

Magnetic resonance detection of advanced atrial cardiomyopathy increases the risk for atypical atrial flutter occurrence following atrial fibrillation ablation

Elisenda Ferró^{1,2}, Núria Pérez D¹, Till Althoff D^{1,2,3}, Eduard Guasch D^{1,2}, Susana Prat^{1,2}, Adelina Doltra^{1,2}, Roger Borrás D^{1,4}, José María Tolosana D^{1,2}, Elena Arbelo D^{1,2,5}, Marta Sitges D^{1,2,5}, Andreu Porta-Sánchez D¹, Ivo Roca-Luque D^{1,2}, Lluís Mont D^{1,2,5†}, and Jean-Baptiste Guichard D^{1,2,5,6,7}*[†]

¹Institut Clínic Cardiovascular, Hospital Clínic, Universitat de Barcelona, Carrer Villaroel, 170, 08036 Barcelona, Catalonia, Spain; ²Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Carrer del Rosselló, 149, 08036 Barcelona, Catalonia, Spain; ³Department of Cardiology and Angiology, Charité-University Medicine, Berlin, Germany; ⁴Centro de Investigación Biomédica en Red e Salud Mental (CIBERSAM), Madrid, Spain; ⁵Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Avinguda Monforte de Lemos, 3-5, 28029 Madrid, Spain; ⁶INSERM, SAINBIOSE U1059, University Hospital of Saint-Étienne, 10 rue de la Marandinière, 42270 Saint-Priest-enJarez, France; and ⁷Cardiology Department, University Hospital of Saint-Étienne, 42 Avenue Albert Raimond, 42270 Saint-Priest-en-Jarez, France

Received 15 July 2023; accepted after revision 30 August 2023; online publish-ahead-of-print 26 September 2023

Aims	Recurrence of arrhythmia after catheter ablation of atrial fibrillation (AF) in the form of atypical atrial flutter (AFL) is com- mon among a significant number of patients and often requires redo ablation with limited success rates. Identifying patients at high risk of AFL after AF ablation could aid in patient selection and personalized ablation approach. The study aims to assess the relationship between pre-existing atrial cardiomyopathy and the occurrence of AFL following AF ablation.
Methods and results	We analysed a cohort of 1007 consecutive AF patients who underwent catheter ablation and were included in a prospective registry. Patients who did not have baseline cardiac magnetic resonance imaging and late gadolinium enhancement (LGE-CMR) or did not experience any recurrences were excluded. A total of 166 patients were included gathering 56 patients who underwent re-ablation due to AFL recurrences and 110 patients who underwent re-ablation due to AF recurrences $(P = 0.11)$. A multiparametric assessment of atrial cardiomyopathy was based on basal LGE-CMR, including left atrial (LA) volume, LA sphericity, and global and segmental LA fibrosis using semiautomated post-processing software. Out of the initial cohort of 1007 patients, AFL and AF occurred in 56 and 110 patients, respectively. An age higher than 65 [odds ratio (OR) = 5.6, 95% confidence interval (CI): 2.2–14.4], the number of previous ablations (OR = 3.0, 95% CI: 1.2–7.8), and the management of ablation lines in the index procedure (OR = 2.5, 95% CI: 1.0–6.3) were independently associated with AFL occurrence. Furthermore, several characteristics assessed by LGE-CMR were identified as independent predictors of AFL recurrence after the index ablation for AF, such as enhanced LA sphericity (OR = 1.3, 95% CI: 1.1–1.6), LA global fibrosis (OR = 1.03, 95% CI: 1.01–1.07), and increased fibrosis in the lateral wall (OR = 1.03, 95% CI: 1.01–1.04).
Conclusion	Advanced atrial cardiomyopathy assessed by LGE-CMR, such as increased LA sphericity, global LA fibrosis, and fibrosis in the lateral wall, is independently associated with arrhythmia recurrence in the form of AFL following AF ablation.

* Corresponding author. Tel: +34 93 2271778; fax: +34 93 4513045. E-mail address: jbguichard@recerca.clinic.cat

 † The last two authors shared senior authorship.

 $\ensuremath{\mathbb{C}}$ The Author(s) 2023. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Graphical Abstract



Advanced atrial cardiomyopathy assessed by LGE-CMR as a predictor of atypical atrial flutter occurrence following atrial fibrillation ablation. Two aspects of atrial cardiomyopathy, specifically increased LA sphericity and LA global fibrosis, are independent predictors of atypical atrial flutter onset compared to atrial fibrillation recurrence following catheter ablation. aOR, adjusted odds ratio; CI, confidence interval; LA, left atrium; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance.

Keywords

Atrial fibrillation • Atrial cardiomyopathy • Atypical atrial flutter • Fibrosis • Atrial remodelling

What's new?

- The study highlights the impact of pre-existing structural atrial remodelling on the occurrence of atypical atrial flutter after ablation for atrial fibrillation.
- Late gadolinium enhancement cardiac magnetic resonance provides relevant assessment of structural remodelling in these patients, with left atrial sphericity, global fibrosis, and fibrosis in the lateral part of the left atrium being independent predictors of the onset of atypical atrial flutter.
- The study emphasizes the crucial role of advanced atrial cardiomyopathy in the occurrence of atypical atrial flutter following ablation for atrial fibrillation.

Introduction

Catheter ablation (CA) of atrial fibrillation (AF) is an essential procedure to maintain sinus rhythm in patients facing paroxysmal and persistent AF.¹ Despite technological improvements, arrhythmia recurrence still occurs in several patients, especially in persistent AF forms.² Atypical atrial flutter (AFL) is a common type of arrhythmia recurrence that is seen in about 10–20% of cases.³ Atypical atrial flutter recurrence is usually more symptomatic than AF and is often associated with tachycardiomyopathy and heart failure. Managing CA for AFL is usually difficult and typically requires re-ablation.⁴ Identifying patients at risk of AFL post-AF ablation may help in patient selection, ablation design, and specific follow-up. Procedure features of the index CA have been associated with AFL recurrences, such as longer ablation time, additional linear lesions associated with the absence of bidirectional line of block at the end of the procedure, and ablation of complex fractionated atrial electrograms.^{5,6} However, these factors may simply indicate a more extensive underlying atrial cardiomyopathy (ACM). The role of late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) in exploring the underlying ACM and analysing the risk for AFL has been less explored.^{7,8} The aim of this study is to assess the relationship between LGE-CMR parameters of ACM and the occurrence AFL following AF ablation.

Methods

Study population

A cohort of 1007 consecutive AF patients included in the AF ablation registry at the Hospital Clínic de Barcelona, University of Barcelona (Spain), between November 2011 and October 2021 were retrospectively screened. Patients without redo procedures (710), as well as those without basal LGE-CMR scans (26), were excluded (*Figure 1*). A total of 56 patients with post-procedure AFL were identified and compared to a randomly selected group of 110 patients with AF recurrence in a 2:1 ratio. Clinical, procedural, and LGE-CMR data were systematically extracted using electronic medical records. The research protocol was approved by the ethics committee of the Hospital Clínic de Barcelona (HCB/2022/0123).

Late gadolinium enhancement cardiac magnetic resonance acquisition protocol

Late gadolinium enhancement cardiac magnetic resonance was performed according to previously described methods.⁹ Briefly, the studies were conducted in sinus rhythm and after external electrical cardioversion using two different 3 T scanners: Magnetom Prisma (Siemens Healthineers, Erlangen, Germany) and Signa Architect (General Electric, Chicago, IL),



Figure 1 Flow chart of the observational retrospective cohort study. Consecutive patients from 2011 to 2021 were screened and pre-selected based on the presence of baseline LGE-CMR and a redo procedure. Fifty-six patients who developed AFL following AF ablation were included in the study. After a 2:1 randomization, 110 patients were included from the pre-selection list of 215 patients with AF recurrence. AF, atrial fibrillation; AFL, atypical atrial flutter; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance.

both equipped with a 32-channel phased array cardiovascular coil. Inversion recovery–prepared T₁-weighted gradient-echo sequences were acquired in axial orientation using electrocardiogram (ECG) gating and a free-breathing 3D navigator, 20 min after administering an intravenous bolus of 0.2 mmol/kg of gadobutrol (Bayer, Leverkusen, Germany). A free-breathing 3D navigator and ECG-gated inversion recovery gradient-echo sequence were applied in axial projection. The sequence parameters for the Magnetom Prisma scanner were as follows: repetition time of 2.3 ms, echo time of 1.4 ms, flip angle of 11°, bandwidth of 460 Hz/pixel, inversion time of 280–380 ms, and acquired voxel size of $1.25 \times 1.25 \times 2.5$ mm. The sequence parameters for the Signa Architect scanner were as follows: repetition time of 6.4 ms, echo time of 2.2 ms, flip angle of 20°, bandwidth of $1.25 \times 1.25 \times 2.4$ mm. A complete left atrial (LA) coverage was typically obtained with 60 slices.

Late gadolinium enhancement cardiac magnetic resonance post-processing protocol

Late gadolinium enhancement cardiac magnetic resonance post-processing was carried out using Adas3D software (Galgo Medical SL, Barcelona, Spain). For the semiautomatic 3D reconstruction of LA and right atrial (RA), the atrial wall was manually traced on each axial plane slice and automatically adjusted to create a 3D shell. Late gadolinium enhancement was quantified based on voxel signal intensities relative to the mean blood pool signal intensity, using a previously validated signal intensity ratio threshold of \geq 1.2 to define LGE indicative of fibrotic tissue^{9,10} (Figure 2). The 3D reconstructions were colour coded accordingly after the exclusion of extra-cardiac structures, such as pulmonary veins (PV), LA and RA appendages. The mitral valve leaflets were used as landmarks to separate LA from the left ventricle, and the tricuspid valve leaflets were used to separate RA from the right ventricle. The LA was automatically divided into seven standardized regions¹¹: anterior, posterior, lateral, and septal wall, floor, and right and left carinas (Figure 2). The LA sphericity was assessed as previously described,⁸ which evaluates the variation between the LA and the sphere that best fits the LA shape. The radius of this sphere is calculated as the mean distance between all points of the LA wall and the centre of mass.

Index LA and RA volumes were indexed by dividing the volumes by the estimated body surface area, using the Dubois and Dubois formula.

Catheter ablation

The cohort of patients in question underwent an index AF CA using either radiofrequency or cryoablation, ¹² with systematic pulmonary vein isolation (PVI) and confirmation of entrance and exit conduction block. For long-standing persistent AF patients, additional linear lesions were performed based on physician discretion. These included the LA roof, box of the posterior wall, and complex fractionated atrial electrograms, with bidirectional conduction block confirmation for each additional ablation line.

During a subsequent redo procedure, the presence of AFL was evaluated using activation and propagation mapping with electroanatomical mapping systems and multipolar mapping catheters, such as LassoNav and Pentaray using CARTO (Biosense Webster, Irvine, CA), IntellaMap Orion using RYHTMIA (Boston Scientific Inc., Marlborough, MA), and Advisor HD Grid using ENSITEX (Abbott, Chicago, IL). The presence of a macro-rentry during the redo procedure was mandatory to confirm the diagnosis of AFL onset during the follow-up.

Follow-up

After the initial AF ablation procedure, antiarrhythmic medications were discontinued after the 3-month blanking period in the absence of AF recurrence. A systematic clinical follow-up including a 12-lead ECG and a 24-h Holter ECG was performed at 3, 6, and 12 months after ablation, then annually. Atrial fibrillation recurrence and AFL occurrence during the long-term follow-up were defined using 12-lead ECG and 24-h Holter ECG leading to indication for a redo procedure.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation, while median–interquartile range was used as appropriate. Categorical variables were expressed as total numbers and percentages. Logistic regression analysis was used to investigate the impact of baseline characteristics on AFL occurrence, with a significance level of P < 0.05. Forward stepwise selection



Figure 2 Graphical examples of the differential level of atrial cardiomyopathy between patients with onset of atypical atrial flutter following ablation of atrial fibrillation and patients with AF recurrence. Based on post-processing LGE-CMR data, different parameters of morphological and structural left atrial remodelling predict the arrhythmia recurrence in the form of atypical atrial flutter compared with atrial fibrillation. (A) Overlay of the T_1 -weighted image with the LGE colour coding based on signal intensity ratios applying thresholds for fibrotic tissue (yellow ≥ 1.2 ; red > 1.32) using ADAS 3D software (Adas3D Medical, Barcelona, Spain). (B) 3D reconstruction of the left atrium with the automatized regionalization: anterior and posterior wall, floor, septum, lateral wall, and right and left carinas. (C) Assessment of LA volume and LA sphericity using ADAS 3D software (Adas3D Medical, Barcelona, Spain). AF, atrial fibrillation; AFL, atypical atrial flutter; LAA, left atrial appendage; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; MV, mitral valve; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

algorithms were employed for constructing the multivariate logistic regression model, where covariates with a P < 0.10 were retained in the final model. The odds ratio (OR) and 95% confidence interval (CI) were also calculated. Furthermore, receiver operating characteristic (ROC) methodology was used to evaluate the predictive capacity of various variables for arrhythmia recurrence in the form of AFL.

All tests used a two-sided type I error of 5%. R software for Windows version 4.2.1 (R Project for Statistical Computing, Vienna, Austria) was used for statistical analysis.

Results

Baseline characteristics

The final cohort included 166 patients, comprising 56 patients with AFL occurrence following AF ablation and 110 patients with AF recurrence. The median duration between the index ablation and the redo procedure due to arrhythmia recurrence was 20 months (interquartile range:

11–37). Table 1 provides a summary of the patients' baseline characteristics. The mean age of the patients was 60 years, 72.0% of whom were men, and 65.5% had paroxysmal AF at index ablation. The mean left ventricular ejection fraction was 54.9%, while the mean LA and RA indexed volumes were 53.5 and 59.6 mL/m², respectively, indicating biatrial dilation. The mean amount of LA fibrosis was 16.1%, corresponding to Stage 2 of the Utah classification.¹³ Additional LA lines were reported in 30.7% of the patients (n = 51), with the roof line being the most frequent (21.7%, n = 36), followed by the posterior box (12.0%, n = 20), mitral line (15.0%, n = 9), and complex fractionated atrial electrogram ablation (11.4%, n = 19).

Predictors of post-atrial fibrillation ablation atypical atrial flutter occurrence

In this study, several factors were found to be associated with AFL occurrence after AF ablation. Univariate analysis showed that age over 65,
 Table 1
 Baseline characteristics of patients with arrhythmia recurrence following AF ablation

	All (n = 166)
Clinical features	
Age (years)	56.97 ± 10.45
Age > 65	44 (26.5%)
Male gender	120 (72.0%)
Body mass index (kg/m ²)	27.5 (25.0–30.8)
Hypertension	87 (52.4%)
Diabetes mellitus	19 (11.4%)
Obstructive sleep apnoea	24 (14.5%)
Initial AF subtype	~ /
Paroxysmal	107 (65.5%)
Persistent	58 (34.9%)
$CHA_2DS_2 VAS_c$ score	1 (0–2)
EHRA score	. ,
Ι	8 (4.8%)
II	131 (78.9%)
III	24 (14.5%)
IV	2 (1.2%)
Previous ablation features	
Number of previous catheter ablation	2 (2–2)
Delay from previous catheter ablation (years)	1.66 (0.94–3.07)
History of additional lines	51 (30.7%)
History of CFAE	19 (11.4%)
CMR features	
Left ventricular ejection fraction (%)	54.92 <u>+</u> 7.97
LA volume index (mL/m ²)	53.50 ± 14.98
LA fibrosis (%)	16.10 ± 14.94
RA volume index (mL/m ²)	59.64 ± 14.46
RA fibrosis (%)	20.07 ± 12.51

AF, atrial fibrillation; CFAE, complex fractionated atrial electrogram; CMR, cardiac magnetic resonance; EHRA, European Heart Rhythm Association; LA, left atrium; RA, right atrium.

diabetes mellitus, obstructive sleep apnoea, persistent AF, higher CHA₂DS₂ VAS_c score, and a higher number of previous AF ablation procedures were linked to AFL recurrence. Additionally, the presence of additional lines and complex fractionated atrial electrogram ablation, higher LA indexed volume, sphericity, and overall fibrosis were also associated with AFL occurrence. The energy used during the indexed ablation procedure (weather cryotherapy, radiofrequency, or laser) was not associated with AFL onset compared with AF recurrence. Multivariate analyses identified several independent predictors of AFL occurrence (Table 2), including age over 65 (OR = 5.61, 95% CI: 2.18–14.41), a high number of previous CA procedures (OR = 3.03, 95% CI: 1.17-7.81), a history of additional lines (2.48, 95% CI: 1.01-6.27), higher LA sphericity (OR = 1.33, 95% CI: 1.11-1.59), and LA overall fibrosis (OR = 1.03, 95% CI: 1.00–1.07). A graphical representation of the association between two ACM features, namely LA sphericity and LA overall fibrosis, and AFL occurrence after AF ablation is shown in Figure 3. The study found that a baseline LA sphericity higher than 80.7% was associated with AFL recurrence with 71% specificity

and 68% specificity (c-statistic 0.74, *Figure 4*). The initial subtype of AF was not found to have an independent association with AFL occurrence.

Left atrial fibrosis as a predictor of atypical atrial flutter occurrence following atrial fibrillation ablation

As LA global fibrosis was found to be an independent predictor of AFL occurrence after AF CA procedure, a regional analysis of fibrosis distribution was conducted and presented in *Table 3*. The level of fibrosis in the lateral aspect, below the LA appendage, was the only independent predictor of AFL occurrence after AF ablation compared with AF recurrence (OR = 1.03, 95% CI: 1.01–1.04), as shown in *Figure 3*. Although not statistically significant, the distribution heterogeneity of LA fibrosis was slightly higher in patients with AFL occurrence after AF CA.

Discussion

Main findings

This study is the first to investigate the impact of pre-existing structural atrial remodelling on AFL occurrence after AF ablation. The study found that various aspects of ACM evaluated by LGE-CMR were independent predictors of AFL occurrence, including increased LA sphericity, LA global fibrosis, and elevated fibrosis in the lateral wall. The results underscore the crucial role of advanced ACM in AFL occurrence following AF ablation.

Atrial cardiomyopathy as a key element for atypical atrial flutter occurrence following atrial fibrillation ablation

Atypical atrial flutter is a frequent and challenging complication following AF ablation due to its persistent and symptomatic presentation, along with diagnostic and therapeutic management.¹⁴ Therefore, defining the risk factors of AFL occurrence after AF ablation may aid in patient selection and procedure design to improve results. Previous extensive LA ablation, which includes iterative CA procedures, longer ablation time, and the management of additional LA lines, ¹⁵ is an established factor for post-AF ablation AFL occurrence.^{5,6} Our study confirms the role of extensive LA ablation in AFL occurrence. However, the need for extensive ablation is likely just a marker of more extensive underlying ACM. The involvement of pre-existing atrial remodelling in the physiology of post-CA AFL is less known.¹⁶ Morphological LA abnormalities, such as dilated LA, have been found to independently predict AFL onset after CA for AF.³ But other features of the extension of ACM assessed by LGE-CMR may be more efficient in predicting AFL occurrence. Atrial fibrosis likely creates slow conduction and structural barriers that enable the development of critical isthmus and AFL onset.¹⁷ Our study itemizes, for the first time, the central role of LA fibrosis in AFL onset after CA for AF. An increased LA sphericity was also strongly and independently associated with AFL onset. Left atrial sphericity is a parameter that assesses LA morphological abnormality and has two major significant strengths: this ACM marker, although characterizing a morphological atrial abnormality, is strongly correlated with fibrosis burden.⁸ Furthermore, this marker is assessable in computerized tomography scans and CMR, without injection of contrast or dedicated acquisition protocol. Of note, LA sphericity is an independent predictor of AF recurrence after CA.¹⁸ The present study confirms the crucial role of ACM in long-term complications following CA for AF.

 Table 2
 Univariate and multivariate logistic regression models to predict arrhythmia recurrence in the form of atypical atrial flutter following ablation of atrial fibrillation

	AF recurrence	AFL occurrence	Unadjusted			Adjusted		
	(n = 110)	(n = 56)						
			OR	95% CI	P-value	OR	95% CI	P-value
Clinical features								
Age > 65	18 (16.4%)	26 (46.4%)	4.43	(2.14-9.18)	<0.01	5.61	(2.18–14.41)	<0.01
Male gender	82 (74.5%)	37 (66.1%)	1.50	(0.75–3.03)	0.67			
BMI	27.2 (24.8–29.7)	29.1 (25.7–32.8)	1.00	(0.98–1.01)	0.82			
Hypertension	52 (47.3%)	34 (60.7%)	1.72	(0.90-3.32)	0.10			
Diabetes mellitus	8 (7.3%)	10 (17.9%)	2.77	(1.03–7.48)	0.04	3.02	(0.84–10.81)	0.09
Obstructive sleep apnoea	10 (9.1%)	13 (23.2%)	3.02	(1.23–7.43)	0.02	_	-	-
AF features								
Persistent AF	33 (30%)	23 (41.8%)	2.07	(1.14–3.76)	0.02	_	-	-
CHADS VAS _c score	1 (0–2)	2 (2–3)	1.54	(1.18–2.03)	<0.01	_	-	-
Previous catheter ablation features								
Number of previous catheter	2 (2–2)	2 (2–3)	3.26	(1.56–6.78)	<0.01	3.03	(1.17–7.81)	0.02
ablation procedures								
Delay from previous catheter ablation	1.7 (1.0–2.9)	1.6 (0.6–4.1)	1.08	(0.94–1.24)	0.31			
History of additional lines	23 (20.9%)	28 (50.0%)	3.78	(1.88–7.59)	<0.01	2.48	(1.01–6.27)	0.05
History of CFAE	8 (7.3%)	11 (19.6%)	3.12	(1.17–8.27)	0.02	-	-	-
CMR features								
Left ventricular ejection fraction	55 ± 8	54 ± 8	0.98	(0.94–1.03)	0.47			
LA indexed volume	50.9 ± 14.5	58.9 ± 15.7	1.04	(1.01–1.06)	<0.01	-	-	_
LA sphericity	79.5 ± 3.1	81.7 ± 2.6	1.33	(1.16–1.54)	<0.01	1.33	(1.11–1.59)	<0.01
LA fibrosis	14.1 ± 12.9	20.1 ± 17.9	1.03	(1.00–1.05)	0.03	1.03	(1.00–1.07)	0.04
RA indexed volume	59.6 ± 13.9	59.0 <u>±</u> 15.7	1.00	(0.98–1.03)	0.92			
RA sphericity	79.8 ± 2.4	79.6 ± 2.2	0.97	(0.84–1.12)	0.65			
RA fibrosis	19.5 ± 11.6	21.3 ± 14.3	1.01	(0.99–1.04)	0.40			

Forward stepwise selection algorithms were used for building up the multivariate logistic regression model. In bold: statistacally significant results, defined as P < 0.05.

AF, atrial fibrillation; AFL, atypical atrial flutter; BMI, body mass index; CFAE, complex fractionated atrial electrogram; CI, confidence interval; CMR, cardiac magnetic resonance; EHRA, European Heart Rhythm Association; LA, left atrium; OR, odds ratio; RA, right atrium.

The central role of late gadolinium enhancement cardiac magnetic resonance in the characterization of atrial cardiomyopathy and atrial fibrillation management

Atrial cardiomyopathy is an emerging concept aimed at improving the management of atrial disease, including arrhythmia or cardioembolic stroke.¹⁹ The ongoing challenge is to efficiently and non-invasively assess the different components of ACM, namely morphological, functional, electrical, and structural LA remodelling, to improve patient management.²⁰ Late gadolinium enhancement cardiac magnetic resonance is a central diagnostic tool for evaluating ACM. This non-invasive imaging tool enables the itemization of LA morphological abnormalities (such as size³ and sphericity⁸), functional abnormalities (global strain^{21,22}), and structural abnormalities via the assessment of fibrosis using LGE.²³ Regarding the assessment of structural remodelling, the novel automated tool to regionalize the LA¹¹ and assess quantitatively the amount of fibrosis reduces inter- and intraobserver variability, making this tool more reproducible. The non-invasive assessment of global

and regional fibrosis using LGE-CMR has already been validated in comparison with the invasive assessment of low-voltage areas using electroanatomical mapping²⁴ and evaluates the crucial impact of fibrosis in arrhythmia recurrence following AF ablation.²⁵

The presence of advanced ACM is a validated predictor of AF recurrence after CA ablation. Both dilated LA,²⁶ LA functional impairment,²⁷ and LA global fibrosis⁷ are predictors assessed by CMR of AF recurrence. This is consistent with our results. In conclusion, advanced ACM is a relevant predictor of worse outcomes after CA, both in terms of AF recurrence and AFL occurrence. Pre-procedural assessment of ACM based on LGE-CMR seems to be useful in selecting patients who would benefit the most from CA for AF.²⁸ Late gadolinium enhancement cardiac magnetic resonance could also be helpful to tailor the ablation procedure for arrhythmia recurrence.^{9,29}

Limitations

The observational and retrospective design of the study has significant limitations. The selection criteria used to set up the cohort may have introduced a selection bias, as only patients with an indication for a redo procedure were included for the assessment of AFL occurrence



Figure 3 Graphical representation of the main predictors of atypical atrial flutter occurrence using a univariate logistic regression model. These graphs represent the probability of atrial flutter onset compared with the recurrence of atrial flutter following catheter ablation for atrial fibrillation concerning three main components of atrial cardiomyopathy assessed by LGE-CMR: left atrial sphericity, global fibrosis, and fibrosis among the lateral wall. Cl, confidence interval; LA, left atrium; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance; OR, odds ratio.



Figure 4 Receiver operating characteristic curve of left atrial sphericity for prediction of post-atrial fibrillation ablation atypical atrial flutter. AUC, area under the curve; LA, left atrium.

and AF recurrence. Therefore, patients who experienced arrhythmia recurrence after CA for AF without undergoing a redo procedure were not included in the cohort. Consequently, we cannot evaluate the incidence of AF and AFL onset during the follow-up among the whole cohort. Cofounders cannot be excluded, as the study aims to identify predictors of AFL occurrence compared with AF recurrence, but the causative role of the studied parameters cannot be established despite multivariate analyses.

Clinical perspectives

This study highlights that advanced ACM assessed by LGE-CMR is predictive of AFL occurrence after AF ablation. Two perspectives can be drawn: on the one hand, early management of AF patients, to avoid advanced ACM, seems to be crucial in improving clinical outcomes.³⁰ On the other hand, selecting patients with the best clinical net benefit regarding endocavity ablation for AF is a key point in avoiding postprocedural complications. It is important to note that the assessment of ACM by LGE-CMR outperformed classical predictors of arrhythmia recurrence after CA for AF, such as persistent AF subtype and LA dilation. Selecting AF patient before CA is crucial in improving post-procedural outcomes and reducing arrhythmia recurrence. A randomized clinical trial is needed to assess the benefit of tailoring the lesion set based on the evaluation of the advanced ACM during CA for AF.
 Table 3
 Univariate and multivariate logistic regression models to predict arrhythmia recurrence in the form of atypical atrial flutter following ablation of atrial fibrillation regarding regional distribution of LA fibrosis

	AF recurrence $(n = 110)$	AFL occurrence $(n - 56)$		Unadjuste	d	Adjusted		
	(– 110)	(– 50)	OR	95% CI	P-value	OR	95% CI	P-value
Regional distribution								
LA floor fibrosis	16.8 ± 26.1	26.1 ± 15.4	1.02	(1.00–1.03)	0.02	-	-	-
LA anterior fibrosis	6.8 ± 10.5	13.8 ± 18.7	1.04	(1.01–1.07)	0.01	-	-	-
LA lateral fibrosis	16.2 ± 19.2	29.2 ± 27.2	1.03	(1.01–1.04)	<0.01	1.03	(1.01–1.04)	<0.01
Posterior LA fibrosis	26.4 ± 22.4	32.2 ± 24.1	1.01	(0.99–1.03)	0.16			
LA carina fibrosis	17.3 ± 20.3	17.1 <u>+</u> 19.6	0.99	(0.98–1.02)	0.94			
LA septal fibrosis	7.7 ± 11.0	10.1 ± 15.4	1.02	(0.99–1.04)	0.28			
Heterogeneity of distribution								
SD regions	11.7 ± 7.9	14.6 ± 8.9	1.04	(0.99–1.08)	0.05	-	-	-

Forward stepwise selection algorithms were used for building up the multivariate logistic regression model. In bold: statistacally significant results, defined as P < 0.05. AF, atrial fibrillation; AFL, atypical atrial flutter; CI, confidence interval; LA, left atrium; OR, odds ratio; SD, standard deviation.

Conclusions

Advanced ACM, assessed by LGE-CMR, such as increased LA sphericity, global LA fibrosis, and fibrosis into the lateral wall, is independently associated with arrhythmia recurrence in the form of AFL following AF ablation. These results suggest the usefulness of pre-procedural ACM assessment in selecting AF patients with an optimal benefit–risk balance.

Acknowledgements

The authors would like to thank Neus Portella and Carolina Sanroman for their secretarial assistance with the manuscript, as well as the nurse team of the arrhythmia unit of Hospital Clínic de Barcelona for their invaluable clinical support. J.B.G. thanks the French Federation of Cardiology (FFC) for their institutional grant support.

Funding

This work is supported in part by grants from the Instituto de Salud Carlos III, Spanish Government, Madrid, Spain (FIS_PI16/00435 – FIS_CIBER16; to L.M.).

Conflict of interest: E.F. reports receiving full salary funding from Medtronic. T.F.A. has received research grants for investigator-initiated trials from Biosense Webster. A.P.-S. has received honoraria as a consultant and lecturer from Abbott, Biosense Webster, and Boston Scientific. E.A. reports honoraria as consultant and lecturer from Biosense Webster and Bayer. M.S. has received grants, consulting honoraria, and speakers' fees from General Electric, Edwards Lifesciences, Abbott Medical, and Medtronic. L.M. reports honoraria as a consultant, lecturer, and advisory board member from Boston Scientific, Abbott Medical, Johnson & Johnson, and Medtronic. He is also a shareholder of Galgo Medical SL. J.B.G. reports honoraria as a consultant from Microport CRM, a lecturer from Microport CRM and Abbott, and unrestricted grant support for a fellowship from Abbott Labs. All remaining authors have declared no conflicts of interest.

Data availability

The authors agree to make data and materials supporting the results or analyses presented in their paper available upon reasonable request.

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C *et al.* 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498.

- Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc* 2013;2:e004549.
- Gucuk Ipek E, Marine J, Yang E, Habibi M, Chrispin J, Spragg D et al. Predictors and incidence of atrial flutter after catheter ablation of atrial fibrillation. Am J Cardiol 2019;**124**: 1690–6.
- Calkins H, Hindricks G, Cappato R, Kim Y-H, Saad EB, Aguinaga L et al. HRS/EHRA/ ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2017;14:e275–444.
- Hoyt H, Bhonsale A, Chilukuri K, Alhumaid F, Needleman M, Edwards D et al. Complications arising from catheter ablation of atrial fibrillation: temporal trends and predictors. *Heart Rhythm* 2011;8:1869–74.
- Chae S, Oral H, Good E, Dey S, Wimmer A, Crawford T et al. Atrial tachycardia after circumferential pulmonary vein ablation of atrial fibrillation: mechanistic insights, results of catheter ablation, and risk factors for recurrence. J Am Coll Cardiol 2007;50: 1781–7.
- Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA 2014;**311**:498–506.
- Bisbal F, Guiu E, Calvo N, Marin D, Berruezo A, Arbelo E et al. Left atrial sphericity: a new method to assess atrial remodeling. Impact on the outcome of atrial fibrillation ablation. J Cardiovasc Electrophysiol 2013;24:752–9.
- Padilla-Cueto D, Ferro E, Garre P, Prat S, Guichard JB, Perea RJ et al. Non-invasive assessment of pulmonary vein isolation durability using late gadolinium enhancement magnetic resonance imaging. Europace 2023;25:360–5.
- Gunturiz-Beltrán C, Borràs R, Alarcón F, Garre P, Figueras I Ventura RM, Benito EM et al. Quantification of right atrial fibrosis by cardiac magnetic resonance: verification of the method to standardize thresholds. *Rev Esp Cardiol (Engl Ed)* 2023;**76**: 173–82.
- Benito EM, Cabanelas N, Nuñez-Garcia M, Alarcón F, Figueras I Ventura RM, Soto-Iglesias D et al. Preferential regional distribution of atrial fibrosis in posterior wall around left inferior pulmonary vein as identified by late gadolinium enhancement cardiac magnetic resonance in patients with atrial fibrillation. *Europace* 2018;20: 1959–65.
- Kuck K-H, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KR et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016;374: 2235–45.
- Mahnkopf C, Badger TJ, Burgon NS, Daccarett M, Haslam TS, Badger CT et al. Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced MRI: implications for disease progression and response to catheter ablation. *Heart Rhythm* 2010;**7**:1475–81.
- Bun S-S, Latcu DG, Marchlinski F, Saoudi N. Atrial flutter: more than just one of a kind. Eur Heart J 2015;36:2356–63.

- 15. Sawhney N, Anousheh R, Chen W, Feld GK. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:243–8.
- Hussein AA, Saliba WI, Martin DO, Bhargava M, Sherman M, Magnelli-Reyes C et al. Natural history and long-term outcomes of ablated atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;4:271–8.
- Cosío FG. Atrial flutter, typical and atypical: a review. Arrhythm Electrophysiol Rev 2017;6: 55–62.
- Bisbal F, Guiu E, Cabanas P, Calvo N, Berruezo A, Tolosana JM et al. Reversal of spherical remodelling of the left atrium after pulmonary vein isolation: incidence and predictors. *Europace* 2014;16:840–7.
- Guichard J-B, Nattel S. Atrial cardiomyopathy: a useful notion in cardiac disease management or a passing fad? J Am Coll Cardiol 2017;70:756–65.
- Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA et al. EHRA/HRS/ APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Heart Rhythm* 2017;**14**:e3–e40.
- Gucuk Ipek E, Marine JE, Habibi M, Chrispin J, Lima J, Rickard J et al. Association of left atrial function with incident atypical atrial flutter after atrial fibrillation ablation. *Heart Rhythm* 2016;**13**:391–8.
- Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. Circ Cardiovasc Imaging 2010;3:231–9.

- Akoum N, Daccarett M, McGann C, Segerson N, Vergara G, Kuppahally S et al. Atrial fibrosis helps select the appropriate patient and strategy in catheter ablation of atrial fibrillation: a DE-MRI guided approach. J Cardiovasc Electrophysiol 2011;22:16–22.
- Bisbal F, Andreu D, Berruezo A. Simplified mapping and ablation of a scar-related atrial tachycardia using magnetic resonance imaging tissue characterization. *Europace* 2015; 17:186.
- Ravelli F, Masè M, Cristoforetti A, Avogaro L, D'Amato E, Tessarolo F et al. Quantitative assessment of transmural fibrosis profile in the human atrium: evidence for a threedimensional arrhythmic substrate by slice-to-slice histology. Europace 2023;25:739–47.
- Montefusco A, Biasco L, Blandino A, Cristoforetti Y, Scaglione M, Caponi D et al. Left atrial volume at MRI is the main determinant of outcome after pulmonary vein isolation plus linear lesion ablation for paroxysmal-persistent atrial fibrillation. J Cardiovasc Med (Hagerstown) 2010;11:593–8.
- Hammerstingl C, Schwekendiek M, Momcilovic D, Schueler R, Sinning J-M, Schrickel JW et al. Left atrial deformation imaging with ultrasound based two-dimensional speckletracking predicts the rate of recurrence of paroxysmal and persistent atrial fibrillation after successful ablation procedures. J Cardiovasc Electrophysiol 2012;23:247–55.
- Bisbal F, Baranchuk A, Braunwald E, Bayés de Luna A, Bayés-Genís A. Atrial failure as a clinical entity: JACC review topic of the week. J Am Coll Cardiol 2020;75:222–32.
- Quinto L, Cozzari J, Benito E, Alarcón F, Bisbal F, Trotta O et al. Magnetic resonanceguided re-ablation for atrial fibrillation is associated with a lower recurrence rate: a casecontrol study. *Europace* 2020;**22**:1805–11.
- Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A et al. Early rhythmcontrol therapy in patients with atrial fibrillation. N Engl J Med 2020;383:1305–16.