CLINICAL RESEARCH

Predicting favourable outcomes in the setting of radiofrequency catheter ablation of long-standing persistent atrial fibrillation: A pilot study assessing the value of left atrial appendage peak flow velocity

Prévoir les résultats favorables après l’ablation par radiofréquence de la fibrillation auriculaire persistante — Étude pilote sur l’intérêt la mesure de la vitesse de l’auricule gauche auriculaire

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KEYWORDS
Atrial fibrillation; Left atrial appendage peak flow velocity; Catheter ablation; Echocardiography; Radiofrequency

Summary
Background. — Catheter ablation is an effective and potentially curative treatment in patients with atrial fibrillation (AF).
Aim. — To test the hypothesis that left atrial appendage peak flow velocity (LAV) assessed by echocardiography can accurately predict successful catheter ablation as well as favourable outcome in the setting of long-standing persistent AF.
Methods. — This prospective pilot study enrolled 40 patients with long-standing persistent AF (age 60 ± 11 years; persistence of AF 4.2 ± 2 years) who underwent a first catheter ablation

Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; IQR, international normalized ratio; LAV, left atrial appendage peak flow velocity; OR, odds ratio; ROC, receiver operating characteristics.
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Background

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia. If untreated, it leads to an increase in cardiovascular morbidity—particularly embolic stroke—and mortality [1]. Catheter ablation has been demonstrated to be a very effective and potentially curative treatment in patients with paroxysmal AF [2–4]. In contrast, results regarding persistent AF, especially long-standing persistent AF, are more controversial, with largely varying success rates [5–7]. Accordingly, in the setting of long-standing persistent AF, the optimization of candidate selection should improve the success rate of these procedures and therefore favourably increase the benefit/risk ratio of this invasive strategy.

A number of variables have been found to have a potential role in predicting successful catheter ablation and recurrence risk: duration of AF; surface electrocardiogram AF cycle length; patient age; left atrial diameter; left ventricular function; and, more recently, magnetic resonance imaging delayed enhancement of the left atrium [8–10].

Taken separately, however, the predictive value of each of these variables remains relatively low and of limited interest in routine clinical practice.

Given the pathophysiology of AF, we hypothesized that high left atrial appendage peak flow velocity (LAV) assessed by transesophageal echocardiography before catheter ablation procedure would accurately predict successful procedure and favourable outcome.

Methods

Study population and exclusion criteria

Forty patients who had undergone first-time radiofrequency catheter ablation for long-standing persistent AF were enrolled from January 2009 and followed until May 2010 (ClinicalTrials.gov ID: NCT01144858). Long-standing persistent AF was defined as AF that has been present for 1 year or more, resistant to at least one electrical or pharmacological procedure using a standardized sequential stepwise protocol. LAV was assessed before the catheter ablation procedure along with classical factors (age, sex, left atrial area, AF cycle length, AF duration and left ventricular ejection fraction), all of which were tested using logistic regression for ability to predict restoration of sinus rhythm during catheter ablation as well as absence of recurrence during a 1-year follow-up.

Results. — Eighteen patients (45%) experienced AF termination during the procedure and 18 patients (45%) did not develop any recurrence during the first 12 months. Multivariable analysis demonstrated that high LAV (> 0.3 m/s) was the only independent predictor of AF termination (odds ratio 5.91, 95% confidence interval 1.06–32.88; \( P = 0.04 \)) and absence of recurrence at 1 year (odds ratio 4.33, 95% confidence interval 1.05–17.81; \( P = 0.04 \)).

Conclusions. — This pilot study demonstrated the feasibility and importance of LAV measurement in the setting of long-standing persistent AF to predict successful catheter ablation and favourable mid-term outcome.

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cardioversion and for which a rhythm control strategy was decided. Exclusion criteria included: age < 18 or > 80 years; severe valvular disease requiring surgery; valve prosthesis; known severe coronary artery disease; atrial and/or ventricular thrombosis; New York Heart Association functional class III—IV; cerebrovascular disease; pulmonary embolism; and latent or manifest hyperthyroidism. All patients gave their written informed consent.

**Echocardiography study**

A complete echocardiographic evaluation was carried out within 48 hours before the procedure using the conventional transthoracic approach and then transoesophageal echocardiography was carried out by two different physicians in a blinded fashion.

First, conventional transthoracic echocardiography was performed before and after AF catheter ablation (IE33 System; Philips Medical Systems, Andover, MA, USA) with routine echocardiographic measurements, using parasternal short and long axes, and apical four- and two-chamber views. The left atrium area was obtained via apical four-chamber zoomed views of the left atrium. Images and pulse Doppler flows of mitral inflow and tissue Doppler imaging at the mitral annulus were acquired from the four-chamber views.

Second, all patients were evaluated before catheter ablation by complete transoesophageal echocardiography with multiplane probes using a 7-MHz transducer (Vivid i; General Electric Medical Health, Horten, Norway). Left atrial spontaneous contrast and thrombus were sought. After a complete analysis of the left atrial appendage at the base of the heart with rotation of the probe between 0° and 180°, the incidence with the best alignment of the cursor with the appendage long axis was selected. The cursor was placed at the entry of the appendage for pulsed Doppler analysis and we considered the average value of 10 consecutive fibrillatory emptying waves (Fig. 1) [11].

**Outcome measures**

The primary outcome was restoration of sinus rhythm during the catheter ablation procedure. The second outcome was absence of recurrence of atrial arrhythmias (AF, atrial tachycardia or flutter) during the year following the procedure.

**Electrophysiological study and catheter ablation procedure**

All patients received effective anticoagulation therapy (vitamin K antagonists, target international normalized ratio [INR] of 2–3) for more than 1 month before ablation. This therapy was interrupted at least 48 hours before the procedure, with a heparin bridge. All antiarrhythmic drugs were discontinued 1 week before the procedure, except for amiodarone, which was maintained.

The electrophysiological study was performed under general anaesthesia using a standard protocol. The following catheters were introduced via the femoral vein: a steerable quadripolar catheter (Xtreme; Sorin Group, Le Plessis-Robinson, France) was positioned within the coronary sinus; a circumferential mapping catheter (Lasso; Biosense Webster, Diamond Bar, CA, USA) was introduced after transseptal access; and a 4-mm externally irrigated-tip ablation catheter (Thermocool, Biosense Webster) was used for mapping and ablation. After transseptal access, a single bolus of heparin (100 IU/kg body weight) was administered. The infusion was adjusted to maintain an activated coagulation time of 300 s or more. The transeptal sheath was also continuously infused with heparinized saline during the procedure.

Surface electrocardiograms (ECGs) and endocardial electrograms were continuously monitored and recorded for off-line analysis (Bard Electrophysiology, Lowell, MA, USA). Following transseptal catheterization, left atrial and coronary sinus electroanatomical mapping (Carto 3; Biosense Webster) was performed during spontaneous AF. Computed tomography registration and fusion of left atrial reconstructions with the electroanatomical map were subsequently performed. Endocardial AF cycle length was determined from intracardiac recordings at the left atrial appendage before ablation and was averaged for 30 consecutive intervals.

In all patients, sequential stepwise ablation described by O’Neill et al. [6], was performed by the same operator, blinded to the echocardiographic data. The procedure was terminated with the step that allowed AF conversion into sinus rhythm and no antiarrhythmic treatment was prescribed during the procedural period or during the procedure. In all cases, circular and linear lesions were verified after sinus rhythm restoration. The first step involved pulmonary vein isolation. The second step included linear ablation in the left atrium: a roof line was drawn between the right and left superior pulmonary veins and, if AF persisted, a mitral isthmus line was drawn from the mitral annulus to the left inferior pulmonary vein and coronary sinus defragmentation was performed. The third step consisted of electrogram-based ablation of complex fractionated atrial electrograms in the left and right atria [5]. Complex fractionated atrial electrogram sites were tagged on the geometry obtained from three-dimensional mapping during AF. Lastly, a cavotricuspid isthmus line was performed only in patients with a history of common atrial flutter with ECG documentation.

When AF was converted to a regular arrhythmia, activation and entrainment mapping were performed to differentiate between focal and re-entrant mechanisms. Atrial tachycardias were targeted for ablation until sinus rhythm was achieved. When sinus rhythm was not restored by ablation, AF or atrial tachycardia was terminated by electrical cardioversion and the procedure was considered as a failure. After restoration of sinus rhythm, assessment of conduction block across the lines was performed in all patients [12]. When necessary, supplemental radiofrequency energy was delivered to achieve block.

**Discharge, follow-up plan and AF recurrence assessment**

Treatment with vitamin K antagonists was resumed 1 day after the procedure and patients were discharged on day 3 receiving low-molecular-weight heparin until they had two
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consecutive international normalized ratios > 2. Patients were assessed before discharge and at the third, sixth and 12th months by clinical interview, echocardiography and 24-h Holter monitoring. In addition, patients were instructed to call their cardiologist in case of sustained palpitation, for immediate ECG recording. Vitamin K antagonists were prescribed for a minimum of 3 months and potentially discontinued in case of low thromboembolic score (CHADS2 score 0 or 1). Amiodarone was continued for at least 3 months in patients who were receiving amiodarone before the procedure and was interrupted in case of no recurrence at 3 months. Recurrence was defined as any symptomatic or asymptomatic atrial arrhythmia lasting > 30 s; it was evidenced by Holter monitoring at 3, 6 and 12 months or by 12-lead ECG in case of symptomatic palpitation at clinical interview.

Statistical analysis

Categorical variables are expressed as number and proportion, and continuous variables are expressed as mean ± standard deviation. Comparison of baseline characteristics of patients with and without AF termination by catheter ablation was performed using the χ² test or Fisher’s exact test (as appropriate) for categorical variables and Wilcoxon’s test for continuous variables. All tests were two-sided. A P value < 0.05 was considered statistically significant.

LAV (highly associated with favourable outcome) was studied by analysis of receiver operating characteristics (ROC) to determine optimal cutoff values for the prediction of successful catheter ablation. ROC was evaluated using a plot of the true positive fraction (sensitivity) versus the true negative fraction (1—specificity) with a continuously varying decision threshold. The best cutoff value was defined as the point combining the highest sensitivity and specificity.

Age, duration of AF, LAV, left ventricular ejection fraction, left atrial area and AF cycle length from the left atrial appendage were considered in a logistic regression model to identify criteria associated with successful catheter ablation procedure. Categorized variables with a P value < 0.20 in univariate analysis were then considered in a logistic regression model to identify independent predictors of AF termination by ablation. A similar analysis was performed regarding the absence of AF recurrence during the 1-year period. All statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The mean age of patients was 59.9 ± 11 years and 34 were men (85%). The mean duration of AF was 4.2 ± 2 years; all (except one patient with a formal contraindication) were receiving amiodarone at the time of the procedure. All patients were symptomatic for dyspnoea and/or palpitations. The mean left ventricular ejection fraction was normal (59.4 ± 9%) despite the presence of structural heart disease in 23 patients (57%), mainly related to ischaemic heart disease. Echocardiography demonstrated moderate-to-severe left atrial enlargement with a mean left atrial area of 26 ± 7.3 cm² (IQR, 20 to 30). Transmural flow variables in persistent AF (peak E and E/e') were measured (82.3 ± 29.8 cm/s and 13.1 ± 2.1, respectively). Spontaneous echo contrast was found in the left atrium in 42% of patients. The group of patients with an LAV > 0.30 m/s had significantly more spontaneous echo contrast than the group of patients with a higher LAV (63% vs 11%; P = 0.001). An electrophysiology study found a mean AF cycle length in the left atrial appendage of around 176 ± 20 ms. LAV was 0.30 ± 0.12 m/s (IQR, 0.24 to 0.34) (Fig. 1).

Procedural results

The results are summarized in Fig. 2. Twenty-six of the 40 patients (65%) had acute termination of AF during radiofrequency ablation (direct AF termination to sinus rhythm or via atrial tachycardia) and 18 patients (45%) in whom sinus rhythm was restored without electrical cardioversion.

Among the 10 patients with direct termination to sinus rhythm, AF termination occurred in two patients (20%) during pulmonary vein isolation and in four patients (40%) during line ablation. Defragmentation of the left atria resulted in direct termination to sinus rhythm in three patients (30%). Defragmentation of the right atria led to termination directly to sinus rhythm in one patient (10%).
AF organized into atrial tachycardia in 16 patients, eight of whom converted into sinus rhythm with further ablation. The atrial tachycardia mechanisms were perimital (n = 4), cavotricuspid isthmus dependent (n = 1) and focal (n = 3). Among the 16 patients with atrial tachycardia, two had AF organization to atrial tachycardia after pulmonary vein isolation, two after roof line, three after mitral isthmus line and six after coronary sinus defragmentation. In the additional three patients, AF organized into atrial tachycardia during subsequent complex fractionated atrial electrogram ablation.

The 14 patients (35%) who did not experience AF termination after stepwise ablation underwent electrical cardioversion.

Mean procedural time was 201 ± 43 minutes with a fluoroscopy time of 46 ± 19 minutes.

**Prediction of AF termination during catheter ablation procedure**

Comparison of baseline characteristics between patients with and without AF termination is shown in Table 1. Using regression analysis, shorter AF duration (odds ratio [OR] 4.86, 95% confidence interval [CI] 1.21—19.47; P = 0.03), high LVA (OR 8.67, 95% CI 2.01—37.36; P < 0.01), smaller left atrial area (OR 3.81, 95% CI 0.99—14.64; P = 0.05) and longer AF cycle length in the left atrial appendage (OR 4.89, 95% CI 1.25—19.19; P = 0.02) were all significantly associated with perprocedural AF termination (Table 2). However, in multivariable analysis, only LAV remained significant (OR 5.91, 95% CI 1.06—32.88; P = 0.04).

Based on ROC curve analysis of LAV (Fig. 3), the optimal cutoff point was 0.30 m/s, with a specificity of 72.8% and a sensitivity of 77.8% for predicting procedural AF.
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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients with and without atrial fibrillation (AF) termination during the procedure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>No AF termination (n = 22)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.1 ± 8.6</td>
</tr>
<tr>
<td>Men</td>
<td>19 (86)</td>
</tr>
<tr>
<td>Duration of AF (months)</td>
<td>56.3 ± 39.0</td>
</tr>
<tr>
<td>LAV (m/s)</td>
<td>0.24 ± 0.09</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57.2 ± 9.2</td>
</tr>
<tr>
<td>Left atrial area (cm²)</td>
<td>28.6 ± 6.1</td>
</tr>
<tr>
<td>AF cycle length (ms)</td>
<td>170.0 ± 20.3</td>
</tr>
<tr>
<td>Peak E (cm/s)</td>
<td>85.4 ± 30.1</td>
</tr>
<tr>
<td>E/e' index</td>
<td>13.2 ± 2.3</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation or number (%) of patients. AF: atrial fibrillation; LAV: left atrial appendage peak flow velocity; LVEF: left ventricular ejection fraction.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Predictive analysis of atrial fibrillation (AF) termination by catheter ablation.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis OR (95% CI)</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>1.28 (0.36–4.60)</td>
</tr>
<tr>
<td>Duration of AF &lt; 25 months</td>
<td>4.86 (1.21–19.47)</td>
</tr>
<tr>
<td>LAV &gt; 0.30 m/s</td>
<td>8.67 (2.01–37.36)</td>
</tr>
<tr>
<td>LVEF &gt; 60%</td>
<td>3.47 (0.90–13.31)</td>
</tr>
<tr>
<td>Left atrial area &lt; 25 cm²</td>
<td>3.81 (0.99–14.64)</td>
</tr>
<tr>
<td>AF cycle length &gt; 175 ms</td>
<td>4.89 (1.25–19.19)</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; CI: confidence interval; LAV: left atrial appendage peak flow velocity; LVEF: left ventricular ejection fraction; OR: odds ratio.

termination; the area under the curve was estimated to be 0.81 (95% CI 0.68–0.95; P < 0.001). The cutoff point of 0.30 m/s corresponded to positive and negative predictive values of 70% and 80%, respectively. Moreover, by combining both LAV > 0.30 m/s and left atrial area < 25 cm², the specificity reached 100% for predicting procedural AF termination (sensitivity, 50%; positive predictive value, 100%; negative predictive value, 71%).

**Prediction of no atrial arrhythmia recurrences during the 1-year follow-up**

The 1-year follow-up was completed in all patients. Overall, sinus rhythm was maintained in 18 patients (45%). Eight patients from the no termination AF group were in persistent sinus rhythm during the follow-up at 1 year. AF cycle length was longer in patients without AF recurrence (167.2 ± 16 ms vs 183.9 ± 17 ms; P = 0.01). There were no significant differences regarding left atrial area, AF duration, left ventricular ejection fraction and demographics between the two groups. In contrast, LAV was higher in the recurrence-free group during the follow-up (0.25 ± 0.10 m/s vs 0.36 ± 0.13 m/s; P = 0.006); AF recurrence rates at 1 year according to LAV (cutoff value fixed at 0.30 m/s) differed significantly (75% vs 35%; P = 0.01) (Fig. 2). Logistic regression analysis is presented in Table 3. In multivariable analysis, only LAV remained significant for predicting AF recurrence (OR 4.33, 95% CI 1.05–17.81; P = 0.04).

**Discussion**

In this pilot study, carried out in the setting of long-standing AF, LAV measurement has been found to be of particular interest in predicting procedural success of catheter ablation as well as arrhythmia recurrence rate at mid term.

Catheter ablation of AF has been used for about 10 years. For long-standing persistent AF, ablation strategies vary considerably between centres and success rates range between 38% and >62% after one procedure [13–15]. To improve global results, optimization of patient selection must be carried out; identification of predictors of favourable outcomes, using minimally invasive measurements, is crucial in this setting.

The concept of a link between LAV and clinical outcome is based on a solid rationale. Important literature emphasized the central role of atrial tissue mass and histology in the pathogenesis of AF [16]. In persistent AF, the left atrium undergoes remodelling processes that are believed to be pathophysiological factors for persistence of AF [17]. In addition to structural remodelling mainly focused on the intercellular matrix, AF causes atrial electrophysiological remodelling, changes in connexin density and distribution, cellular structural remodelling, myolysis and glycogen accumulation, according to the well-known concept summarized as ‘AF begets AF’ [18–20]. LA function is difficult to assess non-invasively and some studies have evaluated left atrial appendage function—particularly LAV—as a surrogate [21]. Peak left atrial appendage emptying velocity appears to be
Table 3 Predictive analysis of the absence of atrial arrhythmia recurrence at 1-year follow-up.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate analysis OR (95% CI)</th>
<th>P</th>
<th>Multivariable analysis OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>0.84 (0.23–3.02)</td>
<td>0.79</td>
<td>4.33 (1.05–17.81)</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of AF &lt; 25 months</td>
<td>1.97 (0.51–7.05)</td>
<td>0.33</td>
<td>2.20 (0.60–8.08)</td>
<td>0.26</td>
</tr>
<tr>
<td>LAV &gt; 0.30 m/s</td>
<td>5.14 (1.30–20.36)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &gt; 60%</td>
<td>1.56 (0.43–5.64)</td>
<td>0.50</td>
<td></td>
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</tr>
<tr>
<td>Left atrial area &lt; 25 cm²</td>
<td>1.60 (0.82–11.44)</td>
<td>0.09</td>
<td>2.25 (0.55–9.28)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; CI: confidence interval; LAV: left atrial appendage peak flow velocity; LVEF: left ventricular ejection fraction; OR: odds ratio.

a complex variable that depends on left atrial function [22]. Left atrium and left atrial appendage are two distinct histological structures. Because of its increased distensibility, the left atrial appendage may increase its haemodynamic function by modulating left atrial pressure-volume relations in states of increased left atrial pressure and volume overload or atrial fibrosis [23]. This replacement of atrial contractile tissue by fibrosis supports our hypothesis that a lower LAV would be associated with a higher rate of catheter ablation procedure success and a higher rate of recurrence at mid-term.

Only a few previous studies have investigated the importance of LAV measured by transoesophageal echocardiography before AF cardioversion. These studies showed that LAV is one of the strongest predictors of atrial dysfunction and sinus rhythm persistence after AF electrical cardioversion [24,25]. In a prospective multicentre study of 193 patients, Antonielli et al. [26] showed that LAV > 0.40 m/s could independently predict sinus rhythm persistence at 1-year after successful electrical cardioversion, with a negative predictive value of 66% and a positive predictive value of 73%. To our knowledge, our pilot study is the first demonstrating that high LAV is a predictor of immediate and mid-term success after AF catheter ablation.

A number of series of patients treated for long-standing persistent AF demonstrated that perprocedural termination of persistent AF is associated with a better clinical outcome [13,27,28]. As in our study, AF termination and long-term persistence of sinus rhythm after AF ablation were strongly linked, with very similar predicting factors [29]. In a study of catheter ablation for persistent AF, Matsuo et al. demonstrated that long AF cycle length on surface electrocardiograms is independently associated with sinus rhythm persistence [9]. Left atrial dimension, a well-known marker of left atrial disease, has been found to be inferior to AF cycle length as a predictor of the occurrence of subsequent atrial tachycardia [30,31]. In a group of 148 patients, Berruezo et al. demonstrated that the anterior-posterior left atrial diameter was an independent predictor of AF recurrence after AF catheter ablation [32]. These findings were confirmed by Shin et al. who found left atrial volume to be a significant predictor of AF recurrence after catheter ablation in a group of 68 patients [33]. In our study, left atrial dimension was significantly associated with perprocedural AF termination in univariate analysis. After adjustment, we noted only a slight trend for predicting arrhythmia recurrence, which remained non-significant mainly due to the limited number of patients enrolled in this pilot study. Significantly dilated atria are generally thought to be associated with a high degree of atrial remodelling, which limits the efficacy of catheter ablation. Recent studies [34] demonstrated that the degree of fibrosis detected by sophisticated imaging systems was highly associated with procedural success and outcome, emphasizing our hypothesis that a low LAV is a predictor of an unfavourable outcome; a recent study by Mahnkopf et al. demonstrated that increased delayed enhancement within the left atrial wall on magnetic resonance imaging is strongly associated with AF recurrence, regardless of the type of AF and the patient’s comorbidities [35]. Additionally, in a cohort of 81 patients, Oakes et al. reported that late gadolinium enhancement of the left atrium on magnetic resonance imaging was correlated with the extent of left atrial fibrosis measured by a voltage map and with the odds of procedural success [10].

Study limitations

Although our study is the first to prospectively evaluate the value of LA appendage velocity in the setting of long-standing persistent AF, we acknowledge some limitations. First, our sample size was small. However, in spite of this relatively low number of patients, the predictive value of LAV was highly significant. Second, as is usual in AF studies, ECG and periodic Holter monitoring may have led to some degree of underestimation of recurrence rates.

Conclusions

In conclusion, in the setting of long-standing persistent AF, high LAV appears to be particularly efficient in accurately predicting AF termination by radiofrequency catheter ablation as well as persistence of sinus rhythm during follow-up. Our results should encourage further studies to confirm the value of considering LAV in routine practice.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.
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