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BACKGROUND Markers of left atrial (LA) shape may improve the prediction of postablation outcomes in atrial fibrillation (AF). Correlations to LA volume and AF persistence limit their incremental value over current clinical predictors.

OBJECTIVE To develop a shape score independent from AF persistence and LA volume using shape-based statistics, and to test its ability to predict postablation outcome.

METHODS Preablation computed tomography (CT) images from 141 patients with paroxysmal (57%) or persistent (43%) AF were segmented. Deformation of an average LA shape into each patient encoded patient-specific shape. Local analysis investigates regional differences between patient groups. Linear regression was used to remove shape variations related to LA volume and AF persistence, and to build a shape score to predict postablation outcome. Cross-validation was performed to evaluate its accuracy.

RESULTS Ablation failure rate was 23% over a median 12-month follow-up. Regions associated with ablation failure mostly consisted of a large area on posteroinferior LA, mitral isthmus, and left inferior vein. On univariate analysis, strongest predictors were AF persistence ($P = .005$), LA indexed volume ($P = .02$), and the proposed shape score ($P = .001$). On multivariate analysis, all 3 were independent predictors of ablation failure, with the LA shape score showing the highest predictive value (odds ratio [OR] = 6.2 [2.5–15.8], $P < .001$), followed by LA indexed volume (OR = 3.1 [1.2–7.9], $P = .019$) and AF persistence (OR = 2.9 [1.2–7.6], $P = .022$).

CONCLUSION Posteroinferior LA, mitral isthmus, and left inferior vein are the regions whose shape have the highest impact on outcome. LA shape predicts AF ablation failure independently from, and more accurately than, atrial volume and AF persistence.

KEYWORDS Atrial fibrillation; Catheter ablation; CT; Left atrial shape; Recurrence; Statistical shape modeling

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a leading cause of heart failure and stroke.[1] Catheter ablation is an appropriate treatment strategy for symptomatic patients.[2] However, arrhythmia recurrence after ablation is frequent and multiple procedures are often required in order to obtain rhythm control over the long term. Approximately 30%–50% of the patients will not have a durable restoration of sinus rhythm after ablation.[3,4] The mechanisms leading to arrhythmia recurrence are still insufficiently understood, although AF persistence and structural remodeling of the atrium seem to play an important role.[5] In clinical practice, measuring left atrial (LA) size on imaging and asking the patient the duration of his most prolonged AF episode are often the only predictors available. Unfortunately, many AF episodes being asymptomatic, the assessment of AF duration is of limited accuracy. Likewise, although several measurements of LA dimensions or volume were shown to be related to postablation outcome, the association remains too weak to efficiently assist clinical decision-making, and no cut-off value of LA size is recommended to select ablation candidates.[6] In order to improve prognostic assessment, some authors have recently introduced shape-based predictors.[7] Indeed, LA deformation during the course of remodeling being anisotropic, this may have incremental value. Several markers of LA shape have been reported, including roof flattening,[8] anteroposterior asymmetry,[9] sphericity,[10,11] and vertical asymmetry.[12] Unfortunately, these parameters are all related to LA enlargement and thus show limited incremental predictive value. The aim of this study was to confirm the hypothesis that LA shape carries prognostic information that is independent of LA size

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KEY FINDINGS

- Statistical modeling identifies a left atrial (LA) shape score whose predictive value outperforms the already reported shape markers.
- The shape score is independent from atrial fibrillation persistence and LA volume, and jointly allows stratifying the risk of ablation failure on a patient-by-patient basis with high predictive value.
- The regions whose shape is more closely associated with ablation failure are a large area covering the inferior part of the posterior left atrium, the left inferior pulmonary vein and the mitral isthmus, and smaller areas located on the antrum of left and right superior veins, the septum, and the anterior wall.

and AF persistence. We have applied a recently developed shape-based statistics framework on a large computed tomography (CT) database, in order to identify a shape-based predictor of arrhythmia recurrence that would be independent from current routine predictors, namely LA size and AF persistence.

Methods

Population

Consecutive patients referred for catheter ablation of AF were prospectively enrolled at our institution. The inclusion criterion was an indication for catheter ablation according to current guidelines. Noninclusion criteria were age <18 years, dilated aortic root >45 mm, pectus excavatus, history of catheter ablation or other percutaneous cardiac interventions, history of cardiac surgery, intracardiac thrombus on cardiac CT, and failure to obtain patient consent. Exclusion criteria were insufficient image quality and failure to retrieve follow-up information. At the time of inclusion, all patients underwent a review of medical history, physical examination, laboratory assessment of cardiovascular risk factor, transthoracic echocardiography (TTE), and contrast-enhanced cardiac CT to rule out thrombus and to assess LA size and shape. Distinction between paroxysmal and persistent AF was made according to the European Society of Cardiology criteria.[6] Mitral regurgitation was considered significant if greater than grade 1 on TTE. Left ventricular dysfunction was considered significant if left ventricular ejection fraction was <45% on TTE. The study was approved by the institutional review board and conformed to the Declaration of Helsinki, and all patients provided informed consent.

Computed tomography

Contrast-enhanced cardiac CT was performed within 48 hours prior to ablation using dual-source CT scanners (SOMATOM Definition or SOMATOM Force; Siemens Medical Solutions, Forchheim, Germany). Prospective electrocardiogram gating was applied to acquire data at end-systole. An intravenous bolus of iomeprol 400 mg/mL (Bracco, Milan, Italy) at the rate of 5 mL/s was followed by a saline flush at the same rate to wash out contrast and prevent beam-hardening artifacts within the superior vena cava and right atrial chamber. Contrast media volume differed between the 2 CT systems and was adapted to patient morphology. A bolus tracking method was applied to acquire data with optimal LA enhancement. Tube voltage and tube current differed between CT systems and were adapted to patient morphology. An intermediate level of iterative reconstruction and a soft tissue convolution filter were applied to reconstruct images at ventricular systole, with axial sections of 0.5 mm thickness and typical in-plane pixel size of 0.4 × 0.4 mm. Mean x-ray exposure was 2.3 ± 1.0 mSv.

Ablation procedure

Catheter ablations were performed without interruption of anticoagulant therapy, initiated at least 4 weeks before procedure. Absence of LA thrombus was systematically checked by CT within 48 hours before procedure. Either radiofrequency ablation or cryotherapy methods were applied. When using radiofrequency ablation, the use of contact force was not mandatory, nor was the use of electroanatomical mapping systems. LA was catheterized under fluoroscopic guidance by venous femoral access followed by transseptal puncture. Heparin anticoagulation adapted to the patient weight was dispensed. In all patients, electrical isolation of the 4 pulmonary veins (PVs) was performed. Complete isolation of PVs was defined by elimination or dissociation of PV potentials, as assessed using a Lasso catheter. Complete block was systematically confirmed after adenosine injection to detect potential dormant conduction. In patients with paroxysmal AF, complete isolation of the 4 PVs was the procedural endpoint. In patients with persistent AF, the procedural endpoint was complete PV isolation and AF termination, and additional ablation could be performed after PV isolation on various targets. These could include linear lesions on the roof or mitral isthmus, focal ablation on areas exhibiting complex fractionated electrograms on contact mapping, or focal ablation on regions exhibiting reentrant drivers on noninvasive electrocardiographic imaging. Preventive ablation of the cavotricuspid isthmus (CTI) was performed in case of a history of atrial flutter. The radiofrequency and fluoroscopy durations and the total duration of the procedure were recorded.

Follow-up

Follow-up was performed during a short hospitalization with a physical examination, a 24-hour electrocardiogram, a stress test, and an echocardiography. Patients were systematically reassessed 3 months after ablation. Then, paroxysmal AF patients were followed at 9 months and persistent AF patients at 6 and 12 months. Patients could also be seen earlier in case of symptomatic recurrence. Long-term follow-up was variable and could be done in our hospital or by the referring cardiologist. Management of anticoagulant and antiarrhythmic therapy was left to the discretion of the referring cardiologist. Arrhythmia recurrence was defined by 1 or more episodes of sustained atrial arrhythmia (>30 seconds) considering a blanking period of 3 months. In case of recurrence, 1 or more ablations could be proposed on a case-by-case basis. The endpoint to assess outcome was multiprocedural failure (ie, arrhythmia recurrence since the last catheter ablation procedure). In patients undergoing multiple procedures, follow-up duration was computed from the date of the last ablation procedure.

Image segmentation

Postprocessing was performed by a radiologist with 5 years' experience in cardiac imaging, blinded to clinical data, using MUSIC software (Multimodality software for specific imaging in cardiology; IHU Liryc, University of Bordeaux / Inria Sophia Antipolis, France). After semiautomated isolation of the left atrium from surrounding structures, the mitral annulus plane was carefully defined following the insertion points of the valve. The LA chamber was then automatically segmented using a region-growing algorithm, the minimum pixel density threshold being derived from 2 regions of interest drawn within the LA blood pool and the left ventricular myocardium. The assessment of LA dimension, volume, and shape (described in the following paragraph) required specific segmentations. A first segmentation included the left atrial appendage (LAA) and the PVs (cut 1 cm from their ostia), for subsequent assessment of the proposed shape score. Then, the PVs and LAA were cut at their ostia to produce 1 segmentation of the LA body, used to compute LA volume, LA anteroposterior diameter, and LA sphericity and vertical asymmetry, and 1 segmentation of the LAA to compute the LAA volume. Image segmentation is illustrated in Figure 1.

LA shape description

We have applied a statistical shape-modeling framework recently described by Bruse and colleagues[13] to efficiently describe 3D anatomy and extract biomarkers. In this framework, a mean shape is computed based on the shape of all patients. Next, the mean shape is deformed automatically to match the LA shape of a given patient. By encoding this morphing process in the form of vectors, one can quantify the specific shape/deformation of each patient.[14] As illustrated in Figure 2A, the mean LA shape (template) is computed as the average LA shape of the whole AF population. By the definition of average, the sum of distances from

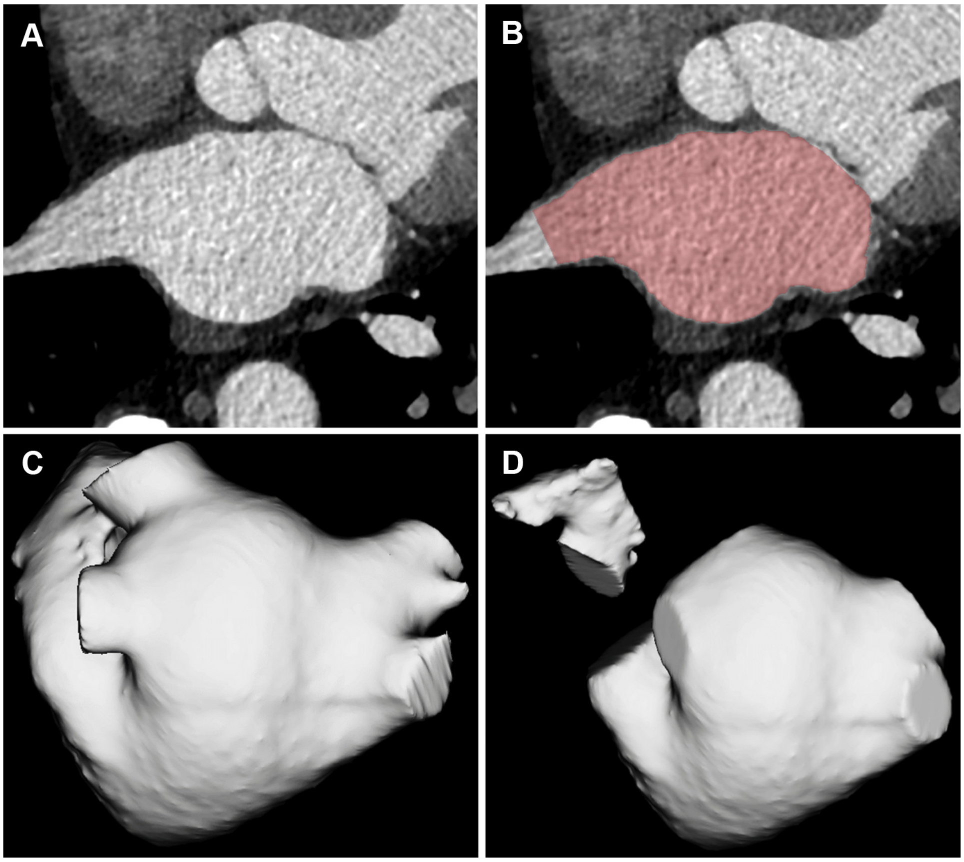

Figure 1 Image segmentation. Arterial-enhanced computed tomography images (**A**) were segmented using 3-dimensional region growing segmentation (**B**) to derive a mesh of the left atrial (LA) geometry comprising the left atrial appendage (LAA) and the first centimeter of pulmonary veins (PVs) (**C**), used to compute the shape score. Then the PVs and the left appendage were cut at their ostia (**C**) to produce 1 mesh of the LA body, used to compute the LA volume, anteroposterior diameter, sphericity, and vertical asymmetry, and 1 mesh of the LAA, used to compute the LAA volume.

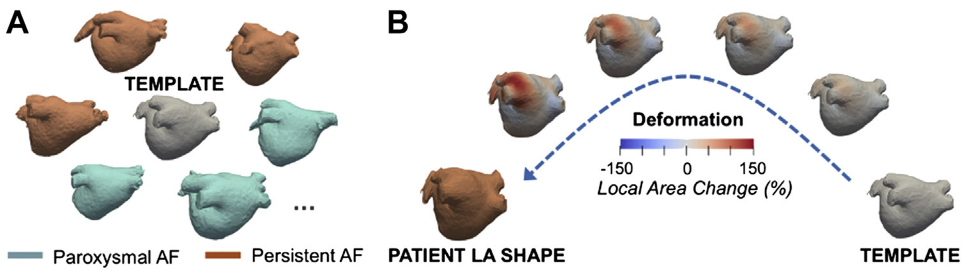

Figure 2 Shape-based statistics. **A:** Firstly, a template left atrial geometry was computed as the average shape among the studied population. **B:** Secondly, the template was deformed to match the specific geometry of each patient, each transformation being considered as an expression of the patient-specific shape. LA = left atrial.

the template to all other LA shapes is minimized, and consequently, the error in the morphing process is minimal. Taking advantage of the point-by-point correspondence established during this process, we could map local area change on the surface of the left atrium for each patient, as shown in Figure 2B. This framework enables to correlate group-wise shape features with clinical indices of interest. In the present work, we used such quantification of LA shapes and related it to catheter ablation outcome to extract associated shape features. Further details on the shape analysis are provided in the Supplemental Appendix. The algorithms are implemented in open source software Deformetrica (Aramis Lab, Paris, France).

Local shape analysis

To get a fine understanding of the link between regional LA remodeling and arrhythmia recurrence, we analyzed local LA shape variations. Registration of the mean shape to match each patient's geometry allowed establishing automatically point-by-point correspondence among all shapes. Then, local area change of each shape was assessed with respect to the mean shape and mapped on the LA surface during the morphing process. We compared the local area change in patients with and without ablation failure, by performing a statistical test (Student t test) to highlight statistically significant differences between the 2 groups. Finally, we analyzed critical regions ($P < .05$) associated with ablation failure and displayed them over the template mesh.

Global shape score

The vectors representing the deformations between the template and all the other LA shapes were used to discriminate between those with and without recurrence. Linear regression with dimension-reduced components was used to analyze the correlations between shape features and arrhythmia recurrence. Readers are referred to the Supplemental Appendix for more details on the partial least squares method.[15] To avoid the risk of over-fitting, the learning and the testing of the shape parameter were performed on different populations. Five-fold cross-validation was achieved by dividing the population randomly into 5 subgroups (4 to train the model, 1 to test the prediction). Thus, the prediction for each patient was built from a model learned from a series of shapes that did not comprise the patient's own LA shape. To analyze shape features that are independent from atrial size and AF persistence, we separated the analysis into 2 sequential partial least squares regressions[16]: the first one to remove the shape variations that are linearly related to LA volume and AF persistence, and the second one to compute the shape patterns that are linearly related to postablation recurrence. This model (implemented in Matlab2017a) allowed us to provide each patient with an LA shape score normalized to the range from 0 to 1, according to the proximity between the studied patient shape and the shape patterns associated with recurrence. The higher the shape score, the more the shape is related to ablation failure. The presented scores are computed over the 5 test sets of the 5-fold cross-validation.

Additional LA descriptors

LA meshes were also used to calculate several other atrial size and shape parameters previously reported in the literature. The LA indexed volume was expressed in mL/m^2 and measured excluding PVs and LAA. The LAA volume and the LA anteroposterior diameter were, respectively, expressed in mL and mm. Sphericity index was calculated after exclusion of PVs and appendage, using the distance between each point of the left atrium and the center of a sphere, according to the method proposed by Bisbal and colleagues.[10] The measurement of vertical asymmetry was performed according to the method proposed by Varela and colleagues.[12] The presence of a left common vein was also noted.

Statistics

The Shapiro-Wilk test was used to determine whether quantitative data conformed to the normal distribution. Quantitative variables were expressed as mean ± SD in case of normal distribution and median [interquartile range] otherwise. Categorical variables were expressed as fraction (%). Continuous variables were compared using parametric (Student t test) or nonparametric (Mann-Whitney U test) tests according to their normality. Categorical variables were compared using χ^2 test or Fisher exact test. Univariate and multivariate analyses were performed to investigate the relation between predictors and ablation failure. Cut-off values were obtained using a receiver operating characteristic (ROC) analysis in order to categorize continuous variables. Variables were included in the multivariate analysis using a backward stepwise procedure with criteria of $P < .05$ for inclusion in and $P > .10$ for removal from the model. Estimations of the odds ratio (OR) and their 95% confidence interval (CI) were calculated, as well as coefficients of determination (R^2) according to the Nagelkerke method. Probabilities of recurrence according to the most relevant parameters were estimated using a Bayesian approach. All statistical tests were 2-tailed. A P value $< .05$ was considered to indicate statistical significance. Analyses were performed using SPSS 25.0 statistical package software (SPPS, Chicago, IL).

Results

Baseline characteristics

A series of 158 consecutive patients were prospectively enrolled. Seventeen patients (11%) were excluded, owing to inadequate image quality in 11 and failure to obtain follow-up data in 6 cases. Thus, the studied population comprised 141 patients (age 60 [54–67] years, 37 women), including 81 paroxysmal AF (57%) and 60 persistent AF (43%). Patient characteristics are shown in Supplemental Table 1. Paroxysmal and persistent AF patients were clinically comparable except for history of heart failure (P = .03), infarction (P = .046), number of electrical cardioversion ($P < .0001$), and amiodarone therapy (P = .003). All patients underwent isolation of the 4 PVs. Sixty-five patients (46%) had ablation of the CTI, and 50 (35%) had additional lesions. There were more CTI isolation (P = .012) and additional lesions ($P < .0001$) in persistent AF ($P < .001$) than in the paroxysmal AF group. Radiofrequency ($P < .001$), fluoroscopy (P = .005), and total procedure durations ($P < .0001$) were significantly higher in the persistent AF than in the paroxysmal group. Regarding imaging characteristics, there was a significant difference in LA indexed volume (P = .001), LAA volume ($P < .001$), and LA anteroposterior diameter ($P < .001$) between paroxysmal and persistent AF groups. Conversely, there was no difference between groups in terms of LA sphericity (P = .051), vertical asymmetry (P = .87), and shape score (P = .55). Patients with history of prior cardiac surgery or intervention were excluded from this analysis.

Follow-up

The median duration of follow-up was 352 [129–379] days. Recurrence after index procedure occurred in 38 patients (27%), most between 3 and 12 months after catheter ablation. Among these 38 patients, 30 patients (21%) underwent a single redo procedure, 7 patients (5%) underwent 2 redo procedures, and 1 patient (1%) underwent 3 redo procedures. At the end of follow-up, 33 patients (23%) were considered to have catheter ablation failure, including 21 of 60 (35%) persistent and 12 of 81 (15%) paroxysmal AF. In addition, 9 patients (6%) showed complications related to AF or its treatment: 5 (3%) heart failure episodes, 2 (1%) electrical storms, 1 (0.7%) stroke, and 1 (0.7%) death from internal bleeding.

Heterogeneous regional remodeling

Results of local shape analysis reveal that the regions significantly associated with ablation failure were mostly found on a large area extending from the inferior part of the posterior left atrium up to the mitral isthmus, covering the left inferior pulmonary vein (LIPV). More focal differences lay close to the antrum of left and right superior veins, as well as within the septum and anterior wall, as shown in Figure 3 (see also Supplemental Video 1). The increasing of surface area of these regions with respect to the template was an indicator of recurrence. We then removed the influence of volume and AF type on the shapes. This was evaluated quantitatively (Supplemental Table 5), and the important decrease in R2 values demonstrated the effectiveness of our process in removing these correlations.

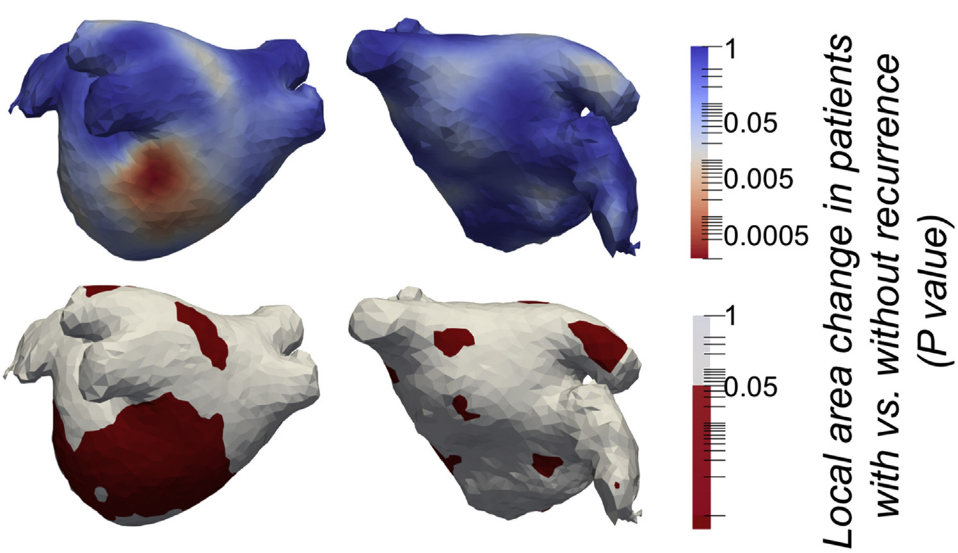

Figure 3 Critical regions implicated in catheter ablation failure. Areas where local area change was greater in patients with vs without recurrence are mapped onto the left atrium template. Upper row: P value color-coded from blue to red. Bottom row: areas with P value $<.05$ shown in red. See Supplemental Video 1. All remodeled regions follow an increase in size.

Interestingly, after removal of shape variations associated with LA volume (Figure 4 and Supplemental Video 2) and AF persistence (Figure 5 and Supplemental Video 3), the shape patterns that were found linearly correlated to postablation recurrence were very different, essentially capturing volume changes in the LAA, expansion of the roof and PV antral areas, and a slightly more posterior and inferior orientation of the PVs, as illustrated in Figure 6 and Supplemental Video 4.

Univariable and multivariable predictors of ablation failure

Univariable correlates of ablation failure are shown in Supplemental Table 2. Among clinical characteristics, ablation failure related to AF persistence (P = .005), alcohol abuse (P = .033), and ischemic cardiomyopathy (P = .047). Patients with ablation failure had longer radiofrequency ablation (P = .03), fluoroscopy (P = .04), and total procedure durations (P = .01), as well as more frequent additional lesions performed after PV isolation (P = .028). Among LA size metrics, there was an association between ablation failure and increased LA indexed volume (P = .019) and anteroposterior diameter (P = .021). LAA volume was not associated with ablation failure. Among LA shape metrics, ablation failure related to LA sphericity index (P = .024) and shape score (P = .001). Vertical asymmetry and the presence of a left common vein were not associated with ablation failure. ROC analysis was performed on all imaging metrics significantly related to ablation failure on univariable analysis. Shape score had the largest area under ROC curve (AUC = 0.7, 95% confidence interval [CI] 0.61–0.79), followed by LA indexed volume (AUC = 0.66, 95% CI 0.55–0.77), AF type (AUC = 0.64, 95% CI 0.43–0.75), LA sphericity (AUC = 0.63, 95% CI 0.52–0.74), and LA anteroposterior diameter (AUC = 0.62, 95% CI 0.51–0.74). Optimal cut-off values to predict ablation failure were 60.8 mL/m^2 for LA indexed volume and 0.509 for shape score. Results from multivariable analysis for the prediction of ablation failure are shown in Supplemental Table 3. Based on the results of univariable analysis,

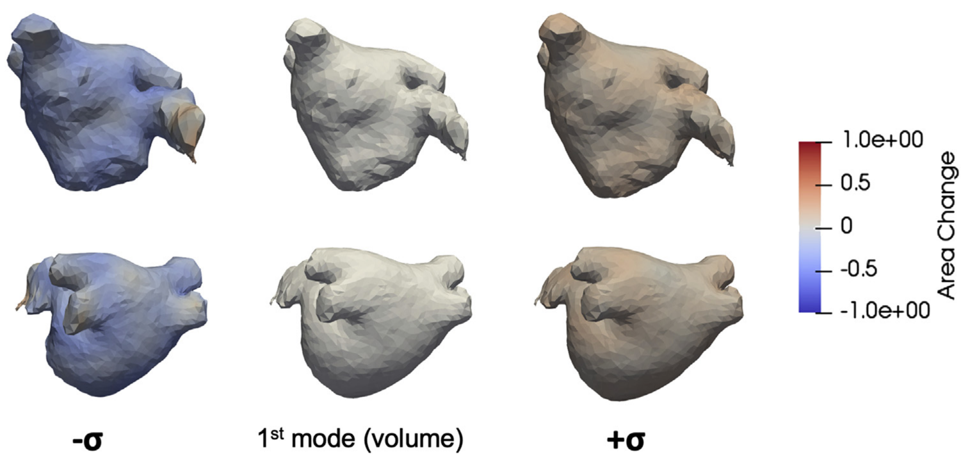

Figure 4 Shape changes with volume. Linear regression with dimension-reduced components was used to analyze the relationships of these shape features with left atrial volume: middle: average atrial shape; left: deformation associated with lower atrial volume; right: deformation associated with larger atrial volume.

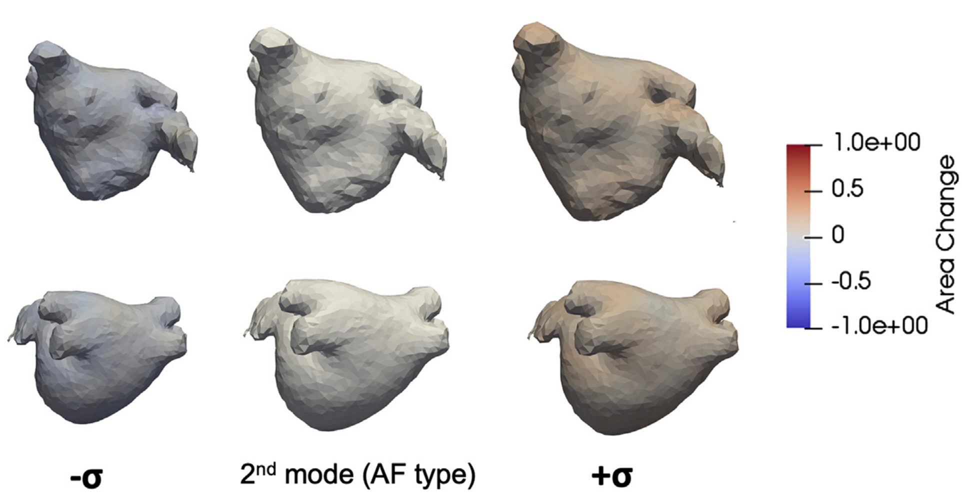

Figure 5 Shape changes with atrial fibrillation (AF) type. Linear regression with dimension-reduced components was used to analyze the relationships of these shape features with AF persistence: middle: average atrial shape; left: deformation associated with paroxysmal AF; right: deformation associated with persistent AF.

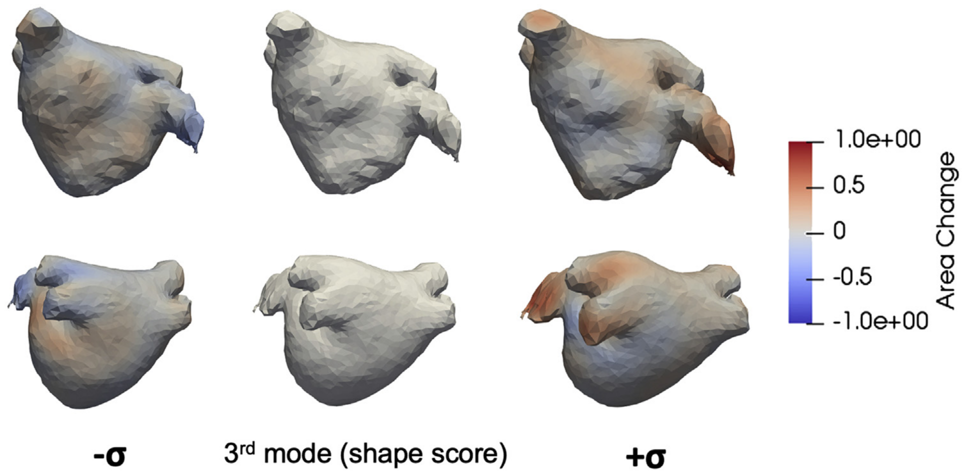

Figure 6 Shape changes with recurrence. Linear regression with dimension-reduced components was used to analyze the relationships of these shape features with postablation recurrence: middle: average atrial shape; left: deformation associated with less recurrence; right: deformation associated with more recurrence.

a multivariable model was built to include the most significant clinical marker (ie, AF persistence), the most significant marker of atrial size (LA indexed volume), and the most significant marker of atrial shape (LA shape score). Results showed that all 3 were independent predictors of ablation failure, with a coefficient of determination of the model of 0.43 according to the Nagelkerke method. LA shape score showed the higher predictive value (odds ratio [OR] = 6.2, 95% CI 2.5–15.8, $P < .001$), followed by LA indexed volume (OR = 3.1, 95% CI 1.2–7.9, $P = .019$) and the AF persistence (OR = 2.9, 95% CI 1.2–7.6, $P = .022$). Correlation analysis between these 3 predictors is shown in Supplemental Table 4. LA indexed volume and AF persistence were significantly, although weakly, correlated, while the LA shape score did not relate to any of these 2 characteristics. Kaplan-Meier arrhythmia-free survival curves depending on LA shape score, LA indexed volume, and AF persistence are shown in Figure 7.

Probabilistic decision tree

Bayesian statistics were used to stratify the risk of ablation failure according to the patient characteristics identified on multivariable analysis. We included sequentially the characteristics LA shape score, LA indexed volume, and AF persistence, in a probabilistic decision tree. Results are shown in Figure 8. Patients with persistent AF, shape score >0.509, and LA indexed volume >60.8 mL/m^2 showed a probability of ablation failure of 0.89 (0.72–1). In contrast, patients with paroxysmal AF, shape score <0.509, and LA indexed volume <60.8 mL/m^2 showed a probability of ablation failure of 0.10 (0–0.22).

Discussion

This study is, to our knowledge, the first to use a statistical modeling approach to learn LA shape features and regional remodeling associated with postablation outcome in patients with AF. Studying a series of 141 CT scans from patients with paroxysmal or persistent AF undergoing catheter ablation, its main findings are as follows: (1) statistical modeling identifies an LA shape score whose predictive value outperforms the already reported shape markers; (2) the shape score is independent from AF persistence and LA volume, and jointly, allows stratifying the risk of ablation failure on a patient-by-patient basis with high predictive value; (3) the regions whose shape is more closely associated with ablation failure are large areas covering the inferior part of the posterior left atrium, the left inferior PV and the mitral isthmus, and smaller areas located on the antrum of left and right superior veins, the septum, and the anterior wall.

LA shape markers associated with recurrence

In order to understand which regions of the left atrium showed shape features implicated in arrhythmia recurrence, local area changes were compared between patients with and without ablation failure. Significant differences were found over 1 large area including the inferior part of the posterior left atrium, the LIPV, and the mitral isthmus, as well as over smaller areas located on the antrum of left and right superior veins, the septum, and the anterior wall. On these areas, local area was larger in patients showing arrhythmia recurrence. This finding brings new insights into critical regions implicated in ablation failure. Our first hypothesis is that these regions are the ones more prone to structural or electrophysiological remodeling, and that this remodeling is indirectly taken into account when analyzing shape. This hypothesis is supported by the fact that the same regions were also found to be common sites for atrial fibrosis on magnetic resonance imaging,[17] low voltage on contact mapping,[18] and reentrant drivers during AF on electrocardiographic imaging.[19] In addition, and as a consequence, these regions are the ones usually targeted by most ablation strategies (PV antral ablation, mitral isthmus line, etc). However, as mentioned above, we cannot rule out potential inherited shape features predisposing to ablation failure. This would require prospectively monitoring shape changes of a very long-term follow-up, which is practically

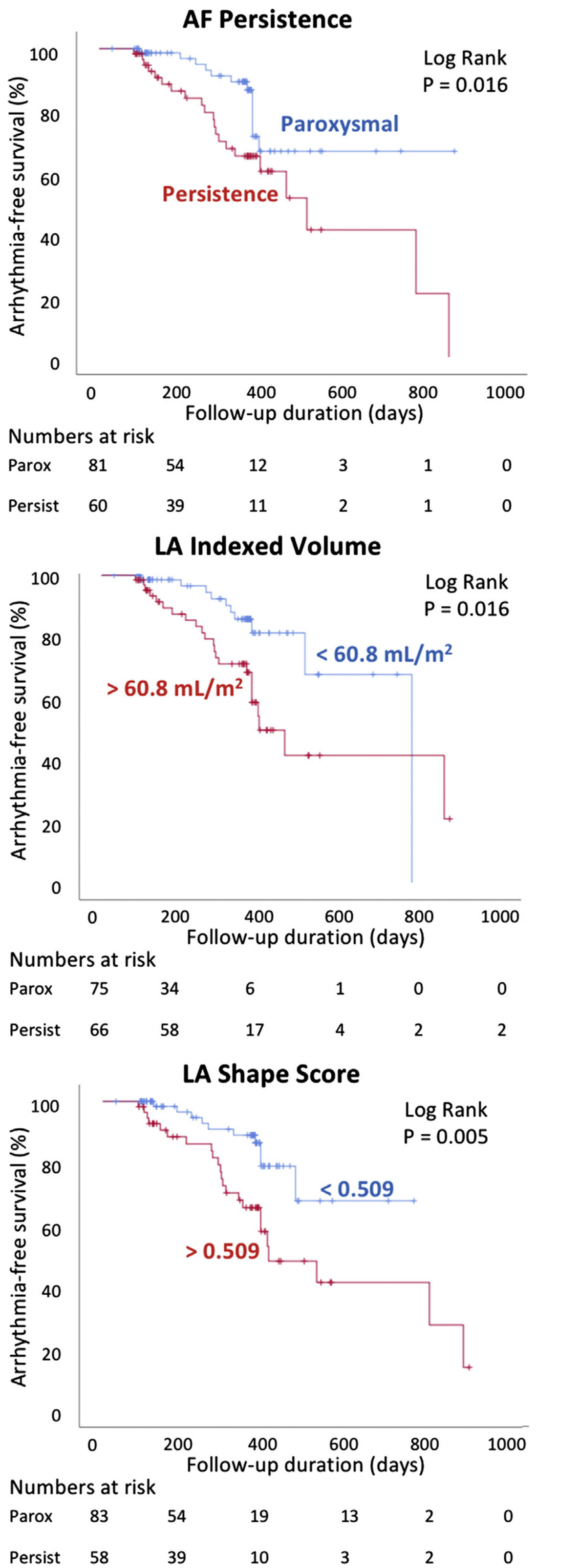

Figure 7 Kaplan-Meier arrhythmia-free survival curves according to atrial fibrillation (AF) persistence, left atrial (LA) indexed volume, and LA shape score.

not achievable. Likewise, the risk of recurrence conferred by a patient's LA shape may be due either to proarrhythmic remodeling or to practical issues that this specific shape confers when performing catheter ablation. Distinguishing between these proarrhythmogenic vs catheter-adverse effects of shape may be partly answered by analyzing shape in controls, which should be the focus of future studies.

LA shape to predict AF recurrence

The characteristics of the studied population are consistent with the usual population of AF patients referred for catheter ablation.[20] Patient outcomes are also consistent with prior reports, with recurrence rates (15% in paroxysmal and 35% in persistent AF over a 1-year median follow-up) in the upper range of previously reported data.[3,4] In the present study, we found the usual clinically available markers (ie, AF persistence and LA size) to be quite weak predictors of postablation outcome. This is also in line with prior studies,[5,11] and reflects the complexity of clinical decision-making in the selection of ablation candidates in AF. Using a novel statistical shape modeling framework,[13] we were able to identify an LA shape score that is by construction independent from atrial size and AF persistence, and that still carries important prognostic value. As compared to previously described shape metrics, namely vertical asymmetry[9] and sphericity,[10] the proposed LA shape score is based on group-wise statistics on the global LA shape rather than on geometrical assumptions and *a priori* hypotheses on LA shape remodeling. Using a detailed mean LA shape as the reference shape instead of a sphere,[11] the computation of LA sphericity is slightly different. Besides, partial least squares regression was applied to deal with the limitation of principal components analysis space[11] by discarding noise in the shape modes. The resulting score was found to be both more closely related to patient outcome and more independent from LA size. Compared with previous literature,[11,12,21] the cardiac phase of imaging acquisition was specified at end-systole, which is important for removing the disturbing variations in shape modeling. When combining the shape score with LA indexed volume and AF persistence in a multivariable model, results showed that all 3 markers remained independent outcome predictors, with LA shape score being the strongest predictor. This demonstrates that LA shape contains important prognostic information that goes beyond LA size. We interpret this finding as possibly related to an asymmetric and heterogeneous regional remodeling process, although in the absence of longitudinal long-term follow-up we cannot exclude potential inherited shape features predisposing to AF or making catheter ablation therapy more challenging. Interestingly, the correlation analysis showed that LA volume and AF persistence were significantly, although weakly, interrelated, while the LA shape score did not relate to both. Still, these 3 markers, being independent outcome predictors, allowed us to apply Bayesian statistics to build a statistical decision tree combining all 3 predictors, resulting in efficient stratification of the recurrence risk in subpopulations. Analyzing such shape score within healthy young individuals would enable clinicians to evaluate the remodeling

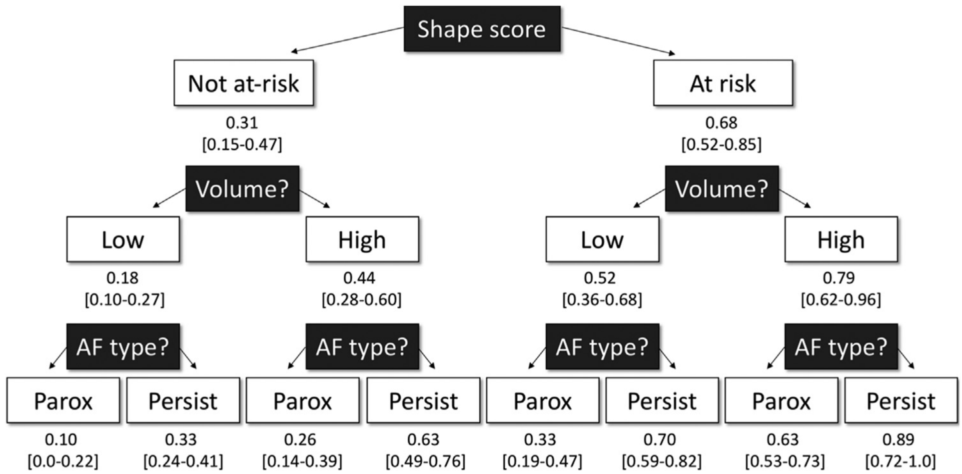

Figure 8 Likelihood of response to catheter ablation according to left atrial shape, volume, and atrial fibrillation (AF) persistence. Bayesian statistics were used to estimate the probability of recurrence for each patient profile, along with a 95% confidence interval.

process and is the topic of on-going work. In the present study, 2 distinct approaches were presented to analyze regional shape features associated with AF recurrence: a first approach directly comparing local area changes between patients with and without recurrence, and a second corresponding to the shape features associated with AF recurrence as captured by our shape score (ie, after removing shape variations owing to LA volume and AF persistence). As expected, these 2 approaches show very different results, the former pointing towards the inferior left atrium and mitral isthmus and the latter rather pointing towards the roof, the PV antra, and PV orientation. We acknowledge here that from a clinical and pathophysiological point of view the shape features captured by our shape score may not be easily interpretable. Indeed, atrial shape features associated with AF recurrence likely result from a complex interplay between an inherited LA shape and an acquired remodeling of this original shape in which LA dilatation and AF persistence play a major role. The rationale to build such a shape score was to capture shape features that are not already present in existing clinically available predictors.

Clinical implications

The use of CT imaging prior to AF ablation is rapidly expanding. The modality is clinically valuable to provide accurate anatomical geometries for procedural registration in electroanatomical mapping systems.[22] More recently, the systematic use of CT has been further justified by its ability to rule out thrombus before ablation.[23] The presented score can be computed with information that can be robustly extracted from 3D CT images. Indeed, contrast-enhanced CT imaging is widely available nowadays and image quality enables fast and robust segmentation of the atrial blood pool. The present study shows that besides anatomy and thrombus, CT images also contain important prognostic information that may be used to personalize patient management, namely LA volume and shape. According to current guidelines, catheter ablation is recommended in patients with symptomatic paroxysmal AF.[2,6] However, arrhythmia recurrence is not uncommon after ablation of paroxysmal AF. In that context, the finding of adverse structural findings on preoperative imaging (LA enlargement and at-risk shape) may be helpful to tailor patient information, and potentially to consider additional ablation targets outside pulmonary veins. In persistent forms of AF, the indications for catheter ablation are still debated, as the results from clinical studies still show high recurrence rates.[3] To improve the rate of response to catheter ablation, one strategy consists of identifying better ablation targets, while another aims at better selecting candidates (ie, identifying patients that are unlikely to respond to therapy). To this day, the decision relies on (1) asking the patient the duration of his or her most prolonged AF episode, which is not a very robust strategy given the prevalence of asymptomatic AF, and (2) measuring LA size, which shows limited incremental predictive power. In the present work, we have applied a statistical shape model to specifically identify a shape-based predictor that is independent from currently available markers. We demonstrate that this shape score can be combined with existing predictors to improve the stratification of the recurrence risk. Probabilities of recurrence can thus be estimated on a patient-by-patient basis. Given the availability of CT techniques, the already existing indications for preprocedural CT,[24] and the easy implementation of fully automated segmentation on CT images,[25] the approach described in the present manuscript may be easily implemented in clinical practice to optimize patient information and/or patient selection. The approach can be extended to magnetic resonance imaging scans as well, according to the availability of images.

Study limitations

The main limitation of the present manuscript is the lack of prospective external validation of the proposed predictor. As mentioned in the methodology, we have applied a 5-fold cross-validation approach to make sure that learning and testing were performed on different populations, and that the score of each patient was built from a population that did not comprise his own LA shape. Thus, the risk of overfitting should be avoided, although we look forward to prospective, and ideally external, validation of our method. Another limitation is the high heterogeneity of ablation strategies, particularly in patients with persistent AF. However, this makes the present series quite consistent with standard practice, as it illustrates the high variety of ablation approaches in persistent AF. Additionally, we observed the shape differences cross-sectionally between subjects and not in a longitudinal fashion; therefore, we cannot discriminate between remodeling processes or innate shape characteristics exposing to arrhythmogenicity or altering ablation therapy. Lastly, as mentioned in the previous paragraph, in the absence of very long-term follow-up and of a control group, the relationship between shape features and atrial remodeling remains a working hypothesis, as we cannot exclude potential innate shape features predisposing to AF or making catheter ablation therapy more challenging. Although this confusion significantly limits the conclusions to draw with respect to AF pathophysiology, it has little impact on the clinical implications of the proposed method.

Availability of the data

The dataset used during the current study is not publicly available owing to the institutional ethics committee governance policy on public use of data. Requests for details on the dataset can be directed to the corresponding author. The atrial template and the meshes along the deformation mode associated with recurrence are available online at https://team.inria.fr/epione/fr/data/atrial-shape-statistics/.

Conclusion

Performing shape-based statistics on a large database of CT images acquired in patients with AF undergoing catheter ablation, we have identified an LA shape score whose predictive value outperforms the already reported shape markers. LA shape predicts ablation failure independently from, and more accurately than, clinically available predictors. Combining LA shape, atrial volume, and AF persistence allows stratifying the risk of ablation failure on a patient-by-patient basis. The regions whose shape is more closely associated with ablation failure are large areas covering the inferior part of the posterior left atrium, the LIPV, and the mitral isthmus, as well as smaller areas located on the antrum of left and right superior veins, the septum, and the anterior wall.

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Disclosures

The authors have no conflicts to disclose.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All patients provided informed consent.

Ethics Statement

The study was approved by the institutional review board and conforms to the Declaration of Helsinki.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.10.013.

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