolar mapping catheters (LassoNav or Pentaray, both Biosense Webster Inc.). Only in two patients the Rhythmia HD mapping system was used with the Orion multipolar mapping catheter (Boston Scientific Inc.).

EAM and individual local electrograms were analyzed by an experienced electrophysiologist blinded to the LGE-MRI data. Regional fibrosis was determined based on bipolar voltage maps including review of critical local electrograms applying a threshold of <0.5 mV. With regard to functional gaps in ablation lesions, bipolar voltage maps and activation maps were analyzed and all local electrograms in the PV as well as the ostial region reviewed. Functional gaps were localized based on all available information.

### 2.6 | Statistical analysis

Analysis was performed using SPSS 24.0 software (SPSS Inc., Chicago, IL). Continuous variables are presented as mean ± SD or median (interquartile range), unless otherwise specified. The Wilcoxon signed-rank test was used to compare two related samples. Inter-rater reliability of LGE-MRI at the different time points in terms of agreement with EAM was assessed by calculating the Cohen's kappa coefficient ($\kappa$). A $p$-value < .05 was considered significant.

## 3 | RESULTS

### 3.1 | Patient population

Patient and procedural characteristics are summarized in Tables 1 and 2. Of 24 patients fulfilling the inclusion criteria of two consecutive LGE-MRI follow-up scans after first-time PVI, two had to be excluded for suboptimal scan quality. The first post-ablation LGE-MRI (3-month follow-up) was performed at a median of 99 days following ablation. The second post-ablation LGE-MRI (late follow-up) was obtained at a median of 28 months following ablation. In 18 of the 22 patients repeat AF ablation was performed subsequent to the late follow-up MRI (median: 1.5 days after the MRI) with the intraprocedural EAM and review of individual local electrograms serving as a reference method to validate the LGE-MRI data with respect to detection of fibrotic tissue and functional gaps.

### 3.2 | Development of LGE-MRI-detected fibrosis over time

We found a consistent decrease in the late gadolinium enhancement over time – both regarding the assessment of total atrial fibrosis as well as ablation-induced fibrosis (Figure 1). Three months post ablation, late gadolinium enhancement indicative of fibrotic tissue, accounted for 27.2% ± 13.2% of the total LA surface area, but only for 15.4% ± 11.0% at the late follow-up scan at a median of 28 months post ablation ($p < .001$). The decrease in late gadolinium enhancement over time was also evident if analysis was restricted only to areas with image intensity ratios that aim to define dense scar (IIR > 1.32: 17.5% ± 10.8% vs. 8.4% ± 8.0%, $p < .001$).

Regarding the assessment of ablation-induced fibrosis, the observed phenomenon was even more pronounced. Three months post ablation, the PV-encircling ablation lines displayed an average late gadolinium enhancement suggestive of fibrotic lesions of 91.7% ± 7.0% of the circumference, as opposed to 62.8% ± 25.0% of the ablation line circumference at a median follow-up of 28 months ($p < .001$). This decrease in late gadolinium enhancement was equally found for the ablation lines encircling the left (94.4% ± 6.1% vs. 68.7% ± 19.8% of the circumference; $p < .001$) and right PVs (89.0% ± 11.4% vs. 54.2% ± 29.0% of the circumference; $p < .001$). The visible trend towards more incomplete late gadolinium enhancement coverage of ablation lines encircling the right PVs versus those encircling the left PVs, which appeared even more pronounced at the late follow-up timepoint, was statistically not significant.

### 3.3 | Regional distribution of fibrosis and validation by EAM

LGE-MRI-predicted distribution of fibrosis and its validation by EAM is summarized in Figure 2. In 18 out 22 patients with a repeat

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**TABLE 1** Patient characteristics

| Parameter | *n* = 22 |
|---|---|
| Age (y) | 56.6 ± 7.5 |
| Female gender | 5 (23) |
| $CHA_2DS_2$-VASc score | 1.2 ± 0.8 |
| Paroxysmal AF | 9 (41) |
| Persistent AF | 12 (55) |
| Long standing persistent AF | 1 (5) |
| LVEF (%) | 56.0 ± 5.0 |
| Left atrial volume index (ml/$m^2$) | 39.6 ± 8.8 |
| Coronary artery disease | 3 (14) |
| Systemic hypertension | 9 (45) |
| Dyslipedemia | 7 (32) |
| Diabetes | 1 (5) |

All values are *n*, (%) or mean ± standard deviation.

**TABLE 2** Index ablation characteristics

| Parameter | *n* = 22 |
|---|---|
| Pulmonary vein isolation (PVI) | 22 (100) |
| Additional ablation lines[a] | 3 (14) |
| Radiofrequency ablation | 20 (91) |
| Cryoballoon ablation | 2 (9) |

All values are *n*, (%) or mean ± standard deviation.

[a]Two patients were treated with PVI plus posterior box ablation, one patient was treated with PVI plus roof line, anterior mitral isthmus line, and CFAE ablation.

ablation procedure subsequent to (median: 1.5 days after) the late follow-up LGE-MRI, high density EAM was used as a reference for qualitative validation of regional fibrosis distribution (median number of mapping points: 2566). The agreement of both, the 3 months LGE-MRI and the late follow-up LGE-MRI (median of 28 months post-ablation), with EAM (median of 1.5 days after the late follow-up LGE-MRI) was tested using the presence or absence of low-voltage areas as a surrogate for fibrosis in the predefined LA segments. Atrial fibrosis was defined as an image intensity ratio (IIR) of >1.2 (LGE-MRI) and a bipolar voltage <0.5 mV (EAM), respectively. While the 3 months LGE-MRI showed good agreement with later EAM (kappa = .78; $p < .0001$; sensitivity: 94.9%; specificity: 89.7%), the agreement of the late follow-up LGE-MRI with subsequent EAM was only weak (kappa = .34; $p < .0001$; sensitivity: 67.9%, specificity: 91.8%). Thus, when using the same thresholds, LGE-MRI at 3 months post-ablation detected and localized atrial fibrosis more accurately than at a median of 28 months post-ablation. As expected, application of lower thresholds improved sensitivity regarding the detection of fibrosis. However, this was at the cost of a decreased specificity, resulting in a worse overall agreement with electroanatomical mapping (see Table 3). Representative examples are presented in Figure 3.

In most of the LA segments (94.8%) that displayed late gadolinium enhancement at 3 months, but not at a median of 28 months post ablation in individual patients, subsequent EAM demonstrated low voltage areas indicative of fibrosis and consistent with the LGE-MRI at 3 months. These data suggest that LGE-MRI at 28 months had failed to detect atrial fibrosis and thus yielded false-negative results.

## 3.4 | Prediction of functional gaps and validation by EAM

In the 18 cases, where a repeat ablation including EAM was performed subsequent to the late follow-up scan, activation and voltage maps as well as review of individual local electrograms were used as a reference to validate the ability of each of the post-ablation LGE-MRI scans to predict functional gaps and PV reconnection (median number of mapping points: 2566). While the 3 months LGE-MRI showed good agreement with EAM at a median of 28 months post ablation regarding the prediction of functional gaps (kappa: .74; $p < .0001$; sensitivity: 91.3%; specificity: 89.7%), the agreement of the LGE-MRI at 28 months (a median of 1.5 days prior to EAM) was only weak (kappa: .29; $p < .0001$; sensitivity: 93.5%; specificity: 46.7%) (Figure 4). Of note, there was no

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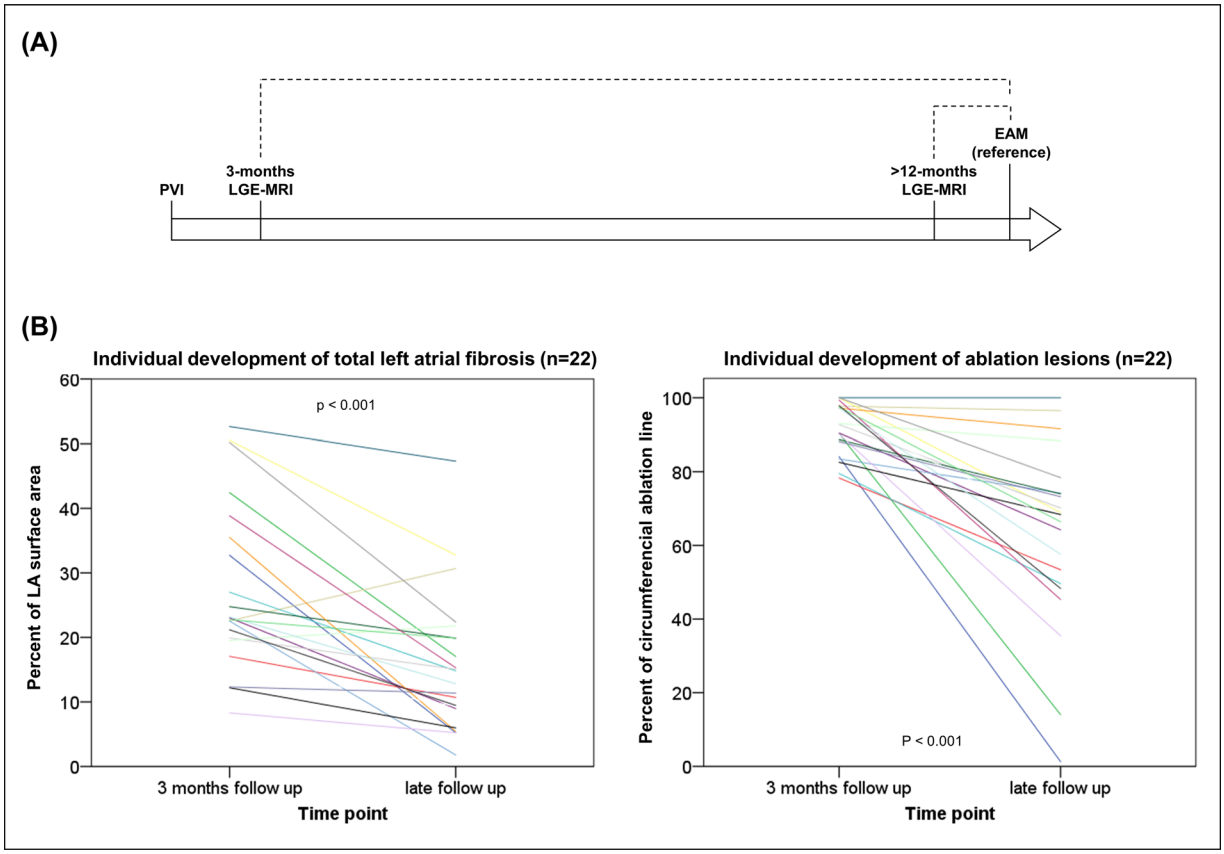


**FIGURE 1** (A) Study design. Analysis of LGE-MRI at a median of 3 months and 28 months post ablation, respectively ($n = 22$), and validation with subsequent invasive EAM serving as a reference (at a median of 1.5 days after the late follow-up LGE-MRI; $n = 18$). (B) Individual development of LGE-MRI-detected fibrosis over time. Quantification of total left atrial fibrosis (left) and ablation induced fibrosis (right) determined by LGE-MRI at a median of 3 months and 28 months post ablation, respectively. Each color represents an individual patient [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 3** Detection of atrial fibrosis depending on time point and threshold

| | 3-Month LGE-MRI | Late follow-up LGE MRI (median 28 months) | | |
|---|---|---|---|---|
| IIR threshold | <1.20 (standard threshold) | <1.20 (standard threshold) | <1.10 (reduced threshold) | <1.05 (reduced threshold) |
| Agreement ($\kappa$) | .78** | .34** | .26** | .16* |
| Sensitivity (%) | 94.9 | 67.9 | 79.4 | 84.8 |
| Specificity (%) | 89.7 | 91.8 | 55.6 | 33.3 |

Predictive value of LGE-MRI regarding the detection of regional fibrosis is shown for the different time-points and different IIR thresholds applied. Indicated is the kappa-agreement of LGE-MRI with electroanatomical mapping regarding the regional presence or absence of atrial fibrosis. Further the sensitivity and specificity of LGE-MRI to detect atrial fibrosis is specified. For all analyses electroanatomical mapping using low voltage (<0.5 mV) as a surrogate for atrial fibrosis served as a reference. IIR, Image Intensity Ratio; $\kappa$, kappa value (measure of agreement).
*$p < .05$;
**$p < .0001$.

clear trend regarding the distribution of agreement according to distinct pulmonary vein segments.

The decrease of LGE coverage of the ablation lines over time was also reflected by an increase in the median number of segments with LGE gaps per patient from 4 (3 months) to 10 (28 months). This observation per se would be suggestive of non-durable ablation lesions. However, in 94.6% of the pulmonary vein segments where the late follow-up LGE-MRI at a median of 28 months indicated a newly appeared gap, while the 3 months LGE-MRI in the same patient displayed continuous LGE, the subsequent repeat procedure with inva-

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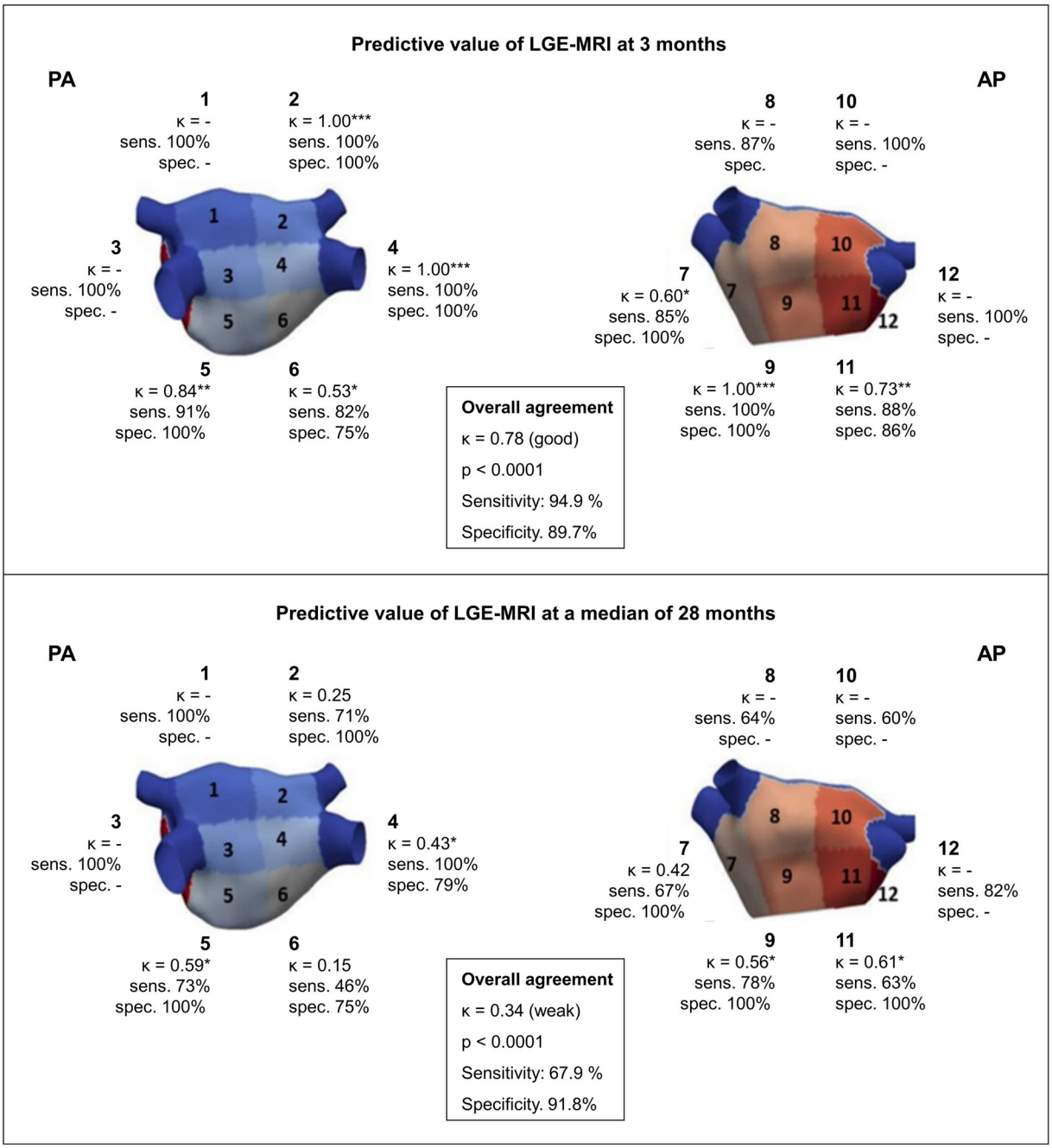


**FIGURE 2** Validation of LGE-MRI-detected regional fibrosis by EAM. Agreement of regional distribution of late gadolinium enhancement with low voltage areas in EAM (3 months LGE-MRI, upper panel; 28 months LGE-MRI, lower panel). PA, posteroanterior view of left atrium; AP, anteroposterior view; $\kappa$, kappa value (measure of agreement); $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$; sens., sensitivity; spec., specificity; -, no statistics were computed because all patients displayed fibrosis in this segment [Color figure can be viewed at wileyonlinelibrary.com]

sive EAM demonstrated durable lesions consistent with the 3 months LGE-MRI. These results suggest that the late follow-up LGE-MRI at a median of 28 months post ablation had failed to fully detect ablation-induced fibrosis in those PV segments. Thus, when using the same thresholds, LGE-MRI at 3 months post-ablation predicted functional gaps more accurately than at a median of 28 months post-ablation. Of note, decreasing the signal intensity threshold for fibrosis detection (IIR) did not enhance the capability of the late follow-up LGE-MRI to reliably detect ablation-induced atrial fibrosis (Table 4). While application of lower thresholds improved specificity regarding the detection of functional gaps, this was at the cost of a decreased sensitivity, resulting in a worse overall agreement with electroanatomical mapping. Representative examples are presented in Figure 3.

In that respect it is also noteworthy that LGE-MRI displayed a very high negative predictive value in terms of exclusion of functional gaps (3 months: 98%, 28 months: 97%), whereas its positive predictive value was somewhat lower (71% at 3 months and 31% at a median of 28 months following ablation).

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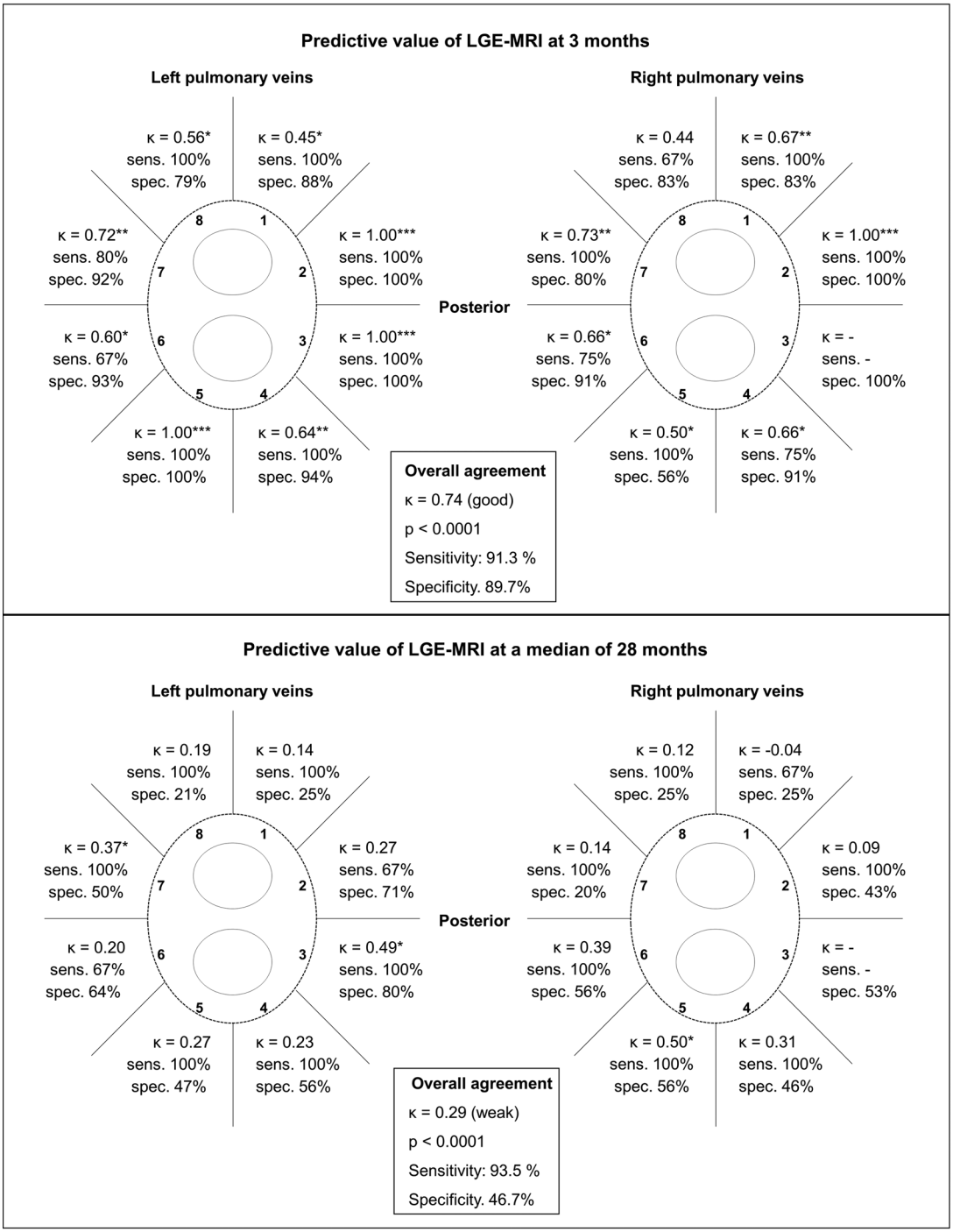


**FIGURE 3** Representative cases. Comparison of bipolar voltage maps with LGE-MRI at the two different time points and with distinct thresholds, respectively, in five representative cases (each row represents one patient)

## 4 | DISCUSSION

### 4.1 | Main finding

In this analysis of serial post-ablation LGE-MRI scans using EAM at the time of repeat-ablation as a reference, we found that over time LGE-MRI loses some of its capability to detect ablation-induced atrial fibrosis. In theory, a decrease in LGE-MRI-detectable atrial fibrotic tissue as observed in this study may also reflect regression of fibrosis and non-durable ablation lesions, respectively. However, validation by EAM proved the observed decrease to be owed to a reduced detectability of ablation-induced atrial fibrosis by LGE-MRI at a median of 28 months following the index ablation. Owed to the reduced sensitivity in the detection of fibrosis, the agreement of LGE-MRI 28 months post

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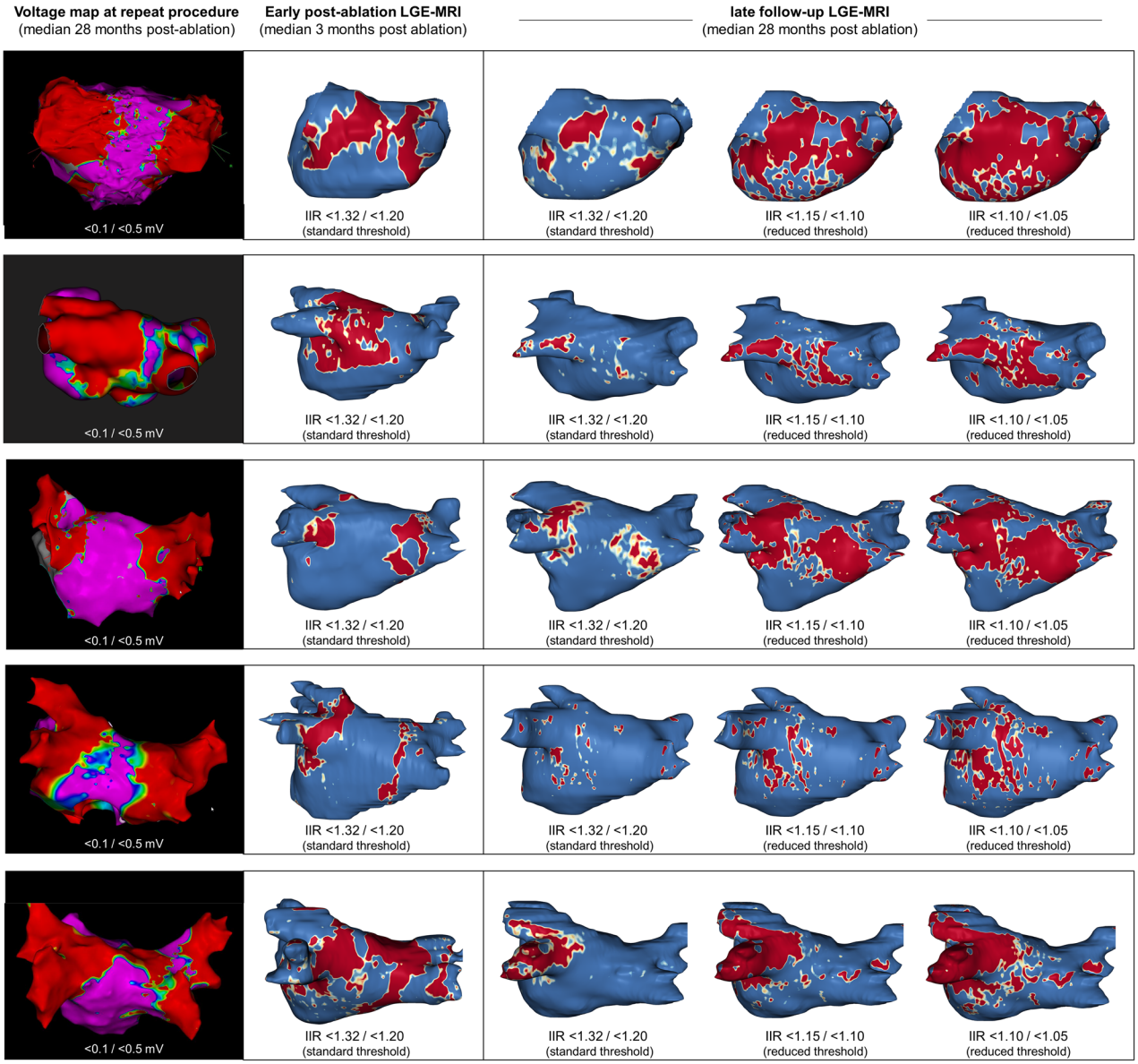


**FIGURE 4** Validation of LGE-MRI-detected gaps by EAM. Agreement of LGE-MRI-detected gaps with functional gaps detected by invasive EAM (3 months LGE-MRI, upper panel; 28 months LGE-MRI, lower panel). $\kappa$, kappa value (measure of agreement); $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$; sens., sensitivity; spec., specificity [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 4** Detection of functional gaps depending on time point and threshold

| | 3-Month LGE-MRI | Late follow-up LGE MRI (median 28 months) | | |
|---|---|---|---|---|
| **IIR threshold** | **<1.20 (standard threshold)** | **<1.20 (standard threshold)** | **<1.10 (reduced threshold)** | **<1.05 (reduced threshold)** |
| **Agreement ($\kappa$)** | .74** | .29** | .10 (n.s.) | .03 (n.s.) |
| **Sensitivity (%)** | 91.3 | 93.5 | 58.7 | 32.6 |
| **Specificity (%)** | 89.7 | 46.7 | 52.2 | 63.1 |

Predictive value of LGE-MRI regarding the detection of functional gaps is shown for the different time-points and different IIR thresholds applied. Indicated is the kappa-agreement of light electroanatomical mapping regarding presence or absence of gaps in corresponding PV segments. Further the sensitivity and specificity of LGE-MRI to detect functional gaps is specified with electroanatomical mapping serving as a reference.
Abbreviation: IIR, image intensity ratio; $\kappa$, kappa value (measure of agreement); n.s., statistically not significant.
$^{**}p < .0001$.

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ablation with subsequent EAM (median: 1.5 days after the late follow-up LGE-MRI) regarding regional distribution of fibrosis and detection of functional gaps was only weak. In contrast, the 3 months LGE-MRI displayed good agreement with EAM at later repeat procedures. Of note, these findings may explain why several groups that performed LGE-MRI at very late time points, immediately prior to repeat ablation procedures, found the method to be inaccurate in the detection of gaps.[7,8]

While the negative predictive value of LGE-MRI regarding exclusion of functional gaps was very high (97%) at three months post ablation, the positive predictive value was somewhat lower (73%). This is in line with previous reports and may reflect the fact that not all anatomical discontinuities of an ablation lesion constitute functional gaps.[3] For example, where anatomical gaps co-localize with non-conducting atrial tissue or sites of dormant conduction, no electrical reconnection will be detected by EAM. Moreover, it has to be considered that even small-electrode catheters may have a limited sensitivity to detect low-amplitude PV signals.

### 4.2 | Previous reports on regression of LGE-MRI detectable fibrosis

While an early decrease of LGE in the acute setting (up to 2 months post injury) has been well explained by interstitial edema and inflammation that typically resolve within 4 weeks as demonstrated histologically,[18,19] this reasoning is not applicable to long-term regression of LGE beyond 3 months post injury as encountered in our study. Of note, such long-term regression of LGE-MRI-detected fibrosis has been previously reported for post-myocardial infarction scar.[11,12] However, it has not been taken into account, that these observations might as well be owed to differences in detectability of fibrosis at distinct stages of scar formation. Unlike for early regression in the acute setting (up to 2 months), there has been no validation of the LGE-MRI data by a reference method in any of the studies, thus the underlying reasons remain obscure. A recent study has also reported on long-term regression of ablation-induced atrial fibrosis as detected by LGE-MRI.[20] However, again, LGE-MRI data was not validated by a reference method, and thus, the decrease of LGE-MRI-detected ablation-induced fibrosis over time was interpreted as non-durable ablation lesions. It was even speculated that the observed regression of LGE-MRI-detected ablation lesions over a period of 2 to 3 years would account for late AF recurrences.[20] Thus, the study presented here is the first one to indicate that it is not the ablation-induced atrial fibrosis that diminishes over time, but the capability of LGE-MRI to detect it. Whether the phenomenon we observed in ablation-induced atrial fibrosis, may similarly apply for the regression of native atrial fibrosis remains to be elucidated. While we found a decrease in the detectability of total atrial fibrosis (i.e., native and ablation-induced) over time, we cannot dissect whether this was merely driven by the failure to detect chronic ablation lesions, as all patients had been previously ablated.

### 4.3 | Sustained cardiac scar remodeling following catheter ablation

The pathology of acute and short-term atrial radiofrequency ablation injury is well established in animal models and patients.[21,22] Over the first 2 months, the response to ablation injury is characterized by coagulation necrosis, hemorrhage, neovascularization, hyperemia and interstitial edema as well as inflammatory cell infiltration. Moreover, proliferating myofibroblasts constantly generate fibrogenic signals that perpetuate tissue repair and promote collagen deposition, resulting in replacement of myocardium with fibrous scar tissue. While long-term histological data on atrial fibrosis and ablation-induced scarring beyond 2 months post-injury are lacking, it has been shown that scar formation and remodeling in response to myocardial infarction is a dynamic and chronically sustained process that continues over years after the initial injury.[23]

### 4.4 | Potential explanations for reduced detectability of fibrosis

Sustained scar remodeling implicates constant changes that affect cellular composition, extracellular space, water content and vascularization, as well as small-vessel permeability and patency and intravascular pressure. These changes in turn, are likely to alter tissue-inherent magnetic properties and wash-in/wash-out kinetics of gadolinium.[24] Against this background, there are several possible explanations for the loss of detectability of fibrosis over time reported here.

One possible explanation could be a combination of scar involution and partial volume effects. The latter refers to individual voxels that are fully covered by scar tissue in the initial scan, but only partially covered by scar in the late follow-up scan, and are thus not appreciated as scar. Partial volume effects are particularly relevant in the thin-walled atrium, where the transmural thickness may not even exceed the width of a single voxel, and post-ablation scar involution and thinning of the tissue will obviously contribute to this effect.[25] Moreover, altered wash-in/wash-out kinetics may impede delivery and accumulation of gadolinium and thus the detection of scar tissue. In particular, the hyperemic state of the scar tissue that can be observed in the first months after ablation and that facilitates distribution of contrast agents like gadolinium, is likely to have diminished over the median follow-up time of 28 months. Finally, the extracellular volume fraction of chronic cardiac scar tissue has been shown to be reduced compared to the acute state, which may also contribute to the reduction in late gadolinium enhancement.[26] However, we can only speculate which aspect may account for the decreasing detectability of fibrosis and what is the relative contribution of the distinct remodeling processes.

Novel imaging techniques may have the potential to overcome some of the above-mention shortcomings in the future. While T1 mapping can directly quantify T1 relaxation times on the scale of individual voxels of interest, Rho T1 sequences detect distinct tissue properties

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compared to conventional T1 or T2 weighted sequences. Both may allow for more accurate tissue characterization with the potential to better discriminate ablation lesions from surrounding tissue, even in the case of diffuse fibrosis or inhomogenous scarring in the thin-walled atrium. Finally, if an impeded gadolinium wash-in accounted for the reduced capability to detect chronic stages of lesion formation, extension of the delay between contrast administration and image acquisition could be considered to allow more time for gadolinium to enter the lesions.

### 4.5 | Clinical implications

Our data has important clinical implications. The ability of LGE-MRI to localize atrial fibrosis and functional gaps in the ablation lines, as well as the feasibility of LGE-MRI-guided (re) ablation have been demonstrated by several groups.[3–5,9,10] Moreover, LGE-MRI has the potential to non-invasively confirm durable pulmonary vein isolation to avoid unnecessary redo procedures. Finally, approaches targeting native atrial fibrosis for the treatment of AF have been investigated, although large randomized trials have failed to prove benefit until now.

The data presented here indicates that the detectability of atrial fibrosis may be dependent on the timing of the LGE-MRI study. This could be particularly demonstrated for post-ablation scarring which was accurately detected 3 months post-ablation but only with weak accuracy at a median of 28 months post-ablation. The good agreement of LGE-MRI 3 months post ablation with EAM at later repeat ablation procedures (median: 28 months post index ablation) indicates that, while the tissue composition may be subject to sustained remodeling, the extent and localization of ablation-induced fibrosis remains rather constant over time. In light of our data and with respect to the emerging LGE-MRI-guided ablation approaches, both for atrial and ventricular arrhythmias, possible changes in detectability of ablation-induced fibrosis as a function of scar remodeling over time, should be taken into account.

### 4.6 | Limitations

Due to the inclusion criteria requiring two post ablation LGE-MRI scans and a planned repeat procedure, the resulting sample size of this study is rather small. However, given the marked effect size and consistency of our observation, the results are still valid. The retrospective nature of our study clearly accounts for further limitations, including variable time points of the late follow-up LGE-MRI. A prospective trial with serial LGE-MRI scans at predefined time points and a predefined validation protocol is underway, but will be of long duration as validation of LGE-MRI must be performed during repeat ablation procedures that will only become necessary in the subset of included patients that suffer AF recurrence. Finally, the reference method of invasive electrophysiology and electroanatomical mapping, albeit without alternative currently, has its own limitations. On one hand, low voltage is only a surrogate and does not necessarily imply fibrosis, and on the other hand, fixed voltage thresholds used to define fibrosis, do not take the considerable inter- and intraindividual variability into account. Moreover, as outlined above, the sensitivity for intracardiac and PV electrograms has certain limits and relies on electrode size, spacing and orientation relative to the propagation wave front.

## 5 | CONCLUSIONS

To our knowledge, this study is the first to show that LGE-MRI loses some of its capability to detect ablation-induced atrial fibrosis over time. The good agreement of LGE-MRI 3 months post ablation with EAM at a later repeat ablation procedure suggests that extent and localization of ablation-induced fibrosis remains rather constant over time. While LGE-MRI 3 months post ablation detected ablation lesions with high accuracy, the predictive value of LGE-MRI at a median of 28 months post ablation was only weak. These changes in detectability of ablation-induced atrial fibrosis over time should be considered, particularly in view of the emerging LGE-MRI-guided therapeutic strategies and ablation approaches. Thus, in order to best assess ablation lesions, LGE-MRI should be performed at 3 months post-ablation rather than at later time points > 12 months post ablation like for example, prior to a planned repeat ablation procedure.

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### CONFLICTS OF INTEREST

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