Reverse Remodeling of the Left Cardiac Chambers After Catheter Ablation After 1 Year in a Series of Patients With Isolated Atrial Fibrillation

Patricia Reant, MD; Stephane Lafitte, MD, PhD; Pierre Jaïs, MD; Karim Serri, MD; Rukshen Weerasooriya, MBBS; Meleze Hocini, MD; Xavier Pillois, PhD; Jacques Clementy, MD; Michel Haïssaguerre, MD; Raymond Roudaut, MD

Background—Isolated atrial fibrillation (AF) is associated with mild enlargement of the left atrium (LA) and left ventricular (LV) diastolic dysfunction. The impact of ablation of isolated AF on left chamber size and function is unclear, and whether diastolic dysfunction is the cause or the consequence of AF remains unknown. The objective of this prospective study was to evaluate the impact of sinus rhythm restoration by catheter ablation on LV diastolic dysfunction, LA morphology, and mechanical function.

Methods and Results—Forty-eight patients with isolated AF were studied by serial echocardiographic studies at baseline and at 1-, 3-, 6-, 9-, and 12-month intervals after radiofrequency ablation. LA dimensions and mechanical function and LV systolic and diastolic functions were evaluated at each time interval. Diastolic function was assessed with conventional Doppler parameters and new indexes such as tissue Doppler imaging, mitral flow propagation velocity, and combined criteria. LV diastolic dysfunction was present in paroxysmal and chronic AF patients with a reduction of tissue Doppler imaging lateral early diastolic peak velocity in 37% (P < 0.001) and 48% (P < 0.01), respectively, compared with healthy control subjects. At the end of the follow-up, LA area decreased significantly by 18% (P < 0.001) in paroxysmal and 23% (P < 0.05) in chronic AF patients. Diastolic function improved significantly with an increase in lateral early diastolic peak velocity of 29% (P < 0.001) in paroxysmal AF and 46% (P < 0.05) in chronic AF patients. A significant increase in LV ejection fraction was also noted for both groups: 7.7% and 18.8%, respectively.

Conclusions—This study demonstrates reverse morphological remodeling of the LA and improvement of LV diastolic and systolic functions after restoration of sinus rhythm by ablation for isolated AF. Because patients with isolated AF have none of the traditional causes of LV diastolic dysfunction, our findings suggest that AF may be partly the cause rather than the consequence of diastolic dysfunction. (Circulation. 2005;112:2896-2903.)

Key Words: atrial fibrillation ● atrium ● catheter ablation ● diastole ● echocardiography

Atrial fibrillation (AF) is the most common arrhythmia, but its pathophysiology remains unclear. AF has been shown to be associated with ventricular and atrial remodeling and deterioration in both left ventricular (LV) diastolic and systolic function. Whether those changes are the cause or the consequence of the arrhythmia remains debatable, even in patients with isolated AF in whom a subclinical diastolic dysfunction has recently been demonstrated.1,2 Catheter ablation for AF has been proved effective, providing arrhythmia control in >70% of patients. The goal of this study was to determine prospectively in patients with isolated AF whether there are measurable changes in systolic, diastolic, and chamber sizes after radiofrequency (RF) ablation. For this purpose, morphological and functional echocardiographic parameters were collected during 12 months after restoration and maintenance of sinus rhythm by catheter ablation of AF.

Methods

Study Population

From February 2002 to December 2003, 48 of 400 consecutive patients referred to our institution (38 men; age, 54.1 ± 10 years; range, 29 to 75 years) with symptomatic isolated AF for 6.1 ± 5.6 and 12 ± 8.8 years of duration for paroxysmal and chronic AF, respectively, were enrolled for RF ablation because of unsuccessful treatment with at least 2 antiarrhythmic drugs.

Isolated AF was defined as AF in the absence of moderate or severe mitral regurgitation (MR) (grade II) and/or mitral stenosis, mitral annular calcification, coronary artery disease, chronic pulmonary disease, systemic hypertension (>140/90 mm Hg), thyroid disease, and diabetes. Patients with an implanted pacemaker were excluded. Isolated AF was confirmed by clinical examination, transthoracic echocardiography, Holter ECG, chest radiography, exercise testing, and laboratory evaluation of thyroid function, blood glucose levels, and electrolytes.
Protocol
A first echocardiographic study was performed to obtain baseline measurements in sinus rhythm for all patients, just before the procedure in paroxysmal AF, and a mean of 1 to 2 days after the procedure for both chronic and paroxysmal AF. Antiarrhythmic drugs were stopped 5 half-lives before the ablation to improve the chances of localizing the arrhythmic triggers. Consequently, the rapid heart rate of chronic AF patients did not allow accurate LV systolic function assessment, and evaluation of LV diastolic function was impossible before the procedure. After ablation, follow-up at 1, 3, 6, 9, and 12 months included echocardiographic studies, clinical history and examination, ECG, Holter ECG, and exercise testing to diagnose recurrences.

Final echocardiographic data were compared with baseline values. All patients provided oral and written informed consent before participating in the study.

AF Classification and Definition of Recurrence
According to ACC/AHA/ESC guidelines,1 there are different degrees of AF: recurrent, paroxysmal, persistent, and permanent. Chronic AF includes persistent and permanent AF. AF recurrence is defined as episodes lasting >30 seconds and is not equivalent to treatment failure.3 However, in our experience, patients with ectopic beats may be misclassified if this cutoff is used. Therefore, we selected a 3-minute duration of palpitations as a safe criterion of recurrence, particularly concerning the risk of thromboembolic complications.

Complete successful treatment was defined as the absence of symptomatic or asymptomatic recurrences; partial successful treatment was defined as recurrences with decreased duration and/or frequency (<70% versus before ablation) and improved quality of life. Failure of ablation was defined as recurrences with duration and/or frequency ≥70% versus before ablation and no clinical improvement.

Electrophysiological Study and Ablation Procedure
A 6F diagnostic catheter (Xtrem, Ela Medical) was positioned in the coronary sinus for pacing and recording. The LA and pulmonary veins (PVs) were accessed with a transseptal sheath (Preface, Biosense Webster) perfused with heparinized glucose at a flow rate (0.9% saline via Cool Pump, Biosense Webster) titrated to achieve catheter (Celsius Thermocool, Biosense Webster) with a flow rate catheter (Biosense Webster) and ablated with a 4-mm irrigated-tip frequency (70% versus before ablation) and improved quality of complications.

Diastolic function was evaluated by integrating mitral Doppler, pulmonary venous flow information,15 and new indexes16 and was graded as follows: 0 (normal diastolic function, normal E/A ratio; S/D >1, Vp >50 cm/s, lateral Ve >10 cm/s, and septal Ve >8 cm/s); 1 (mild diastolic dysfunction; E/A <1, S/D >1, Vp <50 cm/s, lateral Ve <10 cm/s, and septal Ve <8 cm/s); 2 (moderate diastolic dysfunction; normal E/A, S/D <1, Vp <50 cm/s, and Ve <8 cm/s); and 3 (severe diastolic dysfunction; E/A ≥2, Vp and Ve are lowest).

Forty-eight healthy control subjects matched in age and sex (38 men; age, 54 ±9 years; range, 30 to 72 years) were compared to eliminate age-dependent effects.

Reproducibility
A first observer performed all the echocardiograms, and all measurements were later repeated blindly for each parameter. The studies were analyzed offline by a second blinded observer for 10 patients. Intraobserver reproducibility was calculated by the average difference between the 10 measurements realized. Interobserver reproducibility was calculated as the absolute difference divided by the average of the 2 observations for all parameters.

Statistical Analysis
All values were expressed as mean ±SD. Comparisons between the different data for each patient at different time points of assessment and comparisons with healthy volunteers were performed with 2-tailed paired Student’s t test and Wilcoxon-Mann-Whitney rank-sum test as appropriate. A value of P < 0.05 was considered statistically significant.

Results
AF Patients and Procedural Outcome
Clinical characteristics of the AF patients are listed in Table 1. Forty-eight patients were enrolled, and all completed the study protocol. Thirty-three were followed up for 12 months;
the remaining patients were followed up by their cardiologist after 6 or 9 months. Mean follow-up was 11 ± 2.5 months. Twenty-nine (78%) of the 37 paroxysmal AF patients were successfully treated without AF recurrence. Six (54%) of the 11 chronic AF were successfully treated (Table 1). All patients with recurrences were classified as partial success and pooled with patients with complete success. None of them were considered to have had a failure of ablation or required a second procedure.

During the last 6 months before ablation, 32 patients (66%) were on β-blockers, 10 (21%) were on amiodarone, and 22 (46%) were on flecainide; 16 (33%) had a combination of 2 of these drugs.

During the first 6 months after ablation, 22 patients continued to have medical therapies during 3 or 6 months. Most patients were on β-blockers, frequently used to cover the healing period after ablation: 14 (29%) were on β-blockers, 1 (2%) was on amiodarone, and 7 (14%) were on flecainide. None were on dual antiarrhythmic therapy.

However, all patients were free of drugs at baseline evaluation (since 5 half-lives) and 6 months after ablation. As a consequence, all drugs were interrupted for several months at final evaluation, and medical therapy had no effect on the measured parameters after 6 months.

Baseline Pre-AF Ablation Randomization Compared With Normal Subjects
Baseline measures of LA and LV diastolic and systolic functions in AF patients compared with healthy volunteers are shown in Table 2.

At baseline, LA dimensions were significantly greater for AF patients in the 3 views (P<0.001). TDI lateral Ve was reduced by 37% (P<0.001) for paroxysmal AF and by 48% (P<0.01) for chronic AF. Vp was 13% (P<0.01) and 18% lower (P<0.05), respectively. LVEF was significantly reduced by 6.6% (P<0.01) and 18.8% (P<0.01), respectively.

Trends During the Follow-Up

LA Dimensions
After ablation, LA dimensions decreased significantly and progressively in each echocardiographic views (P<0.05) (the Figure). In A4C, for example, longitudinal LA diameter decreased for paroxysmal AF from 59.7 ± 7.3 to 53.19 ± 7.7 mm at the final examination (−11%) (P<0.001) and for chronic AF from 68.4 ± 8.1 to 60.68 ± 6.5 mm (−11%) (P<0.05).

LA Mechanical Function
LA active emptying volume was 7.15 ± 2.6 mL/m² in paroxysmal AF patients before ablation, 6.83 ± 2.9 mL/m² (P=0.42) at day +1, and 6.64 ± 2.3 mL/m² (P=0.26) at 11 months. In chronic AF, LA active emptying volume was 2.67 ± 1.9 mL/m² just after ablation and 4.7 ± 2.14 mL/m² (P=0.15) at 11 months.

LA active emptying fraction was 30.9 ± 13.5% in paroxysmal AF before ablation, 30.5 ± 13.5% (P=0.71) at D +1, and 34.0 ± 11.3% (P=0.22) at 11 months. In chronic AF, LA active emptying fraction was 5.5 ± 3.6% just after ablation and 21.8 ± 11% (P<0.05) at 11 months.

### TABLE 1. Patient Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>Total, Paroxysmal/Chronic</th>
<th>Success, Paroxysmal/Chronic</th>
<th>Recurrences, Paroxysmal/Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>37/11</td>
<td>29 (78.5)/6 (54)</td>
<td>8 (21.5)/5 (46)</td>
</tr>
<tr>
<td>Age, y</td>
<td>53 ± 9/55 ± 11</td>
<td>52.7 ± 9/60 ± 8</td>
<td>55.6 ± 9/50 ± 12</td>
</tr>
<tr>
<td>Sex, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28/9</td>
<td>24/5</td>
<td>4/4</td>
</tr>
<tr>
<td>Female</td>
<td>10/1</td>
<td>6/0</td>
<td>4/1</td>
</tr>
<tr>
<td>Duration of AF, y</td>
<td>6.1 ± 5.6/12 ± 8.8</td>
<td>5.9 ± 6/10.7 ± 3.7</td>
<td>6.7 ± 3/13.8 ± 13</td>
</tr>
</tbody>
</table>

PSLAX indicates parasternal long-axis view.

### TABLE 2. Comparative Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects (n=48)</th>
<th>Paroxysmal AF (n=37)</th>
<th>Chronic AF (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54 ± 9.1</td>
<td>53 ± 9 (P=0.36)</td>
<td>55 ± 11 (P=0.19)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>38/10</td>
<td>28/9</td>
<td>10/1</td>
</tr>
<tr>
<td>Transverse LA diameter PSLAX, mm</td>
<td>36.3 ± 5</td>
<td>44.7 ± 5.7‡</td>
<td>48.2 ± 5.7*</td>
</tr>
<tr>
<td>LA area A4C, cm</td>
<td>17.2 ± 2</td>
<td>24.2 ± 5†</td>
<td>31.6 ± 4.5†</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>66.8 ± 5.4</td>
<td>62 ± 5.7*</td>
<td>53 ± 8.5*</td>
</tr>
<tr>
<td>Ap, cm/s</td>
<td>27.5 ± 3.2</td>
<td>29.9 ± 4.6*</td>
<td>29.7 ± 5.9 (P=0.27)</td>
</tr>
<tr>
<td>Vp, cm/s</td>
<td>55.3 ± 11.2</td>
<td>48.1 ± 9.1*</td>
<td>45.5 ± 11.2 (P&lt;0.05)</td>
</tr>
<tr>
<td>E/Vp</td>
<td>1.02 ± 0.45</td>
<td>1.65 ± 0.38†</td>
<td>1.82 ± 0.37†</td>
</tr>
<tr>
<td>Lateral Ve, cm/s</td>
<td>13.2 ± 2.8</td>
<td>8.3 ± 2.2†</td>
<td>6.8 ± 2.3*</td>
</tr>
<tr>
<td>Lateral E/Ve</td>
<td>4.2 ± 1.9</td>
<td>9.9 ± 3.2†</td>
<td>14 ± 5†</td>
</tr>
</tbody>
</table>

*P<0.01, †P<0.001.
LA filling fraction was 26±9% in paroxysmal AF before ablation, 25±10% (P=0.52) at D+1, and 28±10% (P=0.35) at 11 months. In chronic AF, LA filling fraction was 15±7% just after ablation and 30±5% (P<0.05) at 11 months.

**LV Systolic Function**

LVEF improved progressively and significantly (7.7%) in paroxysmal AF (from 62±5.7% at baseline to 66.8±5% at the final examination; P<0.05) and (18.8%) in chronic AF (from 53±8.5% to 63±7%; P<0.05; the Figure). Nine patients with LVEF <55% baseline had successful ablation, and LVEF improved from 49±7% to 59±7% at 3 months (P<0.05) and to 62±2% at the final examination (P<0.05).

**LV Diastolic Function**

Before ablation, mean E/A ratio was normal in paroxysmal AF; however, 8 patients had relaxation abnormality based on E/A <1 (0.84±0.11). 13 patients had a pseudonormal pattern, and 12 patients had a restrictive pattern (E/A, 2.44±0.42; Table 3), as was the case for all chronic AF patients.

**TABLE 3. Evolution of LV Diastolic Function in Paroxysmal AF**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>D−1</th>
<th>D+1</th>
<th>M+1</th>
<th>M+3</th>
<th>M+6</th>
<th>M+11</th>
<th>%Δ, D−1</th>
<th>P, D−1</th>
<th>%Δ, M+11</th>
<th>P, M+11</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A</td>
<td>1.54±0.68</td>
<td>1.85±0.8</td>
<td>1.42±0.54</td>
<td>1.43±0.44</td>
<td>1.49±0.59</td>
<td>1.37±0.40</td>
<td>20</td>
<td>&lt;0.05</td>
<td>11</td>
<td>0.52</td>
</tr>
<tr>
<td>E/A relaxation abnormality</td>
<td>0.84±0.11</td>
<td>1.26±0.3</td>
<td>1.03±0.28</td>
<td>1.22±0.34</td>
<td>1.17±0.35</td>
<td>1.16±0.1</td>
<td>69</td>
<td>&lt;0.05</td>
<td>69</td>
<td>0.052</td>
</tr>
<tr>
<td>E/A restrictive profile</td>
<td>2.44±0.42</td>
<td>2.66±0.88</td>
<td>1.89±0.56</td>
<td>1.65±0.38</td>
<td>1.96±0.53</td>
<td>1.63±0.29</td>
<td>9</td>
<td>0.43</td>
<td>33</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>S/D</td>
<td>1.09±0.34</td>
<td>0.98±0.3</td>
<td>0.86±0.26</td>
<td>0.94±0.33</td>
<td>0.89±0.3</td>
<td>0.88±0.35</td>
<td>10</td>
<td>&lt;0.05</td>
<td>19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ap, cm/s</td>
<td>29.89±6.6</td>
<td>29.75±3.7</td>
<td>26.85±3.4</td>
<td>25.99±3.3</td>
<td>25.51±3.1</td>
<td>26.36±3.7</td>
<td>0.4</td>
<td>0.77</td>
<td>12</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Vp, cm/s</td>
<td>48.17±9.2</td>
<td>49.01±8.3</td>
<td>52.37±10.1</td>
<td>60.13±12.4</td>
<td>59.36±12.1</td>
<td>60.18±11.9</td>
<td>2</td>
<td>0.07</td>
<td>25</td>
<td>†</td>
</tr>
<tr>
<td>E/Vp</td>
<td>1.66±0.38</td>
<td>1.62±0.41</td>
<td>1.40±0.51</td>
<td>1.29±0.45</td>
<td>1.33±0.31</td>
<td>1.33±0.35</td>
<td>2</td>
<td>0.36</td>
<td>20</td>
<td>†</td>
</tr>
<tr>
<td>Septal Ve, cm/s</td>
<td>6.92±1.69</td>
<td>7.00±1.6</td>
<td>6.93±1.7</td>
<td>7.34±1.83</td>
<td>7.16±1.56</td>
<td>7.7±2.16</td>
<td>1</td>
<td>0.74</td>
<td>11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Septal E/Ve</td>
<td>11.92±4</td>
<td>12.29±3.7</td>
<td>12.31±4.2</td>
<td>10.61±3.4</td>
<td>11.14±3.5</td>
<td>9.97±2.7</td>
<td>3</td>
<td>0.37</td>
<td>16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lateral Ve, cm/s</td>
<td>8.30±2.2</td>
<td>7.95±2.1</td>
<td>8.27±2.2</td>
<td>9.98±2.1</td>
<td>9.34±1.6</td>
<td>10.7±2.3</td>
<td>4</td>
<td>0.075</td>
<td>29</td>
<td>†</td>
</tr>
<tr>
<td>Lateral E/Ve</td>
<td>9.91±3.2</td>
<td>10.32±2.93</td>
<td>9.75±3.1</td>
<td>7.51±2.1</td>
<td>8.31±2.7</td>
<td>7.47±2.2</td>
<td>4</td>
<td>0.073</td>
<td>25</td>
<td>†</td>
</tr>
</tbody>
</table>

*p<0.01, †p<0.001.
patients (E/A, 2.65±1.16). At the final examination, mean E/A did not vary for paroxysmal AF, except for patients with relaxation abnormalities and patients with a restrictive pattern, for whom E/A became normal (1.42±0.37 [P=0.052] and 1.63±0.29 [P<0.005], respectively; Table 3). For chronic AF patients, E/A ratio also became normal (1.28±0.40; P>0.05).

Pulmonary A wave (reverse diastolic peak velocity) decreased significantly in paroxysmal AF from 29.89±4.6 to 26.4±3.7 cm/s (11.6%; P<0.005; Table 3). For chronic AF, there was no significant change (29.7±5.9 to 27.5±3.5 cm/s; P=0.51).

Lateral Ve increased significantly from 8.3±2.2 to 10.7±2.3 cm/s (29%) at the final examination at a mean of 11 months in paroxysmal AF (P<0.001) and from 6.8±2.3 to 9.9±3.2 cm/s (46%) in chronic AF (P<0.05; Table 3). Vp increased significantly from 48.17±9.2 to 60.2±12 cm/s (25%) in paroxysmal AF (P<0.001; Table 3) and from 45.5±11.2 to 66±14.7 cm/s (46%) in chronic AF (P<0.05).

Because changes in LV end-systolic volume could be the driving force behind increases in Vp after ablation, statistical analysis was performed to determine the relation between change in LV end-systolic volume and Vp. No correlation was observed between LV end-systolic volume percentage change and Vp percentage change (in paroxysmal AF, y=0.0069x−0.0529, r=−3.10×10−3; in chronic AF, y=0.1498x−0.1332, r=0.12).

Lateral E/Ve decreased from 9.91±3.2 to 7.47±2.2 (25%) in paroxysmal AF (P<0.001; Table 3 and the Figure) and from 13.98±5 to 7.3±2.4 (48%) in chronic AF (P<0.05; the Figure). Similarly, E/Vp decreased from 1.66±0.38 to 1.33±0.35 (20%) in paroxysmal AF (P<0.001; Table 3 and the Figure) and from 1.81±0.37 to 1.23±0.32 (32%) in chronic AF (P<0.05; Figure 1).

In paroxysmal AF, the mean grade of diastolic dysfunction was 1.67±0.85 at baseline and 0.78±1.05 (P<0.001) (−0.89±1.02) at 11 months. In chronic AF, the grade of diastolic dysfunction was 2.56±0.92 at baseline and 0.63±0.80 (P<0.001) (−1.73±1.00) at 11 months.

**Mitral Regurgitation**

Sixteen paroxysmal AF patients had mild MR (grade 1) before ablation. After ablation, the degree of MR decreased significantly for the overall group (P<0.05): MR disappeared in 4 patients, decreased in 4 patients, and remained stable in 8 patients.

Five chronic AF patients had mild MR (grade 1), 4 patients had moderate MR (grade 2), and the 2 remaining patients had no MR before ablation. After ablation, the degree of MR was significantly reduced for this group (P<0.05): MR disappeared in 3 patients, decreased in 3, and was unchanged in 3 others.

**Complete and Partial Success of Ablation**

Table 4 shows the evolution of LA area and LVEF in patients with/without recurrences. In paroxysmal AF patients without recurrences, the degree of diastolic dysfunction decreased from 1.59±0.84 to 0.70±0.95 (P<0.001) (−0.89±1.05) at 11 months. In patients with recurrences, it decreased from 1.9±0.87 to 1.0±1.25 (P=NS) (−0.9±1.01).

In the chronic group, patients with recurrences, which were all improved clinically, also had significant improvement in different parameters but to a lesser degree than patients without recurrences. In patients without recurrences, the degree of diastolic dysfunction decreased from 2.66±0.52 to 0.66±0.81 (−2.0±1.25). In patients with recurrences, it decreased from 2.5±1.2 to 0.75±0.89 (−1.75±0.92).

**Final Postablation Echocardiography Compared With Normal Subjects**

At final examination, LA size decreased only partially and remained significantly larger than in control subjects; LVEF was normalized (P=NS); and TDI-derived Ve improved only partially.

**Relation Between Duration of AF and Echo Parameters**

No significant correlation was observed between AF duration (years) and LA enlargement or LV dysfunction. The linear regression equations were as follows: for A4C longitudinal LA diameter (mm), y=0.21x+70.2, r=0.17; for LVEF (%), y=−0.001x+0.61, r=0.1; and for lateral E/Ve, y=0.13x+9.88, r=0.22.

**Reproducibility**

The intraobserver and interobserver reproducibilities for the different parameters were adequate overall and are reported in Table 5. The most important difference was observed for Vp, with a mean percent error of 11.7% between observers compared with 3.2% for the same observer.

**Discussion**

This study is the first prospective echocardiographic study with long-term follow-up (mean, 11.0±2.5 months) after RF PV isolation and linear lesions in the LA for isolated AF. This investigation confirms previous observations of the detrimental effects of AF1,2 at baseline, with significant LA enlargement, evidence of LV diastolic dysfunction, and a modest decrease in LVEF in 48 patients with AF.
During the 11 months (mean) of follow-up after restoration of sinus rhythm by catheter ablation, we observed a significant and progressive decrease in LA dimensions, an improvement in LV diastolic function associated with a decrease in LV filling pressures, and an improvement in LV systolic function. We documented reverse morphological LA remodeling and improvement in LV diastolic and systolic functions after AF ablation with the aid of new and well-validated echocardiographic parameters of diastolic function.9–13,15,16 Patients with isolated AF have none of the traditional causes of diastolic dysfunction, and by definition, they are normotensive, do not have LV hypertrophy, and are most unlikely to have any form of infiltrative cardiomyopathy. The study, by demonstrating the partial reversibility of LV diastolic dysfunction after ablation, suggests that this dysfunction can be attributed in part to AF.

Echocardiographic Abnormalities in Patients With Isolated AF

Several recent studies have compared echocardiographic parameters of AF patients with normal subjects. Jaïs et al1 observed in 28 lone AF patients a significant increase in longitudinal LA diameter in A4C. Although conventional echocardiographic diastolic and systolic parameters were apparently normal, an increase in filling pressures was observed at cardiac catheterization. Thamilarasan et al2 reported a significant increase in LA dimensions in 24 lone paroxysmal AF patients, LV diastolic dysfunction (assessed by TDI), and a significant decrease in LVEF. They concluded that their results demonstrated no impairment in atrial contractile function in patients with paroxysmal lone AF (LA fractional area change and atrial filling fraction were 34% [P=NS] and 29% [P=NS] versus 35% and 27%, respectively, in healthy control subjects) but suggested the presence of altered ventricular diastolic function in these patients.

In our study, LA area was increased by 40% in paroxysmal AF and 84% in chronic AF patients. LA mechanical function was not impaired in paroxysmal AF. We observed diastolic abnormalities mainly with the use of new echocardiographic parameters (Table 2). These parameters could potentially allow detection of more subtle LV diastolic abnormalities.

Effect of RF Ablation on LA and LV

This study shows a significant and progressive decrease of LA dilatation after ablation for isolated AF. In A4C, the longitudinal LA diameter decreased by 11% for paroxysmal AF and by 11.2% for chronic AF at the final examination. Moreover, diastolic dysfunction regressed significantly with improvement of Ve, Vp, and combined criteria. We did not observe a normalization of diastolic function and any significant modification of the LA mechanical parameters in paroxysmal AF. However, in chronic AF patients, LA filling fraction and LA active emptying fraction improved significantly, showing increased LA contribution to LV filling and a better LA mechanical function since LV relaxation improved.

A recent study demonstrated that the deleterious role of AF on heart function was reversible when sinus rhythm was maintained with ablation.18 However, LV diastolic function was not assessed. Our results highlight the important contribution of AF suppression by RF ablation, especially for the improvement in LV diastolic and systolic function.

Hsu et al19 studied LVEF at 1, 3, 6, and 12 months after AF ablation in 58 patients with LVEF <45%. They showed an increase in LVEF, with the greatest improvement observed within the first 3 months.

In our study, LVEF was significantly improved at 1 month in chronic AF patients, whereas the improvement was evident in paroxysmal AF patient only at 11 months (the Figure). When LVEF is impaired, as it was most frequently in the chronic group, improvement in LVEF is observed earlier. In fact, it is likely that in cases of significant LV dysfunction, conversion to sinus rhythm will be associated with immediate improvement, followed by further delayed amelioration. However, in patients with paroxysmal AF and mild alterations in LV function, the improvement is much more limited and becomes significant after a longer delay.

Another important point is that all patients with recurrences were not really unsuccessfully treated, as illustrated by clinical amelioration, improvement in diastolic function, and positive changes in LV and LA remodeling in this subgroup.

Pathophysiology

The present study, by demonstrating the partial reversibility of LV diastolic dysfunction after ablation, suggests that this dysfunction can be attributed in part to AF. Similarly, previous studies in animal models clearly suggested electrophysiological and cellular remodeling as a result of AF itself. Wijffels et al19 showed that induction of AF by intermittent rapid atrial pacing in goats led to a shortening of atrial refractoriness with loss of rate adaptation and caused an increase in the rate, inducibility, and stability of AF. Morillo et al20 made similar observations in dogs subjected to sustained rapid atrial pacing and showed the development of atrial enlargement and an increase in mitochondrial size and number with disruption of the sarcoplasmic reticulum (corresponding to morphological and cellular remodeling); they also showed that cryoablation of the posterior LA could eliminate AF. Okhusa et al21 showed alterations in the Ca2+ regulatory proteins of the atrial myocardium in chronic AF patients and that it is conceivable that such anomalies may be involved in the initiation and/or perpetuation of AF. Ausma et al22 observed, after cardioversion of induced sustained AF in goats, LA cellular remodeling with an increase in size of the

---

**TABLE 5. Parameter Variabilities**

<table>
<thead>
<tr>
<th></th>
<th>LA Diameters, %</th>
<th>LA Areas, %</th>
<th>LVEF, %</th>
<th>E, A, %</th>
<th>Ap, %</th>
<th>TDI Ve, %</th>
<th>Vp, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraobserver</td>
<td>2</td>
<td>6.8</td>
<td>5.5</td>
<td>2.4</td>
<td>2.5</td>
<td>3.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Interobserver</td>
<td>5.7</td>
<td>10</td>
<td>10–15</td>
<td>4</td>
<td>6.4</td>
<td>2.2</td>
<td>11.7</td>
</tr>
</tbody>
</table>
atrial myocytes associated with cellular substructures changes of most of the myocytes (loss of myofibrils, accumulation of glycogen, changes in mitochondrial shape and size, and fragmentation of sarcoplasmic reticulum). Zipes et al. demonstrated that arrhythmia could cause a tachycardia-induced atrial cardiomyopathy that results in electrophysiological and anatomic remodeling of the atrium. These changes could facilitate the induction and perpetuation of the arrhythmia. These combined results are in favor of an electrical and mechanical atrial remodeling phenomenon secondary to AF and support the hypothesis of AF-induced cardiomyopathy.

However, diastolic dysfunction reverted only partly, suggesting that this condition may have preexisted and possibly created a favorable environment for the development of AF.

A pathophysiological hypothesis implicates diastolic dysfunction as a cause of isolated AF, combining LA and PV stretch and enlargement resulting from an increase in LV end-diastolic pressure. Stretch could favor AF by inducing an electrophysiological and cellular remodeling phenomenon and worsening of atrial and ventricular mechanical functions. The role of atrial stretch is not clearly established in humans but has been demonstrated in animals such as pigs and rabbits, in which elevation of LV pressure favors LA stretch and dilation. Tsang et al. demonstrated that the presence and severity of diastolic dysfunction are independently predictive of nonvalvular AF in the elderly.

Study Limitations

A limitation of the study is the possibility that RF energy itself could have induced deterioration in atrial or ventricular functions and introduced a confounding variable in the interpretation of the results. However, as observed in paroxysmal AF patients, all echocardiographic parameters were not significantly changed immediately after the procedure. We extrapolated that if RF ablation should not have had an effect on atrial or ventricular function in paroxysmal AF, it could be the same for chronic AF, although these 2 groups are different.

Inclusion of isolated AF patients sent to a specialized center could have introduced a selection bias. In contrast to other studies, we added a clinical index of recurrence to Holter ECG (palpitations of most of 3 minutes’ duration) to avoid false negative of recurrences. If we were to use only Holter ECG evidence of AF, our conclusions would be the same because patients with recurrences also were improved (to a lesser degree).

This nonrandomized, single-arm, longitudinal analysis has limitations in inferring all echocardiographic effects to ablation alone because participation in a clinical study is often associated with changes in medication, sense of well-being, and physical activities that may also affect the measured end points.

It is possible that antiarrhythmic drugs during the 6 months after the procedure may limit the interpretation of the results. These drugs may have reduced the number of occurrences of AF, lengthened the interval between episodes, and potentially improved diastolic function in the first 6 months. However, it is important to note that none of the patients were prescribed these medications at the time of baseline and final assessment (at 11 ± 2.5 months), making a drug effect less likely.

Conclusions and Clinical Implications

This prospective study provides strong evidence that curative ablation of isolated AF, with sinus rhythm restoration and maintenance, improves LV diastolic and systolic functions and is responsible of reverse morphological remodeling of the LA. The results suggest that diastolic function may be caused partly by AF rather than the reverse as is currently thought. Other studies are needed to determine whether curing AF may reduce the incidence of heart failure and mortality. Moreover, the assessment of LV diastolic function with new echocardiographic parameters may lead to improvements in the diagnosis, prognosis, and follow-up of diastolic dysfunction in patients with isolated AF.

References

9. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol. 1997;30:474–480.


Reverse Remodeling of the Left Cardiac Chambers After Catheter Ablation After 1 Year in a Series of Patients With Isolated Atrial Fibrillation
Patricia Reant, Stephane Lafitte, Pierre Jaïs, Karim Serri, Rukshen Weerasooriya, Meleze Hocini, Xavier Pillois, Jacques Clementy, Michel Haïssaguerre and Raymond Roudaut

Circulation. 2005;112:2896-2903; originally published online October 31, 2005; doi: 10.1161/CIRCULATIONAHA.104.523928
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/19/2896

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/