Left Atrial Dysfunction in Patients With Atrial Fibrillation After Successful Rhythm Control for > 3 Months*

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**Background:** Large-scale clinical trials have demonstrated that patients with atrial fibrillation (AF), when treated with a rhythm-control strategy, are still at risk for embolic events. We hypothesized that left atrial (LA) dysfunction persisted even after successful maintenance of sinus rhythm for > 3 months.

**Methods:** A total of 93 patients with AF and satisfactory rhythm control for > 3 months were included. Satisfactory rhythm control was defined as being free of AF based on patient-reported symptoms, monthly ECG follow-up, and ambulatory Holter ECG if needed. Among the 93 patients, 25 patients had sustained AF that was terminated by electrical or pharmacologic cardioversion, while 68 patients had paroxysmal AF under good medical control. Clinical data were obtained, and transthoracic and transesophageal echocardiography were performed after satisfactory rhythm control for > 3 months.

**Results:** Among the 93 patients, 34 patients (37%) had LA dysfunction, defined as LA appendage (LAA) peak emptying velocity < 40 cm/s or spontaneous echo contrast and/or thrombus in the LA or LAA. When compared to the other 59 patients without LA dysfunction, they had larger LA dimension (40 ± 6 mm vs 36 ± 8 mm [± SD], p = 0.018) but did not differ significantly regarding the left ventricular (LV) chamber size, LV ejection fraction, mitral or tricuspid inflow, and ratio of the amplitude of the waves created by early diastolic filling and atrial contraction. We also analyzed the relationship between LA function and clinical risk factors for stroke, including hypertension, diabetes mellitus, coronary artery disease, age > 65 years, and prior cerebral vascular accident. LA dysfunction was found in 10 of 17 patients (59%) with three or more risk factors. The odds ratio for having LA dysfunction was 3.1 (p = 0.04; 95% confidence interval, 1.1 to 9.1) when compared with patients with less than three risk factors.

**Conclusions:** LA dysfunction was present in more than one third of AF patients after satisfactory rhythm control for > 3 months. Patients with higher burden (three or more) of clinical risk factors were more likely to have impaired LA function.

**Key words:** atrial fibrillation; embolization; left atrium; transesophageal echocardiography

**Abbreviations:** ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AF = atrial fibrillation; CAD = coronary artery disease; CCB = calcium-channel blocker; CVA = cerebrovascular accident; DM = diabetes mellitus; LA = left atrial; LAA = left atrial appendage; LV = left ventricular; LVEF = left ventricular ejection fraction; SEC = spontaneous echo contrast; TEE = transesophageal echocardiography

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. It is well known that AF is associated with increased risk of embolic stroke. Loss of left atrial (LA) pumping, dilatation of the LA chamber, and decreased cardiac output may result in blood stasis and therefore a cardiac source of emboli. Converting AF into sinus rhythm followed by long-term maintenance of sinus rhythm can restore LA contraction, decrease LA size, and increase cardiac output. Theoretically, these effects can result in a reduction of thromboembolic events. However, the Atrial Fibrillation Follow-up Investigation of Rhythm Management study and the Rate Control vs Electrical Cardioversion for Persistent

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Atrial Fibrillation Study have demonstrated that management of AF with the rhythm-control strategy offers no advantage over the rate-control strategy regarding survival, stroke, or rehospitalization.

In the present study, we performed both transthoracic echocardiography and transesophageal echocardiography (TEE) in patients with AF who were in long-term (>3 months) sinus rhythm when treated with a rhythm-control strategy. We measured the LA appendage (LAA) peak emptying velocity and assessed the presence of LA/LAA thrombus and spontaneous echo contrast (SEC). According to the American College of Chest Physicians guidelines, hypertension, diabetes mellitus (DM), coronary artery disease (CAD), age >65 years, and prior cerebrovascular accident (CVA) were thought to increase the risk of stroke in AF patients. Therefore, we further analyzed the LA function in patients with these clinical risk factors although they were in normal sinus rhythm. We hypothesized that even after long-term successful rhythm control for AF, LA dysfunction still persisted in some patients.

**Materials and Methods**

**Study Population**

We included 93 consecutive patients (Table 1) who had AF under satisfactory rhythm control for >3 months. The judgment of satisfactory rhythm control was based on patient-reported symptoms, monthly ECG follow-up, and 24-h Holter ECG monitor (Del Mar Medical, Irvine, CA) if needed. The included patients were free from AF (no paroxysmal AF on Holter ECG). A total of 26 Holter ECGs were performed in 20 of the study patients during the periods of maintenance of sinus rhythm. In the other 73 patients, a Holter ECG was not performed, and the judgment of rhythm control was based on patient-reported symptoms and monthly ECG follow-up. Patients with prior cardiac surgery, left ventricular (LV) systolic dysfunction (LV ejection fraction [LVEF] <50%), or significant valvular heart disease (≥grade 3 valvular heart disease by echocardiography) were excluded. Of the 93 patients, 25 had sustained AF persisting for >1 week. The sustained AF was successfully converted to sinus rhythm by electrical or pharmacologic cardioversion, and the patients were free from AF with medical control thereafter. The other 68 patients had paroxysmal AF and became free from AF under medical control with antiarrhythmic drugs. There were 69 men and 24 women (mean age ± SD, 63 ± 12 years; range, 23 to 93 years). Of the 25 patients with sustained AF, 22 patients were cardioverted electrically and the other 3 patients were cardioverted pharmacologically. The duration of AF before cardioversion was 35 ± 44 months (range, 0.5 to 180 months), and the AF-free duration was 25 ± 23 months (range, 3 to 79 months). In patients with paroxysmal AF, the time from the first AF attack was 63 ± 48 months (range, 3 to 240 months). The following clinical information was collected: history of hypertension, DM, CAD documented by positive exercise stress-test result or coronary angiography, stroke, thyroid disease, smoking, and use of cardiovascular medications such as β-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB), antiarrhythmic drugs, digitals, diuretics, and calcium-channel blockers (CCBs) at the time of examination. Most of the patients (85 of 93 patients, 91%) were receiving antiarrhythmic agents, including class Ia, Ic, and III agents, or combinations.

**Echocardiographic Studies**

Transthoracic echocardiography with M-mode, two-dimensional imaging, two-dimensional guided Doppler, and color

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 93)</th>
<th>Sustained AF (n = 25)</th>
<th>Paroxysmal AF (n = 68)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female gender, No.</td>
<td>69/24</td>
<td>21/4</td>
<td>45/20</td>
<td>0.194</td>
</tr>
<tr>
<td>Age, yr</td>
<td>63 ± 12</td>
<td>64 ± 11</td>
<td>63 ± 12</td>
<td>0.565</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52 (56)</td>
<td>11 (44)</td>
<td>41 (60)</td>
<td>0.164</td>
</tr>
<tr>
<td>DM</td>
<td>15 (16)</td>
<td>5 (20)</td>
<td>10 (15)</td>
<td>0.543</td>
</tr>
<tr>
<td>CAD</td>
<td>13 (14)</td>
<td>3 (12)</td>
<td>10 (15)</td>
<td>0.742</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (16)</td>
<td>4 (16)</td>
<td>11 (16)</td>
<td>0.984</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>6 (6)</td>
<td>2 (8)</td>
<td>4 (6)</td>
<td>0.716</td>
</tr>
<tr>
<td>CVA</td>
<td>8 (9)</td>
<td>4 (16)</td>
<td>4 (6)</td>
<td>0.126</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>20 (22)</td>
<td>5 (20)</td>
<td>15 (22)</td>
<td>0.807</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>33 (35)</td>
<td>11 (44)</td>
<td>22 (32)</td>
<td>0.326</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>85 (91)</td>
<td>25 (100)</td>
<td>60 (88)</td>
<td>0.095</td>
</tr>
<tr>
<td>Digitals</td>
<td>13 (14)</td>
<td>9 (36)</td>
<td>4 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>22 (24)</td>
<td>12 (48)</td>
<td>10 (15)</td>
<td>0.001</td>
</tr>
<tr>
<td>CCBs</td>
<td>35 (38)</td>
<td>6 (24)</td>
<td>29 (43)</td>
<td>0.092</td>
</tr>
<tr>
<td>LVEF (M-mode)</td>
<td>64.9 ± 6.1</td>
<td>64.5 ± 5.4</td>
<td>65.1 ± 6.4</td>
<td>0.666</td>
</tr>
<tr>
<td>LA dimension, mm</td>
<td>37.2 ± 7.3</td>
<td>39.1 ± 8.0</td>
<td>36.5 ± 6.9</td>
<td>0.117</td>
</tr>
<tr>
<td>LA dysfunction</td>
<td>34 (37)</td>
<td>9 (36)</td>
<td>25 (37)</td>
<td>0.947</td>
</tr>
<tr>
<td>LA/LAA SEC and/or thrombus</td>
<td>12 (13)</td>
<td>5 (20)</td>
<td>7 (10)</td>
<td>0.220</td>
</tr>
<tr>
<td>LAA peak emptying velocity, cm/s</td>
<td>51.7 ± 21.6</td>
<td>47.5 ± 15.8</td>
<td>53.3 ± 23.3</td>
<td>0.252</td>
</tr>
<tr>
<td>LAA peak emptying velocity &lt; 40 cm/s</td>
<td>29 (31)</td>
<td>8 (32)</td>
<td>21 (31)</td>
<td>0.919</td>
</tr>
</tbody>
</table>

*Data are presented as No. of patients (%) or mean ± SD unless otherwise indicated.
†Sustained vs paroxysmal AF.
Doppler studies was performed (Sonos 5500; Hewlett-Packard; Andover, MA) with a 2- to 4-MHz transducer. M-mode LA dimension and LVEF were measured in the parasternal long-axis view. Transmitral and transtricuspid (end-expiratory phase) pulsed Doppler flow velocities were recorded from the apical four-chamber view with the sample volume positioned between the tips of the mitral or tricuspid leaflets. Assessment of the severity of mitral regurgitation depended on the relative size of the mosaic Doppler jet compared to the LA area.

TEE was performed using a biplane 7.5-MHz transducer. The LA was visualized from the basal short-axis view, and the LAV/LAA were inspected for the presence of thrombus or SEC, which was a dense swirling pattern with fluctuation in intensity but detectable constantly throughout the cardiac cycle. The presence of SEC/thrombus was judged by two cardiologists who were blinded to the study. Discrepancies were solved by a third independent cardiologist. LAA peak emptying velocity was obtained by pulsed-wave Doppler interrogation at the orifice of the appendage. Patients with LAA peak emptying velocity < 40 cm/s or SEC and/or thrombus in LA/LAA detected by TEE were thought to have LA dysfunction.

Statistical Analysis

All values were expressed as mean ± SD. Comparisons between parametric variables were performed using the unpaired Student t test, and comparisons between categorical variables were performed using the χ² test with Yates correction if needed. In multivariate logistic regression analysis, a forward stepwise model was used to include factors with a p value < 0.10. For all tests, a p value < 0.05 was considered statistically significant. All analyses were performed using statistical software (SPSS version 10.0; SPSS; Chicago, IL).

RESULTS

Comparisons Between Patients With Prior Sustained AF and Paroxysmal AF

There was no significant difference regarding the sex; age; coexisting diseases, including hypertension, DM, CAD, thyroid disease, and stroke; and smoking between patients with prior sustained AF and paroxysmal AF (Table 1). More patients with prior sustained AF took digitalis (9 of 25 patients vs 4 of 68 patients, p < 0.001) and diuretics (12 of 25 patients vs 10 of 68 patients, p = 0.001). When compared with patients with paroxysmal AF, patients with prior sustained AF did not differ significantly in respect to LVEF (64.5 ± 5.4% vs 65.1 ± 6.4%, p = 0.666) and LA dimension (39.1 ± 8.0 mm vs 36.5 ± 6.9 mm, p = 0.117). The incidence of LA dysfunction (9 of 25 patients vs 25 of 68 patients, p = 0.947), SEC and/or thrombus in LA/LAA (5 of 25 patients vs 7 of 68 patients, p = 0.220), and LAA peak emptying velocity < 40 cm/s (8 of 25 patients vs 21 of 68 patients, p = 0.919) was not statistically different as well.

Comparisons Between Patients With or Without LA Dysfunction

LA dysfunction was defined as LAA peak emptying velocity < 40 cm/s, or the presence of SEC and/or thrombus in LA/LAA found by TEE (Table 2). Among the 93 patients, 34 patients (37%) had LA dysfunction, including 12 patients (13%) with SEC and/or thrombus, and 29 patients (31%) with LAA peak emptying velocity < 40 cm/s. Seven of 34 patients (21%) had both. When compared with the other 59 patients, the patients with LA dysfunction did not differ significantly with respect to the type of previous AF, sex, age, duration of maintenance of sinus rhythm, hypertension, DM, CAD, thyroid disease, stroke, and smoking. The incidence of LA dysfunction was 32% for those with non-sinus rhythm for > 1 year and 39% for those with normal sinus rhythm for < 1 year (p < 0.514). The proportion of patients receiving β-blockers, ACEI/ARB, antiarrhythmic drugs, digitalis, diuretics, and CCBs was not significantly different either.

In transthoracic studies, the LV end-diastolic dimension, LV end-systolic dimension, LVEF, transmitral and transtricuspid early diastolic peak velocity, late peak atrial systolic velocity, deceleration time of mitral transmitral diastolic peak flow, and mitral ratio of the amplitude of the waves created by early diastolic filling and atrial contraction did not differ significantly between the two groups. However, the LA dimension was larger in patients with LA dysfunction (40 ± 6 mm vs 36 ± 8 mm, p = 0.018). After multivariate logistic regression analysis, larger LA diameter (p = 0.015) remained independently associated with the presence of LA dysfunction.

Comparisons of LA Function in Patients With Three or More Clinical Stroke Risk Factors and Those With Fewer Than Three Clinical Stroke Risk Factors

In patients with AF, age ≥ 65 years, hypertension, DM, CAD, and prior stroke or transient ischemic attack were considered as clinical risk factors for stroke (Table 3). Although all patients in the present study were maintained in sinus rhythm, we compared the LA function in patients with three or more risk factors (n = 17) and those with fewer than three risk factors (n = 76). We found that patients with three or more risk factors had significantly lower LAA peak emptying velocity (41 ± 16 cm/s vs 54 ± 22 cm/s, p = 0.021), and more LA/LAA SEC and/or thrombus (5 of 17 patients vs 7 of 76 patients, p = 0.025). Among the 17 patients with three or more risk factors, 10 patients (59%) had LA dysfunction. When compared to those with fewer than three risk factors, these patients were more likely to have
LA dysfunction, with an odds ratio of 3.1 (p = 0.04; 95% confidence interval, 1.1 to 9.1) in multivariate analysis.

**Discussion**

It has been demonstrated that atrial contractile dysfunction is usually present immediately after a successful cardioversion. However, LA function recovers gradually with time. The time needed for a full recovery is variable among different reports. Some studies have reported that this type of recovery would be completed within 4 weeks, which conventionally guided us to use anticoagulant after cardioversion of AF. A similar study demonstrated gradual elevation of plasma atrial natriuretic peptide concentration concomitantly with recovery of atrial mechanical function to a similar level of the control group within 30 days after cardioversion. However, Bellotti et al demonstrated that LAA function, as detected by TEE, recovered within 1 week in patients with nonvalvular AF who received electrical cardioversion. To our knowledge, no studies have evaluated the LA or LAA function after maintenance of sinus rhythm for > 3 months.

In the present study, more than one third of our patients had LA dysfunction even after maintenance...
of sinus rhythm for > 3 months. We also found a higher incidence (12 of 93 patients, 13%) of LA/LAA SEC and/or thrombus than previously reported. Although SEC and thrombus in the LA/LAA is frequently detected during AF, its incidence in sinus rhythm is much lower. In a large scale TEE survey in 1288 patients in sinus rhythm, Sadanandan and Sherrid12 reported a 2% prevalence of SEC that was associated with an enlarged left atrium (5.6 ± 0.6 cm), a higher prevalence of CVA, and decreased LAA peak emptying velocity (38 cm/s). They also reported that one fourth of the 24 patients with SEC in sinus rhythm had a history of AF or atrial flutter.

There was a 37% incidence of LA dysfunction in the present study. The incidence of LA dysfunction has never been reported after maintenance of sinus rhythm for > 3 months, and the incidence in the present study seems higher than expected. It is possible that LA dysfunction preceded the occurrence of AF, and it would persist even after AF had been abolished. Furthermore, AF may alter the atrial electrophysiologic and structural properties, and some of them are not completely reversible after cessation of AF, especially those with a longer duration.13,14 Nonetheless, our data suggest that some patients with prior AF, although maintaining in sinus rhythm for a long time, still had LA dysfunction and might be at risk for future embolic events. Long-term or even lifelong anticoagulation therapy might be needed for such patients.

Relationship Between Clinical Risk Factors and LA Dysfunction

According to the Atrial Fibrillation Investigators pooled analysis,15 age > 65 years, history of hypertension, DM, CAD, and previous TIA or stroke were identified as independent clinical risk factors for stroke in patients with AF. In our study, we showed that patients with three or more risk factors had a higher incidence of LA dysfunction despite being kept in sinus rhythm. Illien et al16 reported that one fourth of the 24 patients with SEC in sinus rhythm had a history of AF or atrial flutter.

In both the Atrial Fibrillation Follow-up Investigators and the Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation Study,3 patients in the rhythm-control group were still at risk for embolic events, especially those who withdrew from anticoagulation therapy or had inadequate anticoagulation. These findings were compatible with our observation that LA dysfunction persisted in some patients even though they had good rhythm control. Whether these patients benefit from long-term anticoagulation deserves further investigation. Furthermore, it is desirable to identify such patients who are particularly at risk. We demonstrated that patients with higher risk burden were more likely to have LA dysfunction.

The study has some limitations. A control group without any AF was not included in the present study because TEE is a semi-invasive and painful procedure. The baseline echocardiographic study was not performed during AF in these patients, so we could not know the differences of LA function before and after rhythm control for > 3 months. All the patients in the present study were supposed to be in sinus rhythm for > 3 months. However, we did not perform continuous monitoring because it was not feasible during clinical follow-up. We used a combination of history interrogation, office ECG, and ambulatory ECG monitor to exclude patients with AF recurrence. Although we could not exclude the possibility that asymptomatic or transient short episodes of AF occurred during the period, the patients in the present study were in “good rhythm control” from the point of view of both the patients and the clinicians.

In conclusion, the data in this study indicate that some patients with AF had persistent LA dysfunction under appropriate rhythm control for > 3 months. We also found that patients with three or more clinical risk factors were particularly at risk. Whether these patients would benefit from long-term or even lifelong anticoagulant therapy warrants further investigation.

REFERENCES