

# openheart Left atrial strain predicts recurrence of atrial arrhythmias after catheter ablation of persistent atrial fibrillation

Abdul Shokor Parwani, Daniel-Armando Morris, Florian Blaschke, Martin Huemer, Burkert Pieske, Wilhelm Haverkamp, Leif-Hendrik Boldt

**To cite:** Parwani AS, Morris D-A, Blaschke F, *et al.* Left atrial strain predicts recurrence of atrial arrhythmias after catheter ablation of persistent atrial fibrillation. *Open Heart* 2017;4:e000572. doi:10.1136/openhrt-2016-000572

Received 28 November 2016  
Revised 9 February 2017  
Accepted 7 March 2017

## ABSTRACT

**Introduction** Success rates of catheter ablation (CA) of persistent atrial fibrillation (AF) are very variable. Identifying patients in whom sinus rhythm maintenance cannot be achieved after CA is a critical issue.

**Methods** 2D speckle-tracking echocardiography was performed before the first CA procedure in consecutive patients with persistent AF. Left atrial (LA) strain was correlated with recurrence of atrial arrhythmias during the follow-up period of 15 months after one CA procedure with or without antiarrhythmic drugs (primary endpoint). In a secondary analysis, recurrences after two CA procedures were analysed.

**Results** 102 patients were included. Patients with recurrence of atrial arrhythmias after one CA procedure (n=55) had significantly lower LA strain than those without recurrence (LA strain  $9.7\pm 2.4\%$  vs  $16.2\pm 3.0\%$ ;  $p<0.001$ ). Recurrence rate was significantly higher in patients with LA strain  $<10\%$  than in those with LA strain between  $10\%$  and  $14.5\%$  and  $>14.5\%$  (97.7%, 42.1% and 10.3%, respectively;  $p<0.001$ ). In Cox regression analysis including age, comorbidities, left ventricular dysfunction and LA enlargement, low LA strain ( $<10\%$ ) was the strongest factor associated with recurrence of AF (HR 6.4 (2.4–16.9),  $p<0.001$ ). Even after inclusion of a second CA procedure, LA strain  $<10\%$  maintained a high predictive value for recurrence of atrial arrhythmias (86.4% (95% CI 73.3% to 93.6%)).

**Conclusion** In patients with persistent AF, LA strain imaging could be very useful to select those patients who have a high risk of not benefiting from CA.

## INTRODUCTION

The success rate of catheter ablation (CA) of persistent atrial fibrillation (AF) is very variable. Reported success rates range from 30% to 80%, often even despite several ablation attempts.<sup>1–8</sup> Orthodox echocardiographic analyses of the left atrium (eg, left atrial (LA) diameter, LA area or LA volume) are frequently carried out prior to CA with the purpose of detecting LA myocardial alterations which could increase the risk of recurrence of AF after CA.<sup>9–12</sup> Nonetheless, several investigations have recently demonstrated in diverse disorders that new myocardial techniques such as 2D

## KEY MESSAGES

### What is already known about this subject?

- ▶ In previous studies, the normal range and the clinical relevance of the myocardial function of the left atrium using 2D speckle-tracking echocardiography (2DSTE) in patients with atrial fibrillation (AF) have been reported. In patients with paroxysmal AF, the assessment of diastolic and systolic left atrial (LA) myocardial function using 2DSTE can distinguish patients with high or low risk for recurrence of AF after catheter ablation (CA) therapy.
- ▶ The clinical relevance of LA strain in patients with persistent AF is unknown and difficult to determine.

### What does this study add?

- ▶ In our study, LA strain could also be assessed in patients with persistent AF. During a follow-up period of 15 months, patients with low LA strain ( $<10\%$ ) had significantly worse results with CA in comparison with those without low LA strain. Low LA strain was the principal factor associated with recurrence of AF after CA. The predictive value of low LA strain for recurrences of atrial arrhythmias remained high even after redo procedures. Therefore, in patients with persistent AF, the analysis of LA strain could be of great usefulness to select those patients with a high risk of poor outcomes.

### How might this impact on clinical practice?

- ▶ LA strain analysis prior to ablation might help identifying patients with persistent AF with a high risk of recurrences of atrial arrhythmias even after two ablation procedures.

speckle-tracking echocardiography (2DSTE) are able to detect myocardial alterations of the LA even when conventional echocardiographic analyses are normal.<sup>13 14</sup> Hence, using 2DSTE before CA could significantly improve the management of patients with persistent AF, because these myocardial analyses, unlike conventional techniques could identify LA myocardial alterations linked to



CrossMark

Department of Cardiology,  
Charité – Universitätsmedizin  
Berlin, Berlin, Germany

**Correspondence to**  
Dr Leif-Hendrik Boldt; leif-hendrik.boldt@charite.de

high risk of recurrence of AF as well as LA myocardial characteristics with low risk for AF recurrence.

Recent studies using 2DSTE have demonstrated the incremental clinical value of LA strain imaging over other clinical and echocardiographic factors to predict recurrence of AF after CA in patients with paroxysmal AF.<sup>14–17</sup> However, the clinical relevance of LA strain imaging in patients with persistent AF remains poorly understood. Recently, just one small study suggested that a low value of LA strain could be an important factor linked to recurrence of AF after CA in patients with persistent AF.<sup>17</sup> Nevertheless, that study was limited due to the small number of subjects with persistent AF (n=27), the short follow-up period (just 6 months, including the blanking period of the first 3 months) and because the determination of the cut-off of LA strain to predict recurrence of AF was determined by analysing only patients in sinus rhythm.<sup>17</sup> Most patients with persistent AF, however, present with AF at the time of echocardiographic analysis. The purpose of this study was to validate the hypothesis, that in patients with persistent AF, analysis of the left atrium using LA strain imaging with the patient being in AF at the time of analysis could be of great usefulness to select those patients who have the highest risk of not benefiting from CA.

## METHODS

### Study population

We included consecutive patients  $\geq 18$  years of age with persistent AF in whom the first CA of AF was performed at our centre between January 2010 and January 2013. Persistent AF was defined according to the diagnostic criteria of the guidelines on AF and CA of the Heart Rhythm Society (HRS).<sup>18</sup> Only patients with AF at the time of the echocardiographic analysis which was performed in the week prior to CA were included. The indication for CA was symptomatic persistent AF refractory or intolerant to antiarrhythmic medication. Informed consent was obtained from all subjects.

To create a homogenous group of patients for this study, the following patients were excluded:

- ▶ History of long-standing persistent AF (>12 months of continuous AF)
- ▶ LA diameter >55 mm
- ▶ Left ventricular ejection fraction (LVEF) <50%
- ▶ Significant valvular heart disease (mild, moderate or severe mitral or aortic stenosis, and moderate or severe mitral, tricuspid or aortic regurgitation)
- ▶ Unstable coronary artery disease (unstable angina pectoris or acute myocardial infarction within the last 30 days, subjects waiting for coronary artery bypass graft or within 90 days postoperatively, subjects with chronic stable angina and patients with evidence of myocardial ischaemia assessed by stress echocardiography)
- ▶ Severe pulmonary disease (requirement of supplemental oxygen or need of treatment with corticoids)

- ▶ Severe kidney disease (glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup>, history of renal transplantation and dialysis)
- ▶ Severe chronic liver disease or history of liver transplantation
- ▶ Congenital heart disease
- ▶ Pericardial disease characterised by pericardial effusion (echo-free space in end-diastole  $\geq 5$  mm) or constrictive pericarditis
- ▶ Hyperthyroidism or hypothyroidism.

Furthermore, to minimise underestimations of LA myocardial measurements, patients with poor 2D imaging quality in one or more myocardial segments of the LA (not suitable for analysis by 2DSTE in apical 4-chamber and 2-chamber views) were also excluded from this study.

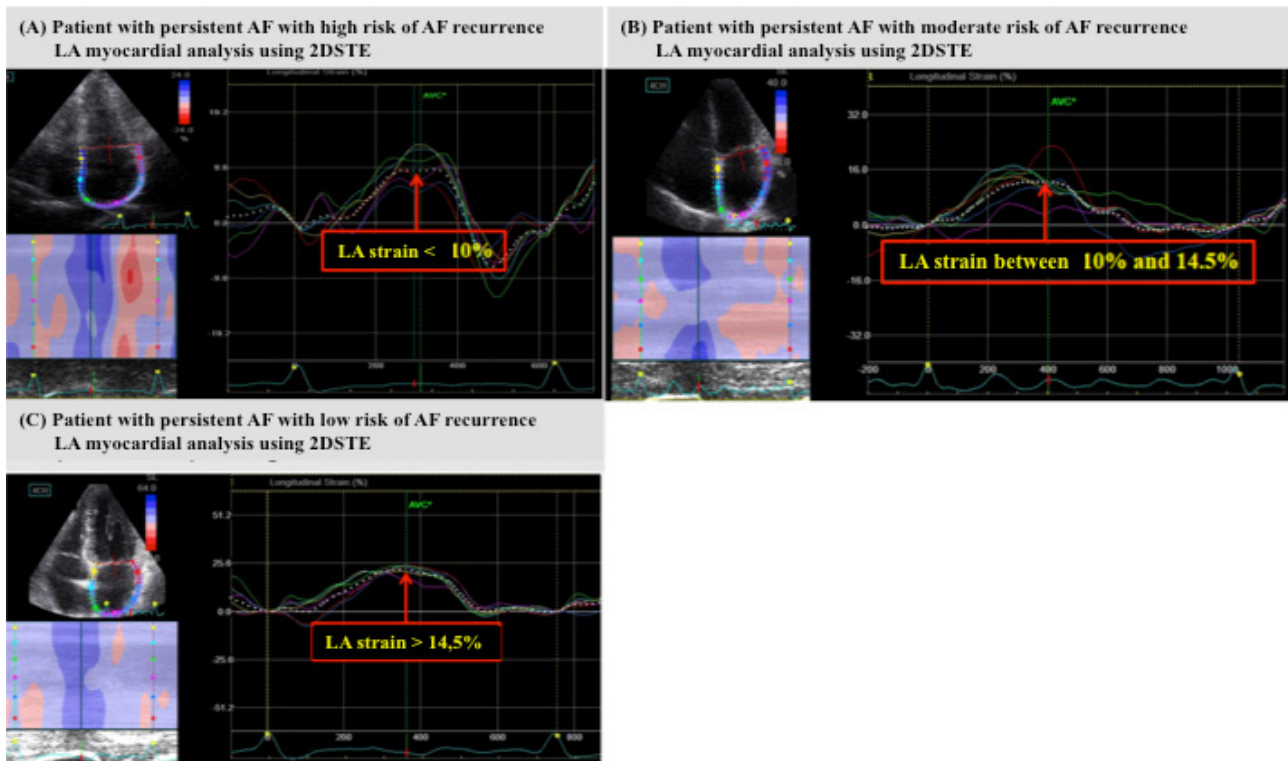
### Conventional and speckle-tracking echocardiography

All patients were examined by transthoracic echocardiography at rest using a Vivid 7 or Vivid E9 ultrasound system (GE-Healthcare) followed by an offline analysis using 2DSTE (Echo-Pac 113.0) in the week prior to CA. The echocardiographic measurements and analyses were performed within 7 days prior to CA and during an episode of persistent AF. Left ventricular (LV) diameters, LV volumes, LV mass, LV hypertrophy and LVEF (Simpson's method), and LA diameter, area, volume and LA enlargement (ie, LA diameter >40 mm, LA area >20 cm<sup>2</sup>, LA volume >58 mL and LA volume index (LAVI) >28 mL/m<sup>2</sup>) were assessed and defined as recommended by the American Society of Echocardiography (ASE).<sup>19</sup> The measurement of LA strain was performed at each LA myocardial segment of the apical 4-chamber and 2-chamber views.<sup>14–20</sup> The average value of LA positive strain peak during the entire cardiac cycle from all LA segments was used for the final value of LA strain (see figure 1a–c).

Furthermore, longitudinal systolic and diastolic function of the LV by means of LV strain and LV early-diastolic strain rate (SRe) analysing all segments of the LV were analysed.<sup>14–20–22</sup> On the basis of previous studies, we defined LV longitudinal systolic and diastolic dysfunction as LV strain > -16% and LV SRe <0.95 s<sup>-1</sup>.<sup>14–20–22</sup> All echocardiographic measurements using 2DSTE (mean frame rates 68.4 $\pm$ 4.2 frames/s) and conventional 2D echocardiography were calculated as the average of three measurements and at conditions of respiratory (<20 breaths/min), haemodynamic (90–180 mm Hg of systolic blood pressure) and electrical (60–100 beats/min) stability. All persons involved in obtaining and analysing echocardiographic data were blinded to the clinical information of the patients and ablation outcomes.

### CA procedure

CA was performed using an open irrigated-tip ablation catheter (IBI Therapy Cool Path Duo or IBI Therapy Cool Flex) and a circular mapping catheter (IBI Inquiry Optima), which were positioned in the



**Figure 1** Myocardial Analysis of the Left Atrium Using 2D Speckle-Tracking Echocardiography. The fragmented white curve indicates the average of LA strain from all segments of the LA. **Figure 1a** corresponds to a patient with persistent AF with high risk for AF recurrence (i.e. LA strain < 10%), whereas **Figure 1b** and **1c** correspond to patients with persistent AF with moderate and low risk for AF recurrence after CA.

left atrium after double trans-septal puncture under fluoroscopic guidance. A steerable sheath (Agilis, St. Jude Medical) was used in all procedures to support manipulation and stability of the ablation catheter. The geometry of the left atrium was reconstructed using a 3D mapping system (Ensite NavX, St. Jude Medical). Wide area circumferential pulmonary vein isolation was carried out with the irrigated-tip catheter with a maximal power of 35 W and a maximal temperature of 43°C. The course of the oesophagus was identified using a SensiTherm (St. Jude Medical) thermal probe. Radio frequency (RF) delivery was terminated and continued with decreased power whenever the oesophageal temperature exceeded 39°C. Complete isolation of all pulmonary veins was thoroughly verified by the circular catheter. Besides pulmonary vein isolation, additional ablation lesions such as LA linear lesion (LA roof line and mitral isthmus line) and ablation of regions with complex fractionated electrograms were placed in case AF could not be electrically cardioverted after pulmonary vein isolation.

#### Primary endpoint and follow-up period

The primary endpoint was the rate of recurrence of AF, atrial flutter (AFL) or atrial tachycardia (AT) (referred to as recurrence of atrial arrhythmias) after the first CA during a follow-up period of 15 months with or without antiarrhythmic drugs. We analysed the first recurrence of AF (defined as any documented episode >30s)

without taking into account early recurrences corresponding to the blanking period of the first 3 months after the initial CA. The patients were followed up in our outpatient clinic after 3 months and then after each 6 months. During these visits, we verified the maintenance of sinus rhythm using Holter monitoring. In addition, all patients were instructed to contact our department in case of any symptoms suggestive of arrhythmia with the purpose of obtaining an ECG or Holter to confirm or exclude recurrence of atrial arrhythmias.

#### Secondary endpoint

The secondary endpoint was the rate of recurrence of atrial arrhythmias after two CA procedures with or without antiarrhythmic drugs.

#### Statistical analysis

Continuous data were presented as mean  $\pm$  SD and dichotomous data in percentage. Differences in continuous variables between groups were analysed using Student's t-test. Categorical variables were compared by  $\chi^2$  test and Fisher's exact test as appropriate. Comparisons between three or more groups were analysed using a one-way analysis of variance. Based on previous findings in patients with paroxysmal AF,<sup>14</sup> we estimated a rate of recurrence of AF to 15 months after CA at 70% in patients with low LA strain and at 15% in those without low LA strain. Thus, in order to detect a possible difference

of 55% in the primary outcome between patients with and without low LA strain, a minimal sample size of 15 subjects in each group was estimated, with the purpose of having a statistical power of 80% with a confidence level of 0.05. Accordingly, assuming a probable rate of excluded subjects at 10–20%, a possible dropout rate at 15–20% and a possible prevalence of low LA strain at about 40%, we targeted to include a total of 100 patients with persistent AF.

To determine the reproducibility of LA strain using speckle-tracking echocardiography in patients with AF, we analysed intraobserver and interobserver variability. Intraobserver variability had a mean absolute difference of  $0.9\% \pm 0.5\%$  (maximum 2.1%). Interobserver variability had a mean absolute difference of  $0.8\% \pm 0.6\%$  (maximum 1.0%).

Receiver operating characteristic curves were calculated to evaluate the association of LA strain with the primary endpoint. An optimal cut-off value was chosen as one with optimal specificity (>90%) and sensitivity (>70%). In addition, we tested the relation of those cut-off points of LA strain to determine the primary endpoint and secondary endpoint. In this regard, a Cox regression analysis was performed. HRs with corresponding 95% CIs were then described. In order to determine the factors related to low LA strain, a logistic regression analysis was performed.

Differences were considered statistically significant when  $p < 0.05$ . All statistical analyses were performed with StatView V.5.0 (SAS Institute) and SPSS Statistics V.22.0 (IBM).

## RESULTS

### Study population and outcomes

A total of 108 patients with persistent AF met the eligibility criteria during the inclusion period. However, six patients could not be enrolled because of poor 2D imaging quality in one or more segments of the. Thus, 102 patients were finally included and followed up during a period of 15 months. Although nine patients (9%) missed one of the scheduled outpatient follow-up visits between months 3 and months 15, AF recurrence status at the final follow-up visit at 15 months could be obtained for all patients.

In the primary endpoint analysis (recurrence of documented atrial arrhythmia after one CA procedure, with or without antiarrhythmic drugs), 55 patients (54%) had a recurrence during the follow-up period. In 31% of the patients with a recurrence, the recurring arrhythmia was paroxysmal AF, in 51% persistent AF and in 18% AFL/AT.

In the secondary endpoint analysis (recurrence of documented atrial arrhythmia after two CA procedures, with or without antiarrhythmic drugs), 42 patients (41%) had a recurrence during the follow-up period.

No patient suffered a sudden death, ventricular tachycardia or acute coronary syndrome during the follow-up

**Table 1** Study population

	Patients with persistent AF (n=102)
<b>Clinical characteristics</b>	
Age (years)	65.7±9.7
Women	33.3%
Body mass index (kg/m <sup>2</sup> )	28.0±5.1
Systolic blood pressure (mm Hg)	123.0±14.4
Diastolic blood pressure (mm Hg)	76.4±9.7
Heart rate (beats/min)	89.7±10.9
CHADS <sub>2</sub> index score	0.9±0.6
CHA <sub>2</sub> DS <sub>2</sub> -VASc index score	2.1±1.2
Duration of AF <12 months	100%
PVI alone	55.9%
PVI + additional LA lesions	44.1%
<b>Comorbidities</b>	
Hypertension	72.5%
Type II diabetes	8.8%
Obesity	32.4%
History of CAD	24.5%
<b>Left ventricular characteristics</b>	
LV ejection fraction (%)	56.8±3.8
LV mass (g/m <sup>2</sup> )	97.5±23.0
LV longitudinal systolic function (strain) (%)	-13.5±3.1
LV longitudinal diastolic function (SRe) (s <sup>-1</sup> )	1.25±0.36
<b>Left atrial characteristics</b>	
LA diameter (mm)	41.1±4.7
LA area (cm <sup>2</sup> )	20.9±5.3
LA volume (mL)	62.5±27.3
LA volume index (LAVI) (mL/m <sup>2</sup> )	30.9±12.3
LA strain (%)	12.7±4.2

Data are expressed as mean ± SD or percentages. Additional LA lesions, LA linear lesions (LA roof line and mitral isthmus line) and ablation of regions with complex fractionated electrograms. AF, atrial fibrillation; CAD, coronary artery disease; LA, left atrial; LV, left ventricular; PVI, pulmonary vein isolation; SRe, early-diastolic strain rate.

time. Baseline characteristics of the patients are shown in [table 1](#).

### Characteristics of patients with recurrence of AF after one CA procedure (primary endpoint)

Patients with recurrence of AF after one CA procedure were principally characterised by a lower LA strain in comparison with those without AF recurrence (LA strain  $9.7 \pm 2.4\%$  vs  $16.2 \pm 3.0\%$ ;  $p < 0.001$ ; see [table 2](#)). In contrast, LA volumetric characteristics (analysed by conventional echocardiography) were similar in patients with and without recurrence of AF (see [table 2](#)). Furthermore, it is important to note that there were no significant



**Table 2** Characteristics of patients with recurrence of AF after one catheter ablation procedure (primary endpoint)

	Recurrence of AF (n=55)	Non-recurrence of AF (n=47)	p Value
<b>LA myocardial characteristics</b>			
LA strain (%)	9.7±2.4	16.2±3.0	<0.001
<b>LA volumetric characteristics</b>			
LA diameter >40 mm	54.5%	44.7%	0.325
LA area >20 cm <sup>2</sup>	50.9%	34%	0.088
LA volume >58 mL	50.9%	40.4%	0.294
LA volume index >28 mL/m <sup>2</sup>	60%	38.3%	0.029
<b>LV characteristics</b>			
LV hypertrophy	50.9%	48.9%	0.844
LVEF (%)	57.0±4.4	56.5±2.9	0.550
LV longitudinal systolic dysfunction	89.1%	68.1%	0.008
LV longitudinal diastolic dysfunction	23.6%	8.5%	0.041
<b>Clinical characteristics</b>			
>75 years of age	18.2%	6.4%	0.076
Type II diabetes	9.1%	8.5%	0.919
Hypertension	80%	63.8%	0.069
Obesity	29.1%	36.2%	0.451
History of CAD	32.7%	14.9%	0.037
CHADS <sub>2</sub> score ≥2	18.2%	17%	0.879
CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2	76.4%	48.9%	0.003
PVI alone	52.7%	59.6%	0.492
PVI + additional LA lesions	47.3%	40.4%	0.492
Duration of AF <12 months	100%	100%	>0.999

Data are expressed as mean ± SD and percentages. Recurrence and non-recurrence of AF during the follow-up period of 15 months. Additional LA lesions, LA linear lesions (LA roof line and mitral isthmus line) and ablation of regions with complex fractionated electrograms. LV longitudinal systolic and diastolic dysfunction was defined as LV strain > -16% and LV SRe <0.95 s<sup>-1</sup>, respectively. LV hypertrophy = LV mass ≥96 g/m<sup>2</sup> in women or ≥116 g/m<sup>2</sup> in men.

AF, atrial fibrillation; CAD, coronary artery disease; LV, left ventricular; LVEF, left ventricular ejection fraction; PVI, pulmonary vein ablation; SRe, early-diastolic strain rate.

differences in the duration of AF or in the type of CA between patients with and without AF recurrence (see table 2).

#### Association of LA strain with recurrence of AF after one CA procedure (primary endpoint)

LA strain showed a significant association with both recurrence and non-recurrence of AF (area under the curve:

0.941;  $p < 0.001$ ) (see figure 2a and b). The best cut-off point related to recurrence of AF was a value of LA strain at 10% (specificity 97.9% and sensitivity 78.2%), whereas the best cut-off point linked to non-recurrence of AF was a value of LA strain at 14.5% (specificity 92.7% and sensitivity 74.5%) (see figure 2a and b). Thus, a value of LA strain between 10% and 14.5% was determined as moderate risk regarding the risk of AF recurrence. There was no association of LA strain with the type of arrhythmia recurrence (eg, paroxysmal or persistent AF or AT).

#### Incremental clinical value of LA strain over conventional LA measurements and comorbidities to predict recurrence of AF after one CA procedure (primary endpoint)

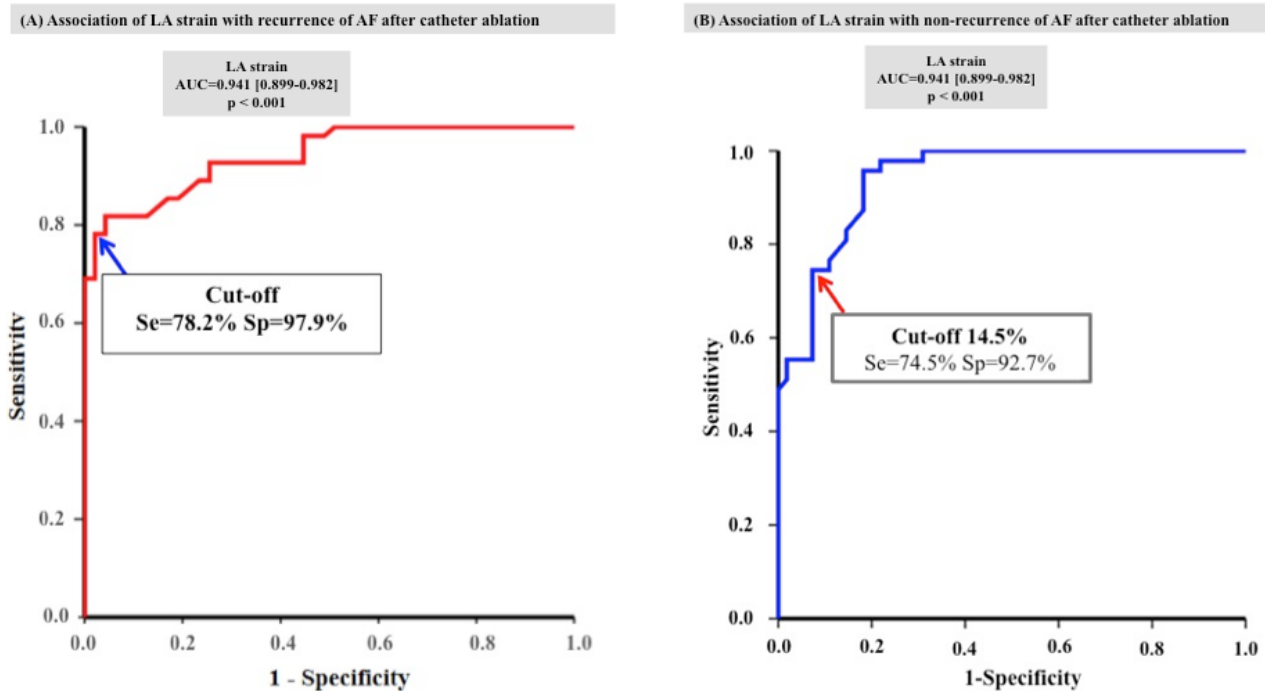
With the purpose of evaluating clinical and echocardiographic factors linked to recurrence of AF after CA, a univariate and multivariate Cox regression analysis was performed. Standard measurements of the left atrium such as LA diameter >40 mm, LA area >20 cm<sup>2</sup>, LA volume >58 mL and LAVI >28 mL/m<sup>2</sup> (ie, LA enlargement) were only weakly associated with recurrence of AF. Analysing the effect of age, comorbidities and LV characteristics on the recurrence of AF, there was also only a poor link between these clinical factors and recurrence of AF after CA. The CHADS<sub>2</sub> index and the CHA<sub>2</sub>DS<sub>2</sub>-VASc index with a score ≥2 were also only weakly associated with recurrence of AF. In addition, LV characteristics such as LV diastolic and systolic dysfunction and LV hypertrophy were also feeble predictors of AF recurrence after CA (table 3).

An LA strain showed a strong association with recurrence of AF after CA. An LA strain <10% was a strong predictor of AF recurrence (HR 6.4 (2.4–16.9),  $p < 0.001$ ; table 3), whereas an LA strain between 10% and 14.5% and >14.5% presented moderate and low risk for AF recurrence (HR 0.7 (0.3–1.4),  $p = 0.305$  and HR 0.2 (0.05–0.7),  $p < 0.001$ ; respectively). In relation to these findings, the rate of recurrence of AF during the entire follow-up period was significantly higher in patients with LA strain <10% than in those with LA strain between 10% and 14.5% and LA strain >14.5% (15 months AF recurrence rate: 97.7%, 42.1% and 10.3%, respectively;  $p < 0.001$ ; see figure 3a and b).

In contrast, concerning conventional LA measurements, there were no important differences in the rate of recurrence of AF between patients with or without LA enlargement (LA diameter >40 mm vs ≤40 mm = recurrence of AF 58.8% vs 49%,  $p = 0.325$ ; LA area >20 cm<sup>2</sup> vs ≤20 cm<sup>2</sup> = recurrence of AF 63.6% vs 46.6%,  $p = 0.088$ ; LA volume >58 mL vs ≤58 mL = recurrence of AF 59.6% vs 49.1%,  $p = 0.294$  and LAVI >28 mL/m<sup>2</sup> vs ≤28 mL/m<sup>2</sup> = recurrence of AF 64.7% vs 43.1%,  $p = 0.029$ ).

#### Accuracy of LA strain to predict recurrence and non-recurrence of AF after one CA procedure (primary endpoint)

An LA strain <10% had a high positive predictive value (PPV) to determine recurrence of AF after CA (97.7% (95% CI 88.2% to 99.6%)) (see table 4).



**Figure 2** AF, atrial fibrillation; AUC, area under the curve; Se, sensitivity; Sp, specificity.

Likewise, an LA strain >14.5% had a high PPV to determine non-recurrence of AF (89.7% (95% CI 76.4% to 95.9%)) (table 4).

#### Association of LA strain with recurrence of AF after two CA procedures (secondary endpoint)

An LA strain was also significantly associated with recurrence of atrial arrhythmias in the secondary outcome analysis (recurrence of atrial arrhythmias after two CA procedures, with or without antiarrhythmic drugs). The rate of recurrence of atrial arrhythmias after two CA procedures in patients with LA strain <10% was significantly higher than in those with LA strain between 10% and 14.5% and LA strain >14.5% (AF recurrence rate: 86%, 11% and 5%, respectively; p<0.001).

#### Accuracy of LA strain to predict recurrence and non-recurrence of AF after two CA procedures (secondary endpoint)

Even after two CA procedures, an LA strain <10% had a high PPV for recurrence of atrial arrhythmias (86.4% (95% CI 73.3% to 93.6%)). Likewise, an LA strain >14.5% had a high PPV to determine non-recurrence of atrial arrhythmias after two CA procedures (94.9% (95% CI 83.1% to 98.6%)).

#### Clinical factors associated with low LA strain

With reference to the factors that could be linked to low LA strain, the combination of comorbidities (determined by CHA<sub>2</sub>DS<sub>2</sub>-VASc index ≥2) and the longitudinal function of the LV were the principal variables associated with low LA strain (table 5). In addition, but to a lesser extent, LA enlargement was also linked to low LA strain (table 5).

## DISCUSSION

CA is an established method for the treatment of patients with paroxysmal AF.<sup>8 18</sup> However, in patients with persistent AF, the results of CA are very variable. While some patients considerably benefit from this procedure, in others, sinus rhythm cannot be maintained for a reasonable amount of time, sometimes even despite several extensive ablation attempts.<sup>1 8 18</sup> In the present study, we performed a comprehensive analysis of the factors associated with the results of CA in a large group of patients with persistent AF, in whom CA was performed with state-of-the-art technology.<sup>18</sup> During a follow-up period of 15 months, we found that patients with low LA strain (<10%) had significantly worse results with CA in comparison with those without low LA strain. In a multivariate Cox regression analysis including clinical and echocardiographic factors, we found that a low LA strain was the principal factor associated with recurrence of AF after CA.

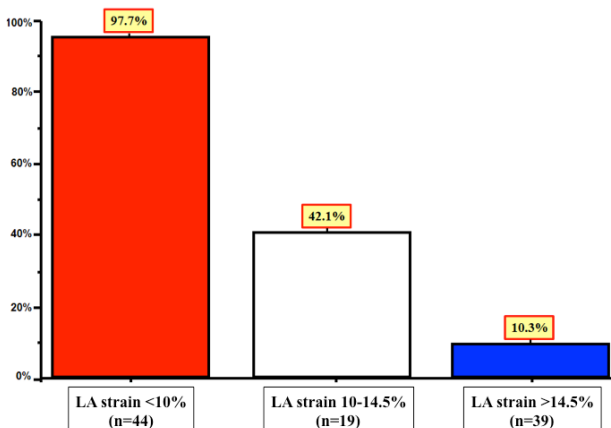
Patients with persistent AF included in previous studies that validated CA were pseudo-characterised as ‘without structural LA alterations’ using conventional echocardiographic measurements such as LA diameter or LA volume.<sup>7 8 18</sup> These orthodox analyses were carried out with the purpose of excluding LA myocardial alterations which could generate recurrence of AF after CA.<sup>9-12</sup> However, recent studies have demonstrated in diverse disorders that with the use of 2DSTE it is possible to detect myocardial alterations of the LA even when conventional echocardiographic analyses are normal.<sup>13 14</sup> In line, the guidelines on AF and CA highlighted that volumetric LA measurements should be considered with caution because complex LA myocardial alterations linked to

**Table 3** Clinical and echocardiographic predictors of recurrence of AF after one catheter ablation (CA) procedure (primary endpoint)

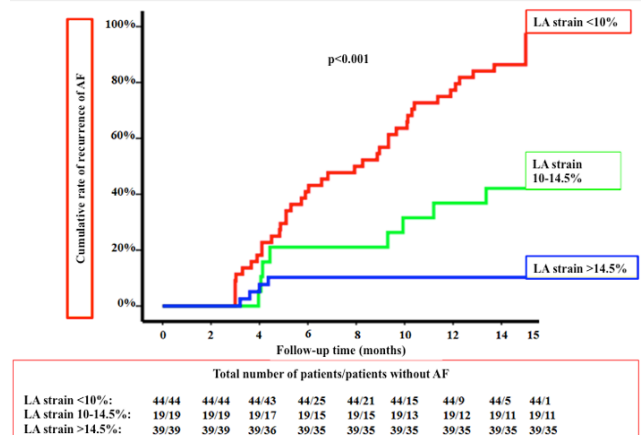
Predictors	Recurrence of AF after one CA procedure					
	Univariate Cox analysis			Multivariate Cox analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
<b>LA myocardial characteristics</b>						
LA strain <10%	9.5	4.9 to 18.5	<0.001	6.4	2.4 to 16.9	<0.001
LA strain 10–14.5%	0.7	0.3 to 1.4	0.305	0.7	0.3 to 1.4	0.305
LA strain >14.5%	0.07	0.02 to 0.2	<0.001	0.2	0.05 to 0.7	<0.001
<b>LA enlargement</b>						
LA diameter >40 mm	1.3	0.7 to 2.2	0.281	0.9	0.4 to 1.9	0.978
LA area >20 cm <sup>2</sup>	1.5	0.9 to 2.6	0.107	1.5	0.9 to 2.6	0.107
LA volume >58 mL	1.3	0.7 to 2.2	0.330	1.3	0.7 to 2.2	0.330
LAVI >28 mL/m <sup>2</sup>	1.8	1.0 to 3.0	0.033	1.6	0.5 to 5.2	0.376
<b>LV function and remodelling</b>						
LV hypertrophy	0.9	0.5 to 1.6	0.923	0.8	0.4 to 1.5	0.579
LV longitudinal systolic dysfunction	2.4	1.0 to 5.7	0.036	0.4	0.1 to 1.5	0.214
LV longitudinal diastolic dysfunction	1.5	0.8 to 2.9	0.161	0.5	0.2 to 1.2	0.146
<b>Clinical characteristics</b>						
>75 years of age	1.7	0.8 to 3.4	0.122	0.4	0.1 to 1.4	0.187
Type II diabetes	0.9	0.3 to 2.3	0.861	0.4	0.1 to 2.0	0.289
Hypertension	1.7	0.9 to 3.4	0.091	1.8	0.8 to 4.1	0.121
Obesity	0.8	0.4 to 1.4	0.499	0.5	0.2 to 1.0	0.087
History of CAD	1.7	0.9 to 3.0	0.059	2.0	0.9 to 4.5	0.076
CHA <sub>2</sub> DS <sub>2</sub> -VAsc score ≥2	2.2	1.2 to 4.1	0.011	0.8	0.3 to 2.1	0.802
CHADS <sub>2</sub> score ≥2	1.0	0.5 to 2.0	0.989	1.5	0.4 to 5.6	0.471
PVI alone	0.9	0.5 to 1.6	0.887	0.9	0.5 to 1.6	0.887
PVI + additional LA lesions	1.0	0.6 to 1.7	0.887	0.6	0.3 to 1.3	0.250

Recurrence of AF during the follow-up period of 15 months. Additional LA lesions, LA linear lesions (LA roof line and mitral isthmus line) and ablation of regions with complex fractionated electrograms. LV longitudinal systolic and diastolic dysfunction was defined as LV strain > -16% and LV SRe <0.95 s<sup>-1</sup>, respectively. LV hypertrophy = LV mass ≥96 g/m<sup>2</sup> in women or ≥116 g/m<sup>2</sup> in men. AF, atrial fibrillation; CAD, coronary artery disease; LAVI, LA volume index; LV, left ventricular; PVI, pulmonary vein ablation; SRe, early-diastolic strain rate.

(A) Rate of recurrence of AF after catheter ablation in relation to the values of LA strain



(B) Rate of recurrence of AF after catheter ablation during follow-up period regarding the values of LA strain



**Figure 3** AF, atrial fibrillation.

**Table 4** Accuracy of LA strain to predict outcomes after one catheter ablation (CA) procedure (primary endpoint)

Recurrence of AF after one CA procedure					
	Specificity (95% CI)	Sensitivity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
LA strain <10%	97.9% (88.9% to 99.6%)	78.2% (65.6% to 87.1%)	97.7% (88.2% to 99.6%)	79.3% (67.2% to 87.7%)	87.3% (80.8% to 93.7%)
Non-recurrence of AF after one CA procedure					
	Specificity (95% CI)	Sensitivity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
LA strain >14.5%	92.7% (82.7% to 97.1%)	74.5% (60.5% to 84.7%)	89.7% (76.4% to 95.9%)	81.0% (69.6% to 88.8%)	84.3% (77.3% to 91.4%)

Recurrence and non-recurrence of AF during the follow-up period of 15 months. AF, atrial fibrillation; NPV, negative predictive value; PPV, positive predictive value.

recurrence of AF could not be detected by conventional analyses of the LA.<sup>18</sup>

Recent investigations using LA strain imaging evidenced LA myocardial abnormalities linked to recurrence of AF after CA in patients with paroxysmal AF, which were not detectable by volumetric measurements of the left atrium.<sup>14</sup>

In addition, several studies showed the superiority of LA strain over conventional LA measurements and comorbidities to predict recurrence of AF after CA in subjects with paroxysmal AF.<sup>14–17</sup> However, the clinical relevance of LA strain imaging exclusively in patients with persistent AF, especially those who present with AF at the time of LA strain

**Table 5** Clinical and echocardiographic variables linked to low LA strain

Low LA strain (LA strain <10%)						
Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
<b>LA enlargement</b>						
LA diameter >40 mm	2.2	1.0 to 5.0	0.047	2.8	0.8 to 10.3	0.105
LA area >20 cm <sup>2</sup>	2.7	1.2 to 6.0	0.016	2.7	0.8 to 6.0	0.199
LA volume >58 mL	2.1	0.9 to 4.7	0.060	2.1	0.8 to 4.5	0.099
LAVI >28 mL/m <sup>2</sup>	3.7	1.6 to 8.6	0.002	11.3	0.6 to >100	0.094
<b>LV function and remodelling</b>						
LV hypertrophy	1.1	0.5 to 2.5	0.689	0.7	0.2 to 2.4	0.674
LV longitudinal systolic dysfunction	10.2	2.2 to 46.8	0.003	8.6	1.3 to 56.7	0.025
LV longitudinal diastolic dysfunction	5.6	1.6 to 18.8	0.005	7.5	1.3 to 41.1	0.019
<b>Comorbidities</b>						
>75 years of age	3.4	0.9 to 12.1	0.051	4.9	0.5 to 43.4	0.148
Type II diabetes	1.0	0.2 to 4.2	0.934	2.5	0.2 to 29.4	0.443
Hypertension	3.0	1.1 to 7.9	0.026	1.6	0.3 to 6.7	0.496
Obesity	0.9	0.4 to 2.2	0.920	0.3	0.1 to 1.2	0.095
History of CAD	1.6	0.6 to 3.9	0.305	0.3	0.1 to 1.3	0.131
CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2	4.5	1.7 to 11.3	0.001	5.3	1.3 to 20.9	0.017
CHADS <sub>2</sub> score ≥2	1.0	0.3 to 2.9	0.902	0.2	0.1 to 2.0	0.172

LV longitudinal systolic and diastolic dysfunction was defined as LV strain > -16% and LV SRe <0.95 s<sup>-1</sup>, respectively. LV hypertrophy = LV mass ≥96 g/m<sup>2</sup> in women or ≥116 g/m<sup>2</sup> in men.

CAD, coronary artery disease; LAVI, LA volume index; LV, left ventricular; SRe, early-diastolic strain rate.



analysis is so far unknown. In the present study, we found that a low LA strain (<10%) was strongly linked to recurrence of AF after CA in patients with persistent AF even after two CA procedures. On the contrary, we evidenced that in these patients conventional LA measurements as well as comorbidities were not predictive for recurrence of AF. Therefore, we consider that the analysis of the left atrium using LA strain imaging could be of great importance in the management of patients with persistent AF.

Since patients with persistent AF are often admitted with AF for counselling regarding therapeutic options, performing LA 'functional' analyses in sinus rhythm in these patients is often difficult and inconsistent.<sup>23–27</sup> On the other hand, when LA analyses are performed during AF, LA myocardial measurements such as LA strain may be able to indirectly indicate the grade of LA fibrosis.<sup>28–30</sup> In this regard, recent findings have proven the strong correlation of the grade of LA fibrosis as detected by cardiac MRI using dedicated software algorithms with LA strain in patients with persistent AF.<sup>28–29</sup> In agreement, recent studies have demonstrated a significant link between the severity of LA fibrosis and the recurrence of AF after CA.<sup>30–34</sup>

### Limitations

Some considerations should be taken into account on this study. Recent studies evidenced that 2DSTE values of the LV vary between different software packages such as GE, Philips and Toshiba.<sup>35</sup> Thus, while there are no data showing a variability between different ultrasound software packages regarding LA analyses, LA strain values should be considered according to the ultrasound software package used (namely, the GE software was used in this study, which so far is the most extensively validated software to analyse the LA with 2DSTE).<sup>13–14, 20, 23, 30</sup> Furthermore, we did not compare the echocardiographic analyses of the left atrium with those performed by MRI, which recently has shown that it might have an interesting role in patients with persistent AF because it could detect LA fibrosis.<sup>31–34</sup> Notwithstanding, recent findings evidenced a significant inverse relationship between the grade of LA fibrosis and the values of LA strain.<sup>28–30</sup> Additionally, it is worth mentioning that the cut-off of LA strain to predict recurrence of AF after CA could only be applied to patients with the characteristics of inclusion of this study. Hence, patients with continuous AF >12 months or subjects in sinus rhythm might present different values of LA strain to determine recurrence of AF after CA.

### CONCLUSIONS

Low LA strain (<10%) during AF is highly predictive for recurrence of atrial arrhythmias after one or two CA procedures in patients with persistent AF. Our findings suggest that analysis of LA strain could be of great usefulness to stratify patients with persistent AF prior to CA. These results should be further evaluated in multicentre trials.

**Competing interests** None declared.

**Patient consent** Patients included in this study had signed the patient consent form of our department approved by the ethics committee of Charité.

**Ethics approval** Charité – Universitätsmedizin Berlin ethics committee. The institutional review board approved this study (clinical research project EA211513).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** There are no additional unpublished data from the study.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

### REFERENCES

- Nault I, Miyazaki S, Forclaz A, *et al.* Drugs vs ablation for the treatment of atrial fibrillation: the evidence supporting catheter ablation. *Eur Heart J* 2010;31:1046–54.
- Brooks AG, Stiles MK, Laborde J, *et al.* Outcomes of longstanding persistent atrial fibrillation ablation: a systematic review. *Heart Rhythm* 2010;7:835–46.
- Hayward RM, Upadhyay GA, Mela T, *et al.* Pulmonary vein isolation with complex fractionated atrial electrogram ablation for paroxysmal and nonparoxysmal atrial fibrillation: a meta-analysis. *Heart Rhythm* 2011;8:994–1000.
- Chen HS, Wen JM, Sn W, *et al.* Catheter ablation for paroxysmal and persistent atrial fibrillation. *Cochrane Database Syst Rev* 2012;4:CD007101.
- Sorgente A, Tung P, Wylie J, *et al.* Six year follow-up after catheter ablation of atrial fibrillation: a palliation more than a true cure. *Am J Cardiol* 2012;109:1179–86.
- D'Ascenzo F, Corleto A, Biondi-Zoccai G, *et al.* Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. *Int J Cardiol* 2013;167:1984–9.
- Mont L, Bisbal F, Hernández-Madrid A, *et al.* Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* 2014;35:501–7.
- Camm AJ, Lip GY, De Caterina R, *et al.* Focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Europace* 2012;2012:1385–413.
- Everett TH, Wilson EE, Verheule S, *et al.* Structural atrial remodeling alters the substrate and spatiotemporal organization of atrial fibrillation: a comparison in canine models of structural and electrical atrial remodeling. *Am J Physiol Heart Circ Physiol* 2006;291:H2911–23.
- Takahashi Y, O'Neill MD, Hocini M, *et al.* Effects of stepwise ablation of chronic atrial fibrillation on atrial electrical and mechanical properties. *J Am Coll Cardiol* 2007;49:1306–14.
- Nishida K, Sarrazin JF, Fujiki A, *et al.* Roles of the left atrial roof and pulmonary veins in the anatomic substrate for persistent atrial fibrillation and ablation in a canine model. *J Am Coll Cardiol* 2010;56:1728–36.
- Hunter RJ, Liu Y, Lu Y, *et al.* Left atrial wall stress distribution and its relationship to electrophysiologic remodeling in persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2012;5:351–60.
- Mondillo S, Cameli M, Caputo ML, *et al.* Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. *J Am Soc Echocardiogr* 2011;24:898–908.
- Morris DA, Parwani A, Huemer M, *et al.* Clinical significance of the assessment of the systolic and diastolic myocardial function of the left atrium in patients with paroxysmal atrial fibrillation and low CHADS<sub>2</sub> index treated with catheter ablation therapy. *Am J Cardiol* 2013;111:1002–11.
- Hwang HJ, Choi EY, Rhee SJ, *et al.* Left atrial strain as predictor of successful outcomes in catheter ablation for atrial fibrillation: a two-dimensional myocardial imaging study. *J Interv Card Electrophysiol* 2009;26:127–32.
- Mirza M, Caracciolo G, Khan U, *et al.* Left atrial reservoir function predicts atrial fibrillation recurrence after catheter ablation: a two-dimensional speckle strain study. *J Interv Card Electrophysiol* 2011;31:197–206.

17. Hammerstingl C, Schwekendiek M, Momcilovic D, *et al.* Left atrial deformation imaging with ultrasound based two-dimensional speckle-tracking predicts the rate of recurrence of paroxysmal and persistent atrial fibrillation after successful ablation procedures. *J Cardiovasc Electrophysiol* 2012;23:247–55.
18. Calkins H, Kuck KH, Cappato R, *et al.*; On behalf of Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. *Heart Rhythm* 2012;9:632–96.
19. Lang RM, Bierig M, Devereux RB, *et al.* Recommendations for chamber quantification. *J Am Soc Echocardiogr* 2005;18:1440–63.
20. Morris DA, Gailani M, Vaz Pérez A, *et al.* Left atrial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. *J Am Soc Echocardiogr* 2011;24:651–62.
21. Morris DA, Boldt LH, Eichstädt H, *et al.* Myocardial systolic and diastolic performance derived by 2-dimensional speckle tracking echocardiography in heart failure with normal left ventricular ejection fraction. *Circ Heart Fail* 2012;5:610–20.
22. Morris DA, Otani K, Bekfani T, *et al.* Multidirectional global left ventricular systolic function in normal subjects and patients with hypertension: multicenter evaluation. *J Am Soc Echocardiogr* 2014;27:493–500.
23. Shih JY, Tsai WC, Huang YY, *et al.* Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation. *J Am Soc Echocardiogr* 2011;24:513–9.
24. Dogan A, Gedikli O, Ozaydin M, *et al.* Mitral annular velocity by Doppler tissue imaging for the evaluation of atrial stunning after cardioversion of atrial fibrillation. *Int J Cardiovasc Imaging* 2009;25:113–20.
25. Thomas MD, Kalra PR, Jones A, *et al.* Time course for recovery of atrial mechanical and endocrine function post DC cardioversion for persistent atrial fibrillation. *Int J Cardiol* 2005;102:487–91.
26. Mattioli AV, Sansoni S, Lucchi GR, *et al.* Serial evaluation of left atrial dimension after cardioversion for atrial fibrillation and relation to atrial function. *Am J Cardiol* 2000;85:832–6.
27. Sanders P, Morton JB, Kistler PM, *et al.* Reversal of atrial mechanical dysfunction after cardioversion of atrial fibrillation: implications for the mechanisms of tachycardia-mediated atrial cardiomyopathy. *Circulation* 2003;108:1976–84.
28. Kuppahally SS, Akoum N, Burgon NS, *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.
29. Kuppahally SS, Akoum N, Badger TJ, *et al.* Echocardiographic left atrial reverse remodeling after catheter ablation of atrial fibrillation is predicted by preablation delayed enhancement of left atrium by magnetic resonance imaging. *Am Heart J* 2010;160:877–84.
30. Cameli M, Lisi M, Righini FM, *et al.* Usefulness of atrial deformation analysis to predict left atrial fibrosis and endocardial thickness in patients undergoing mitral valve operations for severe mitral regurgitation secondary to mitral valve prolapse. *Am J Cardiol* 2013;111:595–601.
31. Oakes RS, Badger TJ, Kholmovski EG, *et al.* Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. *Circulation* 2009;119:1758–67.
32. Mahnkopf C, Badger TJ, Burgon NS, *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.
33. Marrouche NF, Wilber D, Hindricks G, *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.
34. McGann C, Akoum N, Patel A, *et al.* Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. *Circ Arrhythm Electrophysiol* 2014;7:23–30.
35. Biaggi P, Carasso S, Garceau P, *et al.* Comparison of two different speckle tracking software systems: does the method matter? *Echocardiography* 2011;28:539–47.