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ELECTROPHYSIOLOGY

# The individual relationship between atrial fibrillation sources from CARTOFINDER mapping and atrial cardiomyopathy

## The catch me if you can trial

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## Abstract

**Background:** Targeting individual sources identified during atrial fibrillation (AF) has been used as an ablation strategy with varying results.

**Objective:** Aim of this study was to evaluate the relationship between regions of interest (ROIs) from CARTOFINDER (CF) mapping and atrial cardiomyopathy from late gadolinium enhancement (LGE) cardiovascular magnetic resonance imaging (CMR).

**Methods:** Twenty consecutive patients underwent index catheter ablation for persistent AF (PERS AF). Pre-processed LGE CMR images were merged with the results from CF mapping to visualize harboring regions for focal and rotational activities. Atrial cardiomyopathy was classified based on the four Utah stages.

**Results:** Procedural success was achieved in all patients ($n$ = 20, 100%). LGE CMR revealed an intermediate amount of 21.41% ± 6.32% for LA fibrosis. ROIs were identified in all patients (mean no ROIs per patient $n$ = 416.45 ± 204.57). A tendency towards a positive correlation between the total amount of atrial cardiomyopathy and the total number of ROIs per patient (regression coefficient, $\beta$ = 10.86, $p$ = .15) was observed.

**Abbreviations:** AI, ablation index; CF, CARTOFINDER; HPSD, high power short duration; LAMRT, left atrial macro-reentrant tachycardia; LGE, late gadolinium enhancement; PERS AF, persistent atrial fibrillation; PVI, pulmonary vein isolation; RFCA, radiofrequency-guided catheter ablation; ROIs, regions of interest; WACA, wide antral circumferential ablation.

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The degree of fibrosis and the presence of ROIs per segment showed no consistent spatial correlation (posterior: $\beta = 0.36$, $p$-value ($p$) = .24; anterior: $\beta = -0.08$, $p = .54$; lateral: $\beta = 0.31$, $p = 39$; septal: $\beta = -0.12$; $p = .66$; right PVs: $\beta = 0.34$, $p = .27$; left PVs: $\beta = 0.07$, $p = .79$; LAA: $\beta = -0.91$, $p = .12$). 12 months AF-free survival was 70% ($n = 14$) after ablation.

**Conclusion:** The presence of ROIs from CF mapping was not directly associated with the extent and location of fibrosis. Further studies evaluating the relationship between focal and rotational activity and atrial cardiomyopathy are mandatory.

**KEYWORDS**
atrial cardiomyopathy, atrial fibrillation, CARTOFINDER, catheter ablation, magnetic resonance imaging

## 1 | INTRODUCTION

Mechanisms initiating and perpetuating atrial fibrillation (AF) are still not completely understood. Prior studies identified predictors for AF recurrence, emphasizing a correlation between cardiac remodeling and AF.[1] Radiofrequency-guided catheter ablation (RFCA) is an established treatment for persistent AF (PERS AF) but ablation strategies are heterogeneous. Despite improvements in ablation technology, imaging modalities, and ablation techniques, AF recurrence following ablation remains an issue.[1] Targeting individual sources identified during AF has been used as an ablation strategy with varying results.[2–5] Recently, the CARTOFINDER (CF) module was introduced as a novel approach to reveal and visualize individual arrhythmia substrates (focal or rotational) inside the 3D-mapping system. In parallel, the use of late-gadolinium enhancement (LGE) cardiovascular magnetic resonance imaging (CMR) has been established to determine the extent of atrial cardiomyopathy. The aim of this study was to evaluate the individual relationship between mapping for focal and rotational regions of interest (ROIs) from CF and the severity of atrial cardiomyopathy in patients with persistent AF (PERS AF).

## 2 | METHODS

This prospective observational single center study included 20 consecutive patients undergoing RFCA for symptomatic and drug refractory PERS AF between 2020 and 2022. AF was defined adherent to the current ESC-guidelines for the diagnosis and management of AF.[1] Procedural data, complications and early, 3-, 6- and 12-month recurrence rates were evaluated. Following a 3-month blanking period, arrhythmia recurrence was defined as a documented symptomatic episode of any atrial tachycardia (AT)/AF > 30 s. The study was performed in compliance with the principles outlined in the Declaration of Helsinki and approved by the Institutional Ethics Committee (Reg. No. 2019–563).

### 2.1 | Magnetic resonance imaging and fibrosis imaging

The patients underwent a 3D LGE CMR, as well as a contrast-enhanced magnetic resonance angiography and cine imaging. The high-resolution LGE images of the LA were obtained 15 to 30 min after gadolinium-based contrast injection. This was accomplished using a 3D inversion-recovery prepared, respiration-navigated, and electrocardiogram (ECG)-triggered gradient-echo pulse sequence with fat saturation. The scan time for the LGE CMR studies was expected to last between 8–12 min, depending on the patient's rhythm and respiratory pattern. After data acquisition, the CMR data were evaluated and processed using the Corview image processing and analysis software, developed by Marrek in Salt Lake City, Utah. Following 3D reconstruction, the degree of LA fibrosis was classified into four Utah stages, based on the amount of LA wall enhancement from LGE CMR, as a percentage of the total LA wall volume: stage I was defined as less than 10%, stage II as between 10% and less than 20%, stage III as between 20% and less than 30%, and stage IV as greater than or equal to 30%. Afterward, the LA was systematically divided into seven anatomical segments, as shown in Figure 1.

### 2.2 | Procedural management

Left atrial/left atrial appendage (LA/LAA) thrombus formation was ruled out in all patients prior to ablation. Preprocedural LGE CMR imaging was performed for procedural planning and to evaluate the individual anatomy and stage of cardiomyopathy of the LA. Antiarrhythmic drugs (AADs) except for amiodarone were discontinued at least three half-lives before ablation. Anticoagulation with phenprocoumon was continued aiming for an International Normalized Ratio (INR) between 2.0 and 3.0. Direct oral anticoagulants (DOAC) were stopped one half-life before ablation. Pericardial effusion (PE) was ruled out immediately after ablation and the next day thereafter.

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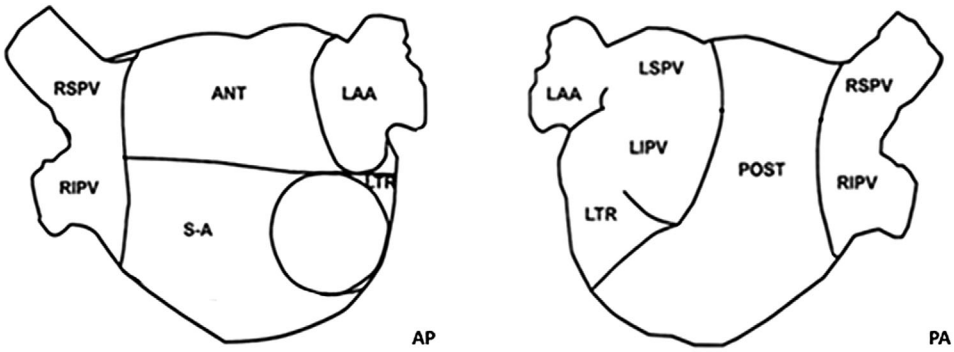


**FIGURE 1** Three-dimensional visualization of the LA segments in AP and PA view; POST, ANT, LTR, S-A, RPVs, RSPV, RIPV, LPVs, LSPV, LIPV, LAA. LA, left atrial; AP, anterior/posterior; PA, posterior/anterior; POST, posterior; ANT, anterior; LTR, lateral; S-A, septal; RPVs, right pulmonary veins; RIPV, right inferior pulmonary vein; LPVs, left pulmonary veins; LSPV, left superior pulmonary vein, LIPV, left inferior pulmonary vein; LAA, left atrial appendage.

Anticoagulation was continued within 4 h after the procedure with phenprocoumon or DOAC when there was no evidence for PE. AADs were prescribed to the operator's discretion for a period of 3 months following ablation.

## 2.3 | Ablation procedure

Ablation was performed under conscious sedation with propofol and analgesia with fentanyl as required. Intravenous heparin was administered to maintain an activated clotting time (ACT) of 300 s throughout the procedure. Catheter ablation was performed with a multipolar mapping catheter (PentaRay, Biosense Webster Inc., Diamond Bar, CA, USA) and an open-irrigated RF-catheter (8 Fr) with a tip-integrated contact force sensor (Thermocool Smart Touch SF, Biosense Webster Inc.). After double transseptal puncture, the catheter was positioned in the LA, and the 3D geometry of the LA was assessed followed by a LA CF map during AF. After reconstruction of the LA, each pulmonary vein ostium was identified by selective pulmonary vein angiography and ablation was performed during AF to give catheter ablation the chance for AF termination. An ablation index (AI) guided 50 Watts (W) high power short duration (HPSD) ablation protocol (AI anterior 550; AI posterior 400) with an irrigation flow of 20 mL/min was applied. A wide antral circumferential ablation (WACA) was done in a point-by-point fashion according to the "close" protocol with an interlesion distance of $\leq$ 6 mm. Ablation beyond PVI was carried out at the operator's discretion including ablation of the cavotricuspid isthmus (CTI), application of LA lines or posterior wall isolation in terms of substrate modification based on information from bipolar voltage mapping. Rotational and focal ROIs in close vicinity to the PVs were included in WACA lines (Figure 2). After completion of ablation lines entrance- and exit-block was confirmed. Procedural success was subsequently reconfirmed after a minimum waiting period of 30 min.

## 2.4 | Ultra-high-density mapping

After restoration of sinus rhythm, the multipolar mapping catheter (PentaRay, Biosense Webster Inc., Diamond Bar, CA, USA) was used to gain information about the localization and distribution of bipolar low voltage areas in the LA wall. Ultra-high-density mapping, aiming for > 1000 mapping points was conducted in all patients. For the atrial voltage maps, the bipolar voltage reference interval was set between 0.05 and 0.5 mV. The amount of LA bipolar low voltage (total and per segment) was measured, using the area measurement tool. The LA was divided into the same segments allowing for a direct individual and segment-based analysis of the relationship between findings from CF and fibrosis from LGE CMR (Figure 1).

## 2.5 | Follow-up

After discharge, follow-up visits were scheduled at 3, 6, and 12 months including routine 72-hour-Holter ECGs and interviews. Unscheduled visits were conducted if required. AT/AF recurrence was judged on ECG documentation and symptoms suggestive of arrhythmia recurrence using the definition from the ESC guideline for the diagnosis and management of AF.[1]

## 2.6 | Endpoint

The aim of this study was to evaluate the relationship between focal and rotational ROIs and atrial cardiomyopathy. Using CF mapping, we intended to identify potential new ablation targets in patients with PERS AF allowing for personalized paths in AF management and improved ablation outcomes.

## 2.7 | Data collection

Data on patients' characteristics, medication, symptoms, and complications were compiled from patients' records and discharge letters. Procedural parameters and clinical aspects concerning RFCA were taken from ablation protocols and procedure related documents. Data were collected prospectively.

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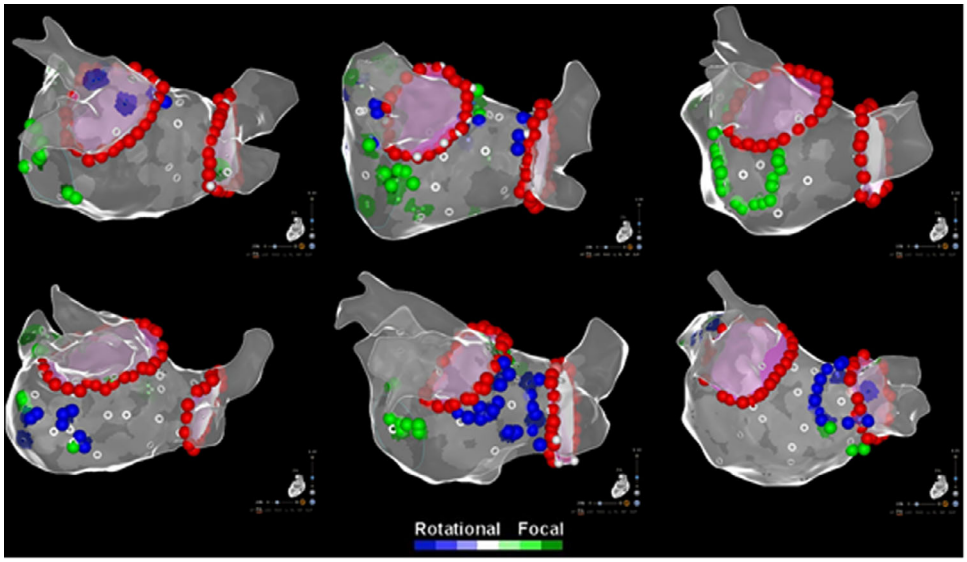


**FIGURE 2** Typical example for our AI-guided 50 W RFCA approach with PVI in a point-by-point fashion. RFCA, Radiofrequency-guided catheter ablation; PVI, pulmonary vein isolation. [Color figure can be viewed at wileyonlinelibrary.com]

### 2.8 | Statistical analysis

Statistical analysis was performed using the free software R. Metrical data were reported by mean and standard derivation whereas categorical and ordinal data were described by their frequencies. The primary analysis (probability for the occurrence of ROIs in each segment depending on its degree of fibrosis) consisted of univariate binary logistic regressions for each segment. Secondary analyses were either performed by linear regression (number of ROIs depending on overall LA fibrosis) or by logistic regression (12-month-AF-free survival depending on LA fibrosis in each segment). The degrees of LA-fibrosis per segment were compared by employing paired Student's *t*-tests. A correction for multiple testing due to the number of pairwise comparisons was performed by the Bonferroni-method. *p*-values $\leq .05$ were considered statistically significant. Due to the exploratory nature of this study, we refrained from correction for multiple testing in all further analyses.

A *p*-value $\leq .05$ was considered statistically significant. Due to the exploratory nature of this study, we refrained from correction for multiple testing in all analyses.

## 3 | RESULTS

### 3.1 | Patients' characteristics

The study population consisted of 20 consecutive patients (69 ± 9 years, 55 % male) undergoing RFCA for PERS AF in conjunction with CF mapping for ROIs and LGE CMR imaging to access the stage of atrial cardiomyopathy. Mean AF duration was 31 months (range 2–89 months). All patients underwent index AF ablation. LA fibrosis was revealed in most patients, predominantly corresponding to Utah stages II and III ($n = 18$, 90%). Baseline characteristics are summarized in Table 1.

### 3.2 | Procedural data

Acute procedural success was achieved in all patients ($n = 20$, 100%). An additional ablation beyond PVI was performed in eight patients (40%). Ablation induced AF-termination was observed in four patients (20%). In one patient (5%) AF-termination was achieved during isolation of the left sided PVs. In two patients (10%) AF changed to left atrial macro-reentrant tachycardia (LAMRT) during ablation. LAMRT were mapped and successfully ablated inside the LA by application of a lateral and an anterior line. In another patient (5%) AF converted to atrial flutter, which was successfully terminated by CTI-ablation. No procedure related complications occurred. Details are presented in Table 2.

### 3.3 | Follow-up

Within the observation period of 12 months, six patients (30%) have had AF recurrence. Half of them ($n = 3$) had received PVI with an additional substrate modification. Four patients (20%) presented with recurrent AF within the 3-month blanking period. Two patients (10%) experienced AF recurrence after the blanking period. One of them (5%) was scheduled for repeat ablation.

### 3.4 | Distribution of ROIs

Focal and rotational ROIs were identified in all patients (mean number of ROIs per patient $n = 416.45 \pm 204.57$). A typical example of

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**TABLE 1** Baseline characteristics.

| Characteristics ($n = 20$) | |
|---|---|
| Age (years) | 69.05 ± 9.03 |
| >Gender, male | 11 (55%) |
| LAD (mm) | 46.70 ± 5.89 |
| LVEF (%) | 52.43 ± 4.57 |
| BMI (kg/m$^2$) | 30.49 ± 5.28 |
| AF-Duration (months) | 31.10 ± 27.76 |
| CHA2DS2-VASc-Score (points) | 3 ± 2 |
| aHT | 20 (100%) |
| Diabetes | 2 (10%) |
| Prior stroke/TIA | 2 (10%) |
| Heart failure | 12 (60%) |
| Beta-blocker | 16 (80%) |
| AADs | 3 (15%) |
| ACE-Inhibitor | 18 (90%) |
| Statin | 10 (50%) |
| Anticoagulation | 20 (100%) |
| **Amount of fibrosis (%)**[a] | |
| Utah stage I (0–10) | 0 (0%) |
| Utah stage II (10–20) | 8 (40%) |
| Utah stage III (20–30) | 10 (50%) |
| Utah stage IV (> 30) | 2 (10%) |

*Note*: Continuous variables are shown as the mean ± SD and categorical variables as the number (%).
Abbreviations: LAD, left atrial diameter; LVEF, left ventricular ejection fraction; BMI, body mass index; AF, atrial fibrillation; aHT, arterial hypertension; AADs, antiarrhythmic agents.
[a]Left atrial fibrosis was measured using the area measurement tool based on bipolar low-voltage.

**TABLE 2** Procedural data and additional ablation beyond pulmonary vein isolation.

| Characteristics ($n = 20$) | |
|---|---|
| Procedure duration (min) | 124 ± 35 |
| Flouroscopy time (min:s) | 06:40 ± 01:48 |
| Flouroscopy dose (yGmy2) | 466.67 ± 356.99 |
| CARTOFINDER mapping, LA (min:s) | 09:30 ± 03:53 |
| Ablation time (min:s) | 26:40 ± 07:51 |
| High density mapping bipolar voltage, LA (min:s) | 07:57 ± 03:01 |
| ROIs from CARTOFINDER, LA ($n$) | 142 ± 46 |
| Mapping points for bipolar voltage, LA ($n$) | 2690 ± 1175 |
| **Additional ablation beyond PVI** | |
| CTI | 5 (25%) |
| LA roof line | 1(< 1%) |
| Anterior line | 5 (25%) |
| Septal line | 1 (< 1%) |
| Lateral line | 1 (< 1%) |
| Box lesion | 5 (25%) |

*Note*: Continuous variables are shown as the mean ± SD.
Abbreviations: LA, left atrium; PVI, pulmonary vein isolation; CTI, cavotricuspid isthmus ablation.

**TABLE 3** Linear regression analysis of the number of regions of interest (focal, rotational, total) and the total amount of left atrium fibrosis (%) per patient.

| Type | Regression coefficient | $p$-value |
|---|---|---|
| Focal | 8.432 | .282 |
| Rotational | 2.423 | .431 |
| Total | 10.855 | .148 |

Abbreviation: LA, left atrium.

ROIs from CF mapping is visualized in Figure 3. The total amount of focal ROIs amounted to 352.55 ± 210.73 (with a cycle length (CL) ranging from 140 to 297 ms). A mean of 63.90 ± 82.03 rotational ROIs was identified (with a CL ranging from 143 to 200 ms). In total, significantly more focal ROIs were observed compared to rotational ROIs ($p < .01$). Focal activity was predominantly documented in the LAA (51%), whereas the highest percentage of rotational ROIs identified in the posterior area of the LA (42%) (Figure 3).

## 3.5 | Distribution of LA-enhancement

LGE based CMR scans revealed an intermediate amount of 21.41 ± 6.16% for LA fibrosis (Table 2). A higher percentage of atrial fibrosis was documented in the posterior area of the LA compared to the lateral (POST vs. LTR, 4.39% ± 2.65% vs. 2.02% ± 1.67%, $p = .030$) and septal region (POST vs. S-A, 4.39% ± 2.65% vs. 2.54% ± 1.86%, $p = .239$) as well as the LAA (POST vs. LAA, 4.39% ± 2.65% vs. 1.89% ± 1.89%, $p = .025$). The percentage of LA-enhancement of the left PVs was higher compared to the right PVs (3.77% ± 1.76% vs. 2.54% ± 1.58%, $p = .411$). The distribution of mean LA-enhancement per segment is visualized in Figure 4.

## 3.6 | Correlation between the degree of atrial fibrosis and the number of ROIs per patient

Linear regression analyses reveal a tendency towards a positive correlation between the total amount of atrial fibrosis and the number of ROIs per patient. Especially for focal ROIs, a trend towards a positive correlation can be assumed. Details are presented in Figure 5. But despite this observation the relationship between the severity of atrial cardiomyopathy and the variety of ROIs did not reach statistical significance, as demonstrated in Table 3.

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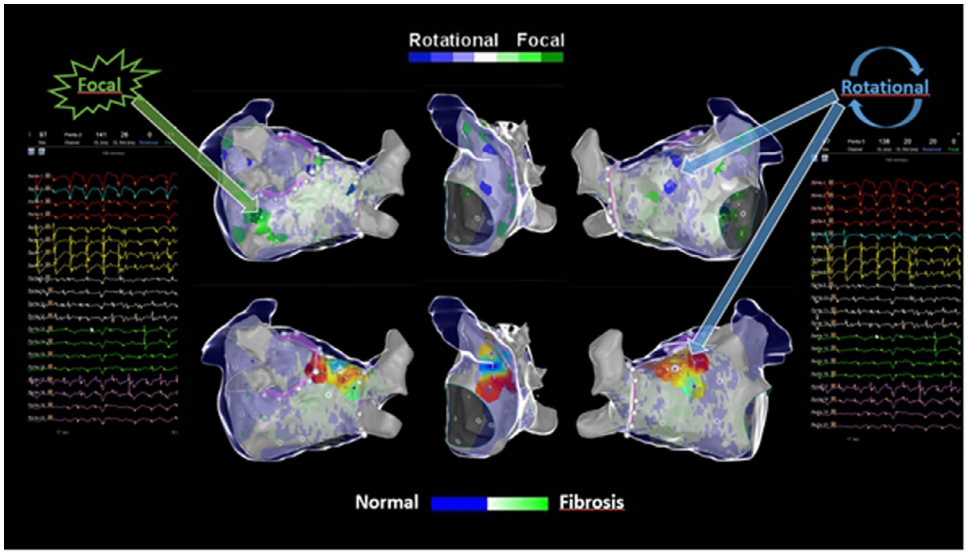


**FIGURE 3** CF-guided mapping for ROIs was conducted automatically utilizing the multipolar PentaRay catheter. Left panel: Focal activation is detected by identifying an S wave in the unipolar electrograms. If S wave patterns preceding activity on neighboring electrodes are detected during at least two consecutive atrial cycles, the site is designated as a focal source. Right panel: Rotational activation is detected by identifying pan-systolic activation occurring in consecutive electrodes. A pan-systolic activation wave is defined as a series of electrograms in consecutive electrodes occupying more than 50% of the local cycle length with a distance of less than 20 mm between the starting and ending points of the wave. Two or more such pan-systolic activations occurring are defined as a rotational activation. Central panel: Typical example for focal (green) and rotational (blue) ROIs revealed from endocardial CF mapping and fusion of 3D electroanatomical reconstruction. CF, CARTOFINDER mapping; ROIs, regions of interest; LA, left atrium. [Color figure can be viewed at wileyonlinelibrary.com]

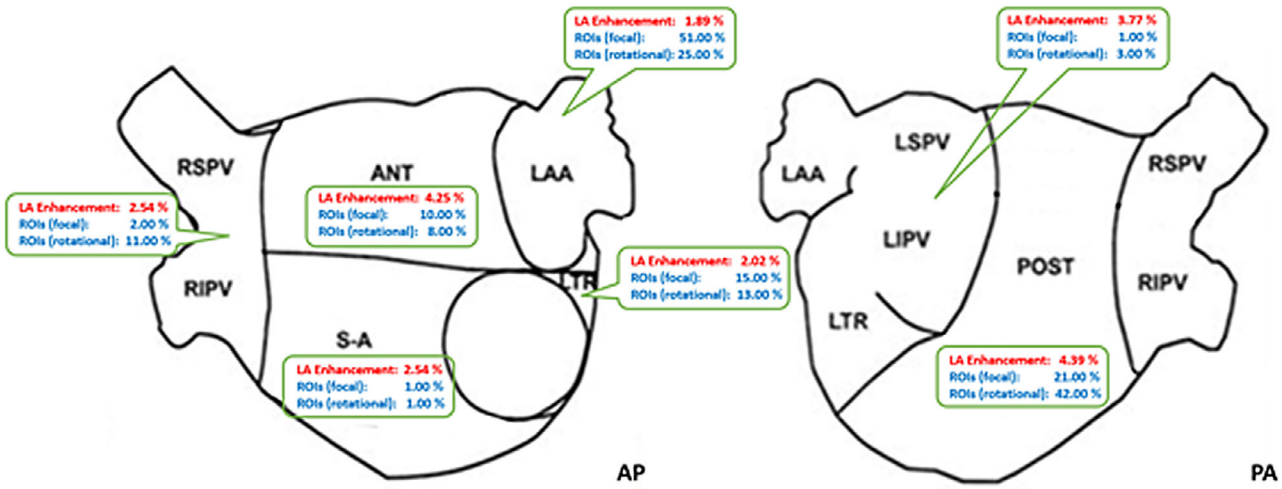


**FIGURE 4** Distribution of mean LA-enhancement (%) from LGE CMR (red) and ROIs (%) (blue) per atrial segment. LA, left atrium; LGE, late gadolinium enhancement; CMR, cardiac magnetic resonance imaging; ROIs, regions of interest; AP, anterior/posterior view; PA, posterior/anterior view; POST, posterior; ANT, anterior; LTR, lateral; S-A, septal; RPVs, right pulmonary veins; RSPV, right superior pulmonary vein, RIPV, right inferior pulmonary vein; LPVs, left pulmonary veins; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; LAA, left atrial appendage. [Color figure can be viewed at wileyonlinelibrary.com]

### 3.7 | Correlation between the degree of atrial fibrosis and the presence of ROIs per LA segment

Univariate binary logistic regression analyses estimated no consistent correlation between the individual amount or distribution of LA fibrosis and the probability for the occurrence of ROIs per segment as summarized in Table 4. The results are illustrated by means of boxplots (see Figure 6).

Figure 7 demonstrates the merging of pre-processed LGE CMR images with the results from CF mapping to visualize fibrotic areas of the LA as well as harboring regions for focal and rotational activities simultaneously to facilitate RFCA.

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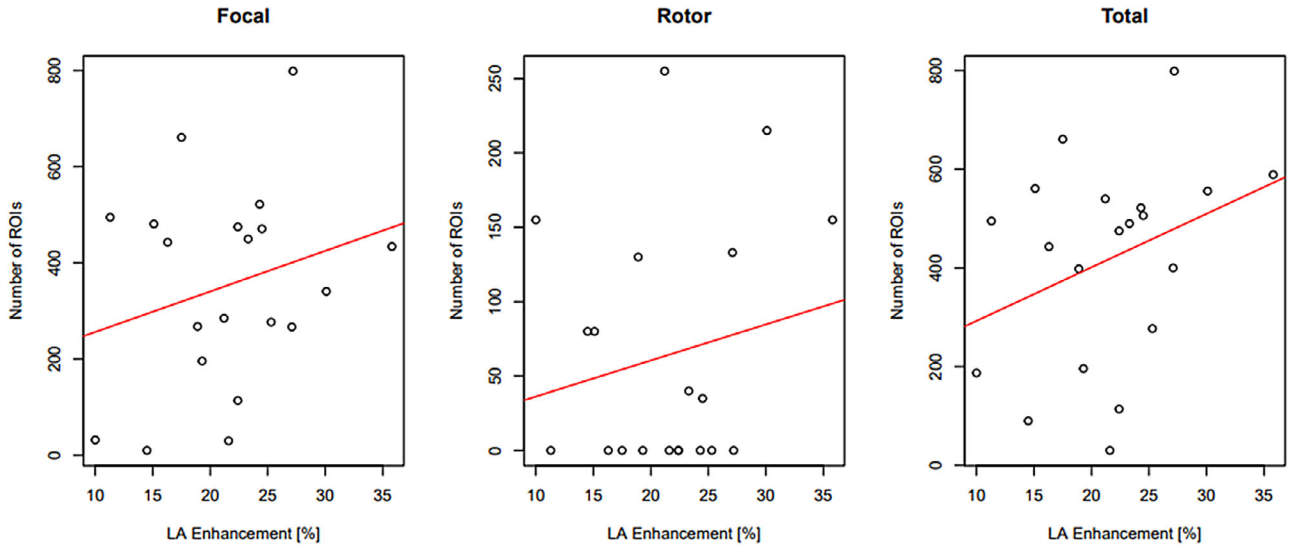


**FIGURE 5** Number of ROIs (focal, rotational, total) per patient depending on the total amount of LA fibrosis (%) by LGE CMR. ROIs, regions of interest; LA, left atrium. [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 4** Logistic regression analysis of the probability for regions of interest and the degree of atrial fibrosis (%) per left atrium segment.

| Segment | Regression coefficient | *p*-value |
|---|---|---|
| Posterior | 0.358 | .237 |
| Anterior | −0.087 | .537 |
| Lateral | 0.308 | .386 |
| Septal | −0.123 | .662 |
| Right PVs | 0.341 | .270 |
| Left PVs | 0.071 | .789 |
| LAA | −0.908 | .115 |

Abbreviations: PVs, pulmonary veins; LAA, left atrial appendage.

**TABLE 5** Logistic regression analysis of the probability of atrial fibrillation recurrence within 12 months and the degree of atrial fibrosis per segment (%).

| Segment | Regression coefficient | *p*-value |
|---|---|---|
| Posterior | 0.334 | .120 |
| Anterior | −0.033 | .826 |
| Lateral | −0.311 | .349 |
| Septal | −0.070 | .791 |
| Right PVs | −0.812 | .153 |
| Left PVs | −0.369 | .249 |
| LAA | 0.158 | .536 |

Abbreviations: PV, pulmonary veins; LAA, left atrial appendage.

### 3.8 | Impact of atrial cardiomyopathy on AF recurrence

By means of boxplot analyses a vague, but not significant, tendency towards a positive correlation was visualized between the amount of atrial fibrosis and AF-recurrence in the posterior segment exclusively. In total, the severity of LA cardiomyopathy was not predictive for AF recurrence during the observation period of 12 months. Details are presented in Figure 8. Logistic regression analyses estimated no consistent correlation between the severity of atrial cardiomyopathy and AF-recurrence within the observation period of 12 months as summarized in Table 5.

## 4 | DISCUSSION

Catch me if you can is the first study evaluating the individual relationship between ROIs from CF mapping and atrial cardiomyopathy from LGE CMR. This study has two major findings:

- First, fibrosis representing the degree and distribution of atrial cardiomyopathy and ROIs have regional variations within the LA.
- Second, the presence and distribution of ROIs from CF mapping are not directly associated with the extent and location of fibrosis.

### 4.1 | LGE CMR imaging in PERS AF

Atrial remodelling processes are suggested to play an important role in the development of AF.[1,4,5] Several studies point out the importance of LGE CMR imaging for the visualization of individual atrial fibrosis prior to the ablation procedure.[4–7] In our study, LGE CMR revealed an intermediate amount of 21.41% ± 6.32% of LA fibrosis consistent with Utah stages II-III. Importantly, no PERS AF patient was assigned to Utah stage I as all patients had more than 10% fibrosis of the LA. The highest amount of atrial fibrosis was revealed at the posterior LA and more fibrosis was observed close to the left-sided PVs as compared to the right-sided PVs (Figure 4). This observation in terms of LA fibrosis distribution is in accordance with results gained from prior studies including PERS AF patients.[8–10]

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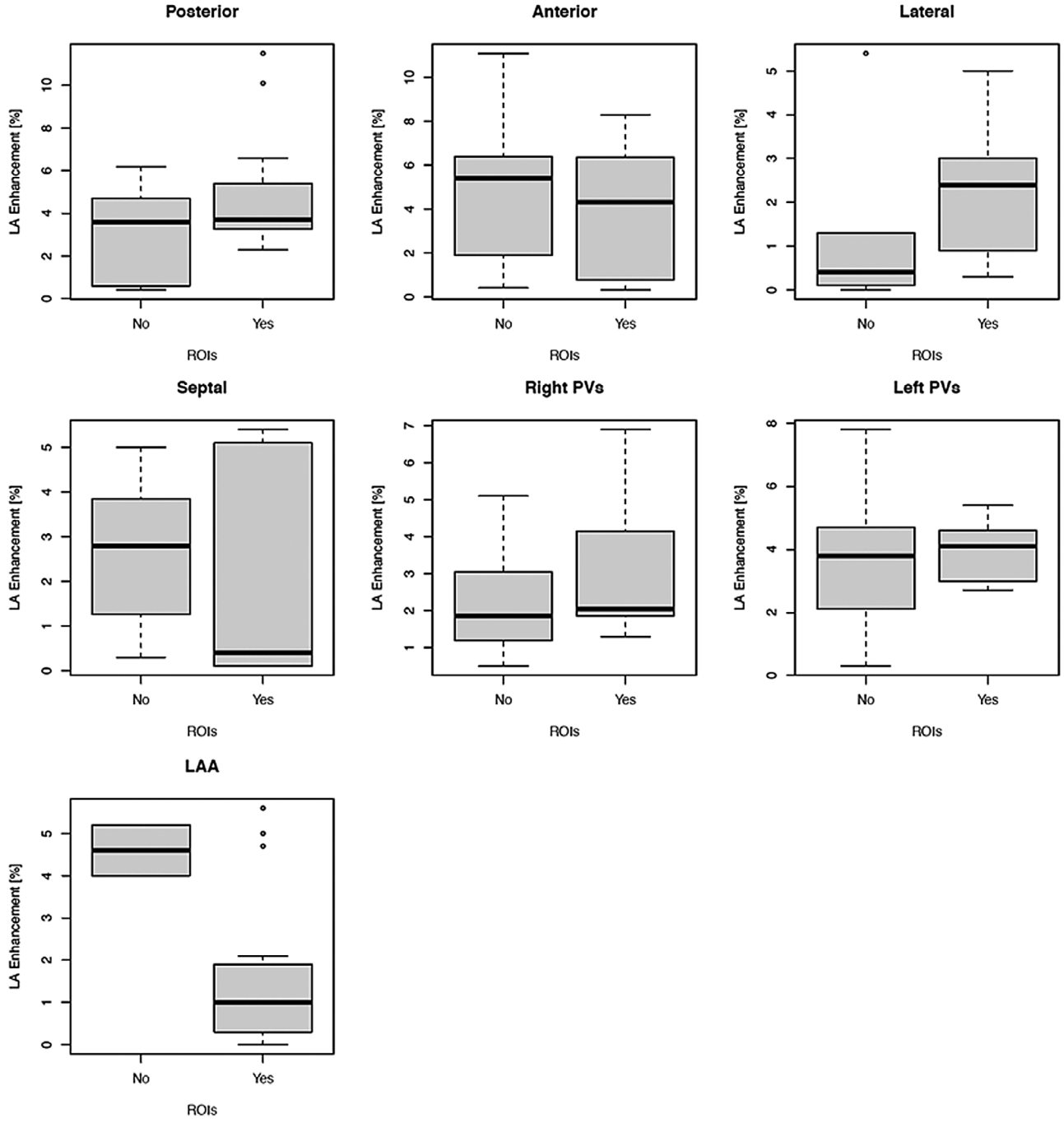


**FIGURE 6** Box plot analysis of the correlation between the percentage of LA enhancement by LGE CMR and the presence of ROIs per segment. LA, left atrium; PVs, pulmonary veins; LAA, left atrial appendage; ROI, region of interest.

## 4.2 | CARTOFINDER mapping in PERS AF

As reported previously, CF-mapping can easily be integrated into the routine workflow for PERS AF ablation.[9,11] In our study, the mean procedure and ablation duration, mapping time for bipolar voltage and additional ROIs, as well as mapping points (Table 2) are comparable to data gathered from prior studies.[9] In line with prior results, ROIs were revealed in all patients with more focal than rotational ROIs and the highest number of focal ROIs was observed in close relationship to the LAA (Figure 4).[9,12] In accordance with another prior study in PERS AF, the vast majority of drivers was distributed among extra PV sites (Figure 4).[13]

## 4.3 | Correlation between ROIs and atrial cardiomyopathy

A prior study did not reveal a significant relationship between the amount and distribution of bipolar low voltage and ROIs from CF.[9] We observed a tendency towards a positive correlation between the total

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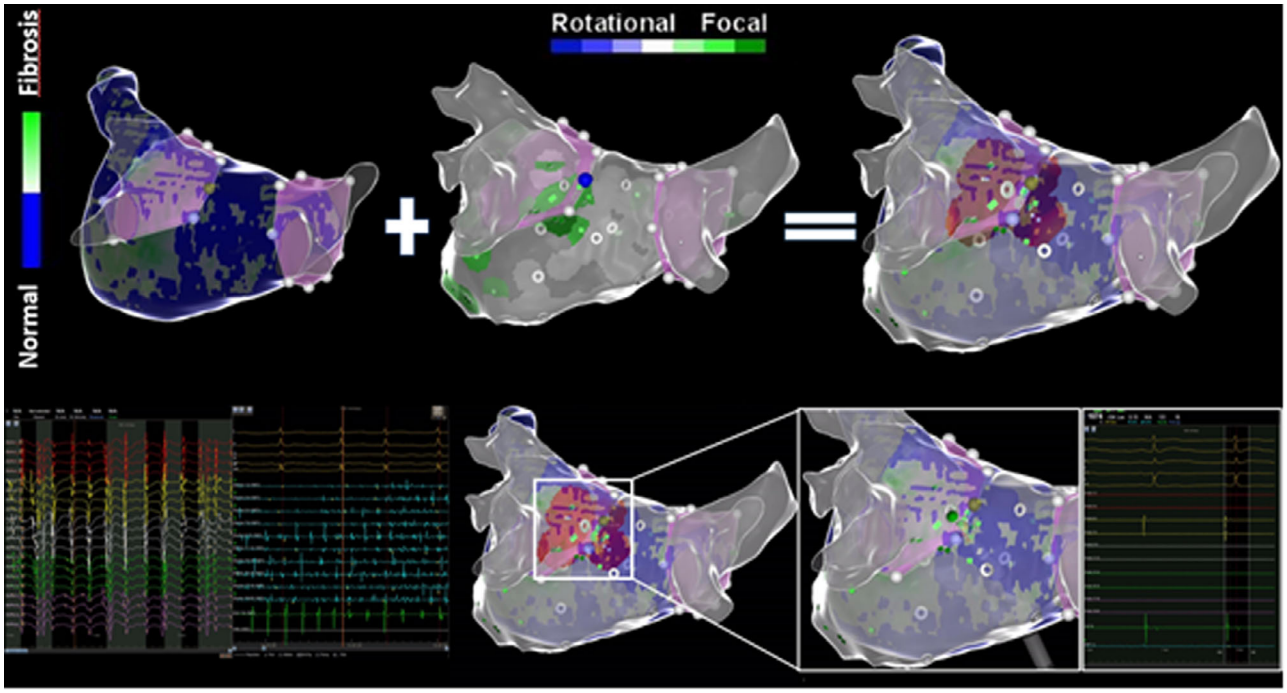


**FIGURE 7** Representative image to demonstrate the individual relationship between distribution of fibrosis and stage of atrial cardiomyopathy and the results from CF mapping aiming for visualization of potential harboring regions for ROIs. Targeting the harboring region at the posterior wall close to the circumferential ablation line for PVI resulted in AF termination (right lower panel). CF, CARTOFINDER; PVI, pulmonary vein isolation; ROIs, regions of interest. [Color figure can be viewed at wileyonlinelibrary.com]

amount of atrial fibrosis from LGE CMR and the number of ROIs per patient. Especially for focal ROIs, a tendency toward a positive correlation can be assumed (Figure 5), however without achieving the level of statistical significance (Table 3). The latter may be related to the small cohort of patients. Per LA segment, no consistent correlation between the degree of fibrosis and the presence of ROIs was found (Figure 6, Table 4). In line with these results prior studies stated, that the presence of rotors was not directly associated with the extent and anatomic location of fibrosis from LGE CMR.[8,10,14] Therefore, the number and distribution of ROIs seems to be individual and not predictable from the stage of atrial cardiomyopathy based on the study results obtained so far.

Nevertheless, further studies are warranted to evaluate the interplay between structural and electrical arrhythmia substrates in more detail. For example, it is still unclear whether fibrosis is the anchor, whether ROIs run along border zones or whether focal and rotational activations have different arrhythmia substrates.

## 4.4 | Impact of atrial cardiomyopathy and ROIs on 12-month AF free survival

In our study, the amount of atrial cardiomyopathy per segment was not associated with AF-recurrence during the observation period of 12 months (Figure 8). This lack of correlation may be primarily caused by the small cohort of patients as the DECAAF study reported on a correlation between individual atrial arrhythmia substrates at baseline and AF-free survival.[4] However, the DECAAF II trial demonstrated that CMR-guided fibrosis ablation plus PVI, compared with PVI catheter ablation only, resulted in no significant difference in atrial arrhythmia recurrence.[5] This raises the question of whether fibrosis is more important in certain areas of the LA than in others. In our cohort of PERS AF patients, we observed a larger amount of atrial fibrosis in the posterior and anterior LA as well as around the left-sided PVs. By means of boxplot analyses a vague tendency towards a positive correlation was visualized between the amount of atrial fibrosis and AF recurrence in the posterior segment (Figure 8, Table 5). In line with these results, prior studies identified the posterior LA wall as an arrhythmogenic trigger in PERS AF as well.[15] Additional research is required.

Ultra-high-density panoramic mapping allows for the reliable visualization of rotors and focal impulse sources.[8,9] Focal activities in close vicinity to the PVs can be successfully targeted during WACA for PVI.[9] These findings act in concert with our study results. However, it remains unclear whether all ROIs should be targeted even in the absence of a corresponding arrhythmia substrate. The studies mentioned above documented that the presence of ROIs was not predictive for AF recurrence.[8,9] These findings are in line with other studies analyzing effects of focal impulse and rotor modulation (FIRM)-guided ablations on patients' outcomes, which demonstrated that an additional FIRM-guided ablation did not provide additional efficacy.[2,3] However, a meta-analysis including data from 10 clinical trials supports the possible benefit of driver ablation as an additional strategy in improving freedom from atrial arrhythmias compared with conventional ablation alone.[16] Since we did not target ROIs independently

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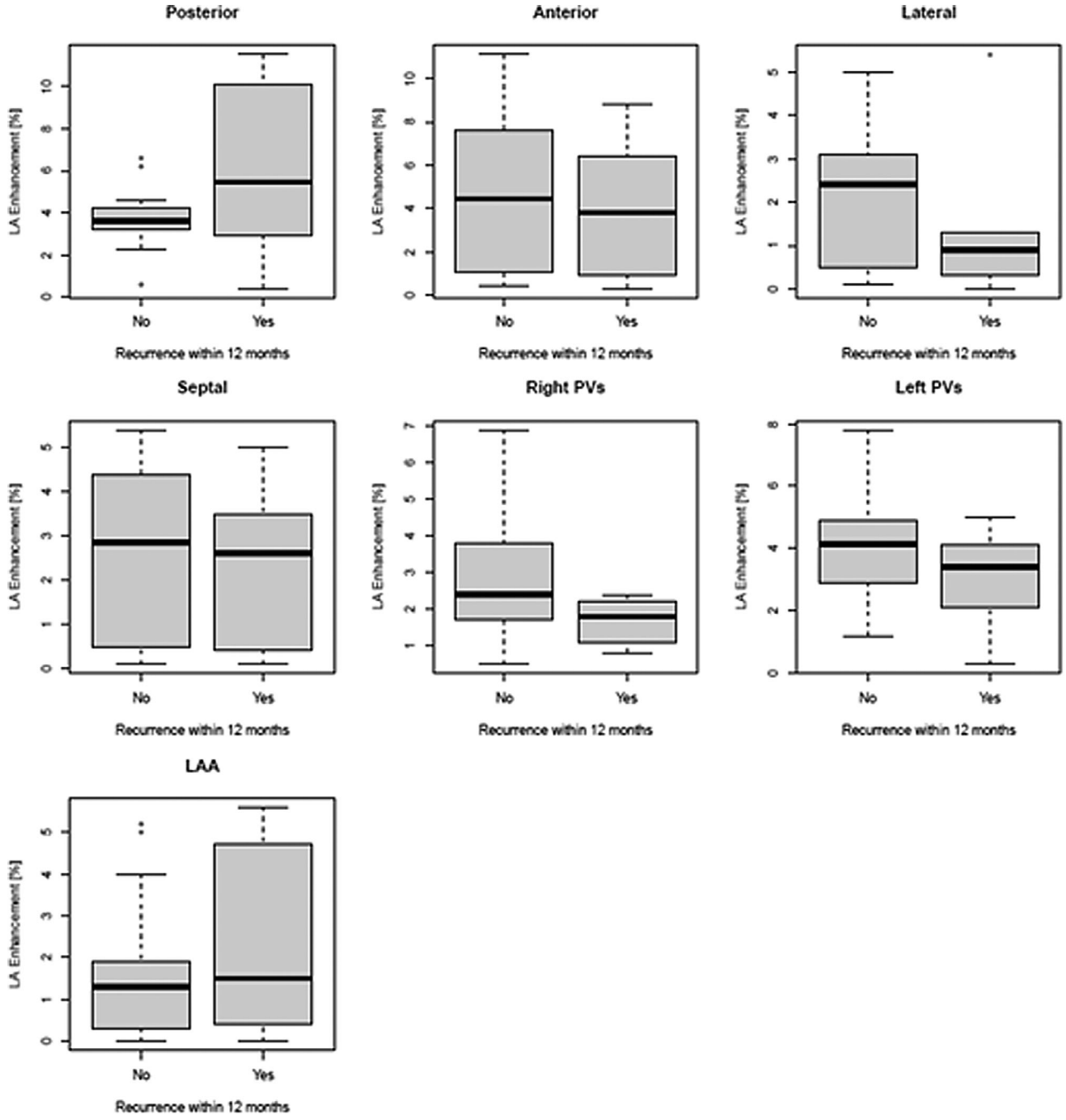


**FIGURE 8** Box plot analyses of LA fibrosis (%) in patients with and without AF recurrences during the observation period prior 12 months. AF, atrial fibrillation; PVs, pulmonary veins; LA, left atrium; LAA, left atrial appendage; AF, atrial fibrillation.

of a corresponding arrhythmia substrate during the ablation procedure, we did not analyze the effect of targeted AF driver ablations on patients' outcome in our present study. As for the ablation strategy, one may speculate that focal ROIs should be ablated selectively, whereas rotational ROIs should rather be enclosed. Further studies are warranted.

Since the origin of ROIs remains unclear to date, one may also suggest a spatial relationship between organized focal and rotational sources and autonomic ganglionated plexi (GPs). As demonstrated in prior studies the cardiac autonomic nervous system (ANS) may be important for the development, maintenance and recurrence of AF. GPs, which are located in close proximity to the LA and PV orifices, may play a mediating role between the extrinsic nerves and the intrinsic portion of the ANS, the atrial neural network.[17,18] One study demonstrated, that focal and rotational sources in the LA often colocalize with regions of autonomic innervations. This spatial relationship was stronger for left than right GPs.[19] Thus, additional research is needed analyzing how GP activity may modulate driver mechanisms for AF and to which extent the targeted ablation of these areas may influence patients' outcome.

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Altogether, clinical findings on ROIs are inconsistent until now. This may also be related to the fact, that not only rotors, but also micro-reentry, focal activity or double layer activation with dyssynchronous activations on the endo- and epicardial surfaces may participate in the maintenance of AF and increase its complexity, making endocardial mapping and ablation insufficient to address the AF-mechanism. Beyond that, different AF-mechanisms may coexist in the same patient.[16]

### 4.5 | Translational outlook

Further research is needed translating basic science into clinical practice and back to further improve individualized paths in AF management. Novel personalized strategies to improve the efficacy of catheter ablation in PERS AF are required. Several studies reported on the correlation of atrial cardiomyopathy and electrical arrhythmia substrates. To date, their specific interplay remains unclear. We revealed a tendency towards a positive correlation between the amount of atrial fibrosis and the number of ROIs per patient. Larger studies are required to validate our initial observations.

## 5 | LIMITATIONS

We primarily seek to gain initial insights in a new method to analyze the correlation between atrial fibrosis from LGE CMR and ROIs from CF mapping. Thus, our study is limited by its' observational design and the small cohort of patients. To analyze the anatomical relationship between findings from CF and fibrosis from LGE CMR, the LA was divided into the same segments but the reliability of the reproducibility of ROIs by the applied methods has not been validated in this study. Beyond that, we did not target ROIs in the absence of corresponding arrhythmia substrates, which limits the comparability to other studies. As we report on initial observations, further research is needed.

## 6 | CONCLUSION

The presence of ROIs from CF mapping is not directly associated with the extent and location of atrial fibrosis. Further studies evaluating the relationship between focal and rotational activity and atrial cardiomyopathy are mandatory.

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### CONFLICT OF INTEREST STATEMENT

P. Sommer is advisory board member of Abbott, Biosense Webster, Boston Scientific and Medtronic. C. Sohns received lecture fees and is a consultant for Biosense Webster, Boston Scientific and Medtronic. The other authors declare to have no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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