Atrial fibrillation (AF) may induce three kinds of atrial remodelling: morphological, contractile, and electrical. Maintenance of sinus rhythm is usually associated with left atrial (LA) volume decrease, but little is known about the evolution of its mechanical properties. We sought to explore LA mechanical and morphological remodelling in patients with lone paroxysmal-AF treated by catheter ablation (CA).

Methods and results
We prospectively included 31 patients (56.4 ± 10 years). We also followed 15 age- and gender-matched controls to get normal values. Each patient had a complete echocardiography at baseline and at 3-month and 1-year follow-up. LA-anatomical reverse remodelling was documented: indexed LA volume decreased from 39 mL/m² at baseline to 31 mL/m² at 1 year (P < 0.001). However, it remained larger than controls (31 vs. 23 mL/m², P = 0.001). LA compliance improved (LA lateral systolic peaks of strain = 50 vs. 31%, P < 0.05) without reaching controls values as estimated by 50 vs. 81%, P < 0.05). LA contractility increased as highlighted by A’-peak velocity (10 cm/s at 1Y-F/up vs. 7.5 at baseline, P = 0.01) and LA late diastolic peaks of strain rate (septal: 2.3 vs. 2.1 s⁻¹, lateral: 2.3 vs. 1.4 s⁻¹, P < 0.05). We show a functional remodelling at 1 year, with most contractile parameters being comparable to controls, whereas LA compliance remains significantly altered.

Conclusion
AF-CA could reverse LA anatomical and functional remodelling. Despite improvement, LA compliance remains altered after 1 year, probably reflecting irreversible fibrosis.

Keywords
Atrial fibrillation • Remodelling • Catheter ablation • Echocardiography • Strain • Strain rate • Tissue Doppler imaging

Introduction
Atrial fibrillation (AF) usually occurs in the context of an atrial substrate produced by alterations in atrial tissue properties referred to as left atrial (LA) remodelling. Despite its prevalence, consequences of AF and its treatment on atrial function (contractility) and structure (collagen content and geometry) remains a subject of much experiment and clinical research. AF is primarily characterized by electrical remodelling (electrophysiologic properties of the tissue). It also leads to structural remodelling. These phenomena are likely to be strongly linked and partly reversible with recovery of function, morphology, and to some extent of electrophysiologic properties of LA tissue.

In recent years, very encouraging results have been published in the treatment of lone AF by catheter ablation (CA). Furthermore, the study of LA function is taking advantage of new technologies, especially using the echocardiography. We and others were able to demonstrate the feasibility and the clinical value of tissue Doppler or strain imaging for the assessment of the atrial mechanical function. Therefore, considering that CA...
might have a beneficial effect on the function and structure of the atria, we sought to study atrial geometry and mechanical properties using classical and emergent tools by transthoracic echocardiography (TTE). We expected to demonstrate a beneficial effect of CA on right and LA remodelling (structural and functional) from baseline up to 1-year follow-up (1Y-F/up).

Methods

Study population

From October 2006 to June 2007, 120 patients were treated by CA for an AF in our centre. The patients we included in our study were selected according to stringent inclusion criteria:

(i) lone paroxysmal AF treated successfully by CA in our centre, according to current guidelines.15
(ii) Patient having a documented old history (>6 months) of paroxysmal recurrent AF with symptoms but being in stable sinus rhythm in the 48 h preceding the ablation therapy in order to perform a dedicated echocardiography.
(iii) Patients had to agree to receive follow-up care: echocardiography at 3- and 12-month post-ablation therapy in our centre according to the protocol.

Lone AF was defined as AF in the absence of moderate or severe mitral regurgitation and/or mitral stenosis, mitral annular calcium, coronary artery disease, chronic cardiopulmonary disease, systemic hypertension (>140/90 mmHg), thyroid disease, and diabetes mellitus. Patients with implanted pacemakers were excluded. Paroxysmal AF was defined by the ACC/AHA/ESC guidelines.15 Patients who required a second procedure, because of AF recurrence during follow-up, were excluded.

Except for echocardiographic assessment, patients were monitored by their primary cardiologist, who was in charge of their drug therapy.

Every patient was symptomatic and came to the ablation therapy because of these severe symptoms. They all got an ECG-Holter recording 3 months after the ablation therapy to make sure that no arrhythmia episode (>10 irregular consecutive beat) could be recorded.

During the same time period, 15 healthy volunteers, comparable in age, gender and blood pressure, were selected as a control group to have references for the LA function assessment by echocardiography. All control subjects had no history of cardiovascular disease. All controls did not use cardiovascular medications and had normal clinical and echocardiographic examinations.

The current study was conducted in accordance with the ethical principles of our institution.

All patients gave informed consent.

Follow-up and echocardiographic assessment

The first echocardiographic assessment took place upon inclusion; 48 h prior to the procedure. The presence of intra-atral thrombi was ruled out by transoesophageal echocardiography. The echocardiography had to be performed in stable sinus rhythm.

Follow-up included clinical evaluation and echocardiographic reassessment at 3-month and 1-year post-ablation. In addition to the echocardiographic reassessment at the 3M-f/up, an ECG Holter and an angio-MRI of the pulmonary veins were conducted in order to rule out any evidence of pulmonary vein stenosis.

Examinations were performed using a Vivid 7 ultrasound platform (GE Healthcare, Horten, Norway) with a synchronously recorded surface electrocardiogram. All images were recorded and analysed according to a predefined method, using the same software analysis system (EchoPAC-PC, version 6.0.1, GE-healthcare, Horten, Norway). Every echocardiographic images were reviewed by a single operator, who was blind to the patients and the time of echocardiographic assessment.

Two-dimensional time-harmonic images were obtained in the para-sternal (for LA diameter measurement and apical two- and four-chamber views, using an optimized frame rate of >70 per s. The maximum LA volume and minimum LA volume were calculated from these apical four- and two-chamber zoomed views of the LA using the biplane method of discs.16,17 We measured the end-systolic volume in two- and four-chamber views. We used only the apical four-chamber view to measure the LA maximal, minimal, and pre-A surface areas. LA emptying fraction was measured according to the formula: (LA end-systolic area _ LA end-systolic area)/LA end-systolic area.

Colour tissue Doppler data were acquired in the same views using narrow windows and high frame rate (>140 per s) to get the best tissue Doppler signal’s quality within the LA walls. Analysis was performed for atrial longitudinal strain rate and strain from the apical zoomed views for the superior segments of LA septum (close to the atrial roof), LA lateral wall, and RA free wall. A computation area of 9 × 5 mm2 with an elliptical shape was chosen (Figure 1). Velocity, strain rate, and strain curves were calculated in all patients over three cardiac cycles and then averaged to obtain mean velocity, strain rate, and strain curves over one mean RR interval. End-diastole was defined as the ECG R peak and end systole was defined as the end of the ECG T wave.

For RA analysis, we analysed only functional parameters.

For diastolic function analysis, mitral flow was recorded by pulsed-wave Doppler and mitral flow propagation velocity by colour M-mode echocardiography.18 For DTI, peak early diastolic velocity (e′) and peak late diastolic velocity (a′) were recorded from a four-chamber view at the atrial and septal border of the mitral annulus. Septal and lateral measures were averaged according to guidelines.18

Ablation procedure

The majority of ablations was performed using an electro-anatomical mapping system (CARTOTM or NAVX®) coupled with a fully integrated ultrasound-imaging system (CARTOMERGE®). In most patients, pulmonary vein ablation was implemented by isolating the pulmonary veins two by two. The pulmonary veins in the remaining patients were isolated individually. Depending on the electrophysiological findings during the procedure and whether pulmonary vein isolation was considered insufficient, supplementary linear radiofrequency ablation lines were created along the mitral isthmus, the roof of the left atrium, an accessory pulmonary vein, or the cavo-tricuspid isthmus.

Reproducibility

Intra- and inter-observer reproducibility were assessed by calculating the difference between the mean values of 10 randomly selected patients. The intra-observer reproducibility is expressed as the mean difference between the 10 measurements (the interval between two analyses for the same patient was more than 15 days). In parallel, the data from 10 randomly selected patients of the study were analysed by an independent operator in order to validate the reproducibility of echocardiographic measurements. We evaluated following measurements: LA lateral e, LA e-rate S, and LA e-rate A (Table 1).

Statistical analysis

Qualitative variables were expressed as numbers and percentages, and quantitative variables were expressed as either means ± standard
deviation or medians with the inter-quartile range. For each variable of interest in AF patients, changes over time (baseline, 3M-F/up, 1Y-F/up) were expressed as the median of individual variations and assessed using one-way repeated measures analysis of variance. A two-sided α level of ≤0.05 indicated statistical significance (\(P\)-value adjustments for multiple comparisons were taken into account). Comparisons between patients and controls at each time point were performed using the Wilcoxon’s rank-sum test. Since multiple tests were carried out, the significant threshold value for these tests was set at \(\alpha = 0.01\).

To explore the links between LA volumes evolution and LV systolic and diastolic functions, we looked for a correlation between LV end-systolic volume and LA volume, using Spearman’s correlation test. Significant threshold value was set at \(\alpha = 0.05\).

Results

Study population

During the inclusion period, 56 patients were screened. At baseline, 10 were excluded because of persistent AF and 6 because refusing to receive follow-up care (patients living far away from our institution). During the study, 9 patients among the remaining 40 (22.5%) were excluded because of requiring secondary procedure for AF recurrence. A total of 31 patients were to participate in the 3M-f/up and 1Y-f/up visits were enrolled in the study (Table 2).

Table 1  Intra- and inter-observer variability for left atrial deformation analysis

<table>
<thead>
<tr>
<th></th>
<th>n = 10</th>
<th>Mean ± SD</th>
<th>Intra-observer</th>
<th>Inter-observer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute difference</td>
<td>Relative difference (%)</td>
</tr>
<tr>
<td>Lateral e (%)</td>
<td>39 ± 19.4</td>
<td>0.45 ± 3.8</td>
<td>5.3</td>
<td>2.85 ± 8.0</td>
</tr>
<tr>
<td>e-rate S (s(^{-1}))</td>
<td>2.6 ± 1.1</td>
<td>0.64 ± 0.66</td>
<td>23.3</td>
<td>0.69 ± 1.15</td>
</tr>
<tr>
<td>e-rate A (s(^{-1}))</td>
<td>−2.9 ± 2.0</td>
<td>−1.35 ± 0.7</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Demographic characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 31)</th>
<th>Controls (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.4 ± 10</td>
<td>55.5 ± 13</td>
<td>ns</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.7 ± 13</td>
<td>68.3 ± 14</td>
<td>0.001</td>
</tr>
<tr>
<td>Size (27)</td>
<td>172 ± 9</td>
<td>169 ± 6</td>
<td>ns</td>
</tr>
<tr>
<td>Body surface area (m(^2))</td>
<td>1.96 ± 0.2</td>
<td>1.79 ± 0.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>80% (25)</td>
<td>80% (12)</td>
<td>ns</td>
</tr>
</tbody>
</table>

The mean age was 56.4 ± 10 years, and 80% (25) were male. Before considering CA, all patients had failed to respond to anti-arrhythmic drugs, including flecainide in 85% and amiodarone in 58% of patients. All of the patients with paroxysmal AF were in stable sinus rhythm upon study inclusion and at the 1Y-f/up. Each anti-arrhythmic treatment was stopped 5 half-times before the echocardiography and the procedure. A total of 15 healthy volunteers comparable in age and gender, and blood pressure agreed to participate in the study. Heart rate, measured at the time of echocardiographic assessment, was comparable between patients and controls at baseline and during follow-up (Table 3).
Capacities, as shown by decrease of A enlargements was accompanied by a reduction of atrial contractile parameters did not differ any more from controls.

### Baseline left atrium parameters

Morphological analysis revealed a significant LA enlargement (diameter: +14%, indexed volume: +70%) in AF patients as compared with the control patients (Figure 2; Tables 3 and 4). This atrial enlargement was accompanied by a reduction of atrial contractile capacities, as shown by decrease of A and A’ wave velocity peaks (−30 and −32%, respectively) (Figure 3), LAEF (−17%), LA active emptying fraction (−25%), and e-rate A values (lateral: −62%; septal: −71%) (Figure 3).

This pump function inflection was accompanied by a decrease of LA compliance (‘reservoir function’), estimated by the following parameters: LA-e (−62 and −60%), e-rate S (−66 and −46%) (lateral and septal values, respectively). Finally, LA ‘conduit function’ (during LV diastolic passive filling) was also significantly altered, as shown by e-rate E values (−60 and −49%, respectively, for lateral and septal values).

### Three months LA parameters

AF patients showed a significant improvement in morphological criteria (LA diameter: −16% and LA indexed volume: −13%, P < 0.001). Yet, LA indexed volume remained significantly larger than controls (Tables 3 and 4).

LA pump function improved, as shown by A and A’ wave velocity peaks and e-rate A increase (85 and 60%, respectively, for lateral and septal values), so that those parameters did not differ any more from controls.

Parameters assessing LA compliance also improved: LA-e (lateral: +26% and septal: +44%) and e-rate S (lateral: +39%, septal: +26%) (Figure 3). Despite enhancement, LA compliance remained altered compared with controls.

### One-year LA parameters

LA diameter did not differ any more from controls, whereas indexed LA volume remained larger (+35%, P < 0.01). Area measures were also significantly reduced, indicating favourable morphological remodelling (Tables 3 and 4).

Pump function enhancement maintained at 1 year. Most of contractile parameters were still comparable to controls, except LAEF and LA active emptying fraction. Considering LA compliance, only lateral values (LA-e and e-rate S) significantly improved at 1 year, however, remaining inferior to controls, reflecting a persistent or irreversible alteration of LA compliance.

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**Table 3** Diastolic function and left ventricular end-systolic volumes in the patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 15)</th>
<th>Study population (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3M-f/up</td>
</tr>
<tr>
<td>LV Filling time</td>
<td>514 (422; 670)</td>
<td>471 (291; 690)</td>
</tr>
<tr>
<td>Peak E wave velocity (cm/s)</td>
<td>73 (64; 97)</td>
<td>74 (67; 84)</td>
</tr>
<tr>
<td>E wave deceleration time (ms)</td>
<td>203 (187; 240)</td>
<td>202 (158; 248)</td>
</tr>
<tr>
<td>Peak A-wave velocity (cm/s)</td>
<td>71 (62; 100)</td>
<td>49 (10; 66)</td>
</tr>
<tr>
<td>E/A</td>
<td>1.1 (0.8; 1.5)</td>
<td>1.3 (1.0; 1.7)</td>
</tr>
<tr>
<td>Vp (cm/s)</td>
<td>47 (40; 50)</td>
<td>42 (33; 54)</td>
</tr>
<tr>
<td>E/Vp</td>
<td>1.5 (1.4; 2.5)</td>
<td>1.9 (1.4; 2.3)</td>
</tr>
<tr>
<td>Lateral E’ (cm/s)</td>
<td>13 (12; 16)</td>
<td>11 (9; 14)</td>
</tr>
<tr>
<td>Lateral A’ (cm/s)</td>
<td>11 (8; 13)</td>
<td>7.5 (3; 9)</td>
</tr>
<tr>
<td>E/E’</td>
<td>5.4 (4.8; 6.1)</td>
<td>6.9 (5.4; 9.6)</td>
</tr>
<tr>
<td>LVESVol (mL)</td>
<td>46 (42; 47)</td>
<td>57 (45; 66)</td>
</tr>
<tr>
<td>LVESVol/BSA (mL/m²)</td>
<td>25.5 (22; 28)</td>
<td>28 (23; 34)</td>
</tr>
</tbody>
</table>

*AF vs. controls, P < 0.05.
†1Y-f/up vs. baseline, P < 0.05.

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Contrarily, body surface area was significantly higher in AF patients (2 vs. 1.8 m², P = 0.004) (Table 2).

**Figure 2** Graphic representation of the indexed left atrial volume from baseline to 12-month follow-up in the lone paroxysmal AF group and in the control group. *P < 0.01 between patients and controls; P < 0.05 between the follow-up values measured in the lone paroxysmal AF group.
Right atrium analysis

RA function analysis highlights significant differences in compliance (RA e: −45% and RA e-rate S: −45%, P < 0.05) and contractility (RA e-rate A: −60%, P < 0.05), between patients at baseline and controls. Despite (non-significant) improvement at 3M- and 1Y-F/ups, criteria studying RA compliance and contractility remained altered (Table 5).
Discussion

The CA treatment, when successful, in patients with lone paroxysmal AF is providing a progressive reverse remodelling of the LA. However, at 1 year, LA- and RA-structural (anatomy and compliance) reverse-remodelling remained incomplete when compared with a control population. TTE is a reliable tool to monitor that LA remodelling (anatomy and function).

Structural remodelling

Studying patients having a paroxysmal lone AF, we were able to observe a significant atrial-structural remodelling with altered compliance (LA and RA systolic strain), altered contractility (a’ at the mitral annulus), and enlargement (LA volumes) (Figure 4). The capability of the atrium to quickly remodel has been stressed in animal studies showing stronger but more transient apoptosis, mitogen-activated protein kinase activation, and inflammatory cell infiltration within the LA compared with the left ventricle when a stressor was imposed. That rapid atrial remodelling lead to fibrosis, promoting AF inducibility. At 1-year follow-up, we observed a structural remodelling, with contractile parameters reaching values comparable to controls. But, according to the LA and RA systolic strain, LA and RA compliance remains altered, probably reflecting the degree of LA fibrosis. The atrial fibrosis might play a key role in AF induction, persistence, and recurrence.

Studies have shown an increased tendency for AF when atrial fibrosis was experimentally induced. The LA wall composition around the pulmonary veins area is especially sensitive to the process of fibrosis and remodelling. That is probably why, placing a region of interest within this region, we observed initial severely blunted LA systolic strains and still altered values at 1-year follow-up. The lesioning role of the CA might also explain this fibrosis, in this location and the persistence of the blunted LA strain. The creation of fibrotic lines around the antrum of the pulmonary veins ostia and sometimes throughout the body of the atrium, almost certainly contributes to the fibrotic burden of the atrium and may impact on atrial compliance. In addition, the initially significant LA enlargement observed despite the fact that only lone paroxysmal AF was studied, reversed incompletely after CA. LA remained enlarged in many patients after 1 year. That is an important result, according to the prognostic role of LA size in regard to the risk of AF recurrence, but also in regard to death and hospitalization for heart failure. Indeed, LA size has been associated to prognosis in many medical conditions.

Imaging of the LA and remodelling

Imaging techniques are now providing new windows to LA and RA anatomy and function. The image integration systems are even now routinely applied for CA. Nevertheless, the relative paucity of the literature regarding especially the evaluation of LA function did motivate our study. We were able to demonstrate the value of TTE to monitor LA remodelling before and up-to 1 year after a successful AF-CA using a multiparametric approach: volume, strain, and velocities. The prior to ablation LA remodelling and its incomplete reverse remodelling, even 1 year after the CA, were the two major results of our study. It was not designed to look for prognostic markers of the success of the CA as we included only patients with successful CA. In a large population-based study, a large indexed LA volume has been demonstrated predictive of a higher risk of cardiovascular events. Patients with a severely increased LA (≥40 mL/m²) had the highest risk for the development of cardiovascular events (hazard ratio 6.6). In regard to Doppler and tissue Doppler post-treatments,

Table 5

Comparison of right atrium characteristics in the patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 15)</th>
<th>Study population (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>RA e</td>
<td>105 (70; 127)</td>
<td>58 (45; 70)*</td>
</tr>
<tr>
<td>RA e-rate S</td>
<td>4.6 (3.7; 6)</td>
<td>3 (2.2; 3.8)*</td>
</tr>
<tr>
<td>RA e-rate E</td>
<td>−3.5 (−6; −2.4)</td>
<td>−3 (−4.2; −2.2)</td>
</tr>
<tr>
<td>RA e-rate A</td>
<td>−5 (−9; −3.9)</td>
<td>−2 (−5; −1)*</td>
</tr>
</tbody>
</table>

*AF patients vs. controls, P < 0.01.
we have been able to estimate and to follow the improvement of atrial contractility (tissue Doppler \(a'\), regional end-diastolic strain rate) and compliance (regional LA and RA systolic e'.).\textsuperscript{3,4} \(a'\) was not significantly different to controls after 3-month post-CA. That \(a'\) velocity had previously been correlated with other traditional parameters of LA function.\textsuperscript{27} \(a'\) velocity has also been shown to be a significant prognostic indicator.\textsuperscript{15}

The measure of atrial strain, so reservoir function, correlates with compliance which is influenced by fibrosis and atrial-tissue ultra structural characteristics.\textsuperscript{34,36,37} Atrial-compliance assessment might have a great clinical value in accordance to the MRI gadolinium enhancement study proposed by Oakes et al.\textsuperscript{21}

**Clinical perspectives**

This incomplete correction of atrial-structural remodelling even 1 year after the CA in lone paroxysmal AF patients might encourage proposing additive therapeutic strategies. With regard to AF prevention, a paradigm shift in therapeutic options from electrical therapy to structural treatments has already been put forth.\textsuperscript{2} To this end, the potential benefit of blocking the renin–angiotensin pathway has been suggested.\textsuperscript{2} But the GISSI-AF trial is discouraging.\textsuperscript{38}

More interestingly, the straight correlation between amounts of fibrosis and success of AF-CA\textsuperscript{21} is encouraging a collaborative strategy, combining the expertise of the electrophysiologist and the specialist in cardiac imaging.

This concept in managing AF patients individually (using the echocardiography) has already been demonstrated for the decision of the timing for cardioversion in the ACUTE-trial.\textsuperscript{39} However, the tools that were used to quantify myocardial structural remodelling are still requiring validation. For these reasons, our study has to be considered as a pilot study warranting further extensive research work.

**Limitations**

The echocardiographic analysis of LA mechanical function could not be performed with enough robustness in patients in AF so in patients not successfully treated by CA (still with paroxysmal AF) and patients in chronic AF.

The recent experience from Oakes et al.\textsuperscript{21} is encouraging the research of atrial fibrosis by MRL. It would be interesting to compare these MRI results with the ones we got by echocardiography.

**Conclusion**

CA could reverse an LA-structural remodelling that has been observed in lone paroxysmal AF patients. Despite improvement, LA volume and compliance remain altered after 1 year. The trans-thoracic echocardiography is providing a tool for simplicity in monitoring of LA characteristics in patients proposed to CA.

**Conflict of interest:** none declared.

**References**


