Prognostic Implication of the Left Atrial Appendage Mechanical Reserve After Cardioversion of Atrial Fibrillation

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Background  This study aimed to demonstrate the long-term prognostic implication of left atrial appendage (LAA) mechanical reserve determined after electrical cardioversion (CV) of atrial fibrillation (AF).

Methods and Results  53 successfully cardioverted chronic AF patients were studied (M/F=40/13, mean age =59±3). LAA emptying velocity (LAAEV) and filling velocity (LAAFV) were measured using transesophageal echocardiography (TEE) before cardioversion, immediately after CV, and with isoproterenol infusion. TEE was done at baseline, 1 month, 3–6 months, and 1 year after CV. At 1-year follow-up, 27 patients remained in sinus rhythm (SR, Group 1) and 26 patients showed AF recurrence (Group 2). Baseline clinical and echocardiographic findings were similar between the 2 groups. Immediately after CV, LAAEV and LAAFV decreased similarly in both groups. With isoproterenol infusion, the increase of LAAEV was greater in group 1 than in group 2. Multivariate analysis revealed that the peak increase of LAAEV after isoproterenol infusion was an independent predictor for SR maintenance (odds ratio 1.044, 95% confidence interval 1.014 to 1.075; p=0.0033). Prediction model consisting of the peak increase of LAAEV (>34.4 cm/s) and E/A ratio immediately after CV (<2.5) showed a good predictability for SR maintenance (correct ratio 69.8%).

Conclusion  This study presents a valid evaluation method for LAA mechanical reserve and demonstrated that LAA mechanical reserve is responsible for the maintenance of SR.  (Circ J 2008; 72: 256–261)

Key Words:  Atrial fibrillation; Cardioversion; Left atrial appendage flow velocity

Atrial fibrillation (AF) is the most common chronic arrhythmia seen in clinical practice and is associated with a high risk of systemic thromboembolism and heart failure.1–3 Chronic AF causes atrial enlargement and impairs ventricular function through loss of coordinative atrial contraction.4,5 Cardiac structural and functional changes caused by chronic AF can be reversed when the sinus rhythm is restored and maintained.6–9 Electrical cardioversion (CV) is the most commonly used method among the several treatment modalities to restore sinus rhythm (SR). Although the immediate success rate of CV has been reported to be up to 70–95%, the rate of long term SR maintenance is only approximately 50–60%.10–14 In addition to AF duration and the left atrial dimension, the left atrial appendage (LAA) mechanical function has been suggested as an important factor for successful CV of AF and the maintenance of SR.15–20 After electrical CV, atrial mechanical stunning develops, which presents as diminished LAA flow velocities.18,21 This atrial stunning can be reversed by isoproterenol infusion.22,23

The LAA is a distinct structure from the left atrium proper, although it lies adjacent to the left atrium. Its function has not been fully elucidated and a valid evaluation method has not been determined in cardioverted AF. In this study, we investigated a valid method for the evaluation of LAA mechanical reserve in cardioverted AF and demonstrated that increases in the LAA emptying velocity (LAAEV) and in the LAA filling velocity (LAAFV) with isoproterenol infusion after CV of AF can predict the long-term maintenance of SR.

Methods

Study Population  Sixty-seven consecutive chronic AF patients who had been successfully cardioverted to SR by direct current electrical CV between 2004 and 2005 were included in this study. Of them, 14 were excluded because of unsuitable echocardiographic image quality or follow-up loss, and a total of 53 patients were finally assessed. The mean age of the patients was 59±3 years (range, 40–76 years) and 40 were male (M/F=40/13). The mean duration of AF was 24±4 months (range, 1–72 months). Associated diseases were hypertension in 26 patients, diabetes mellitus in 3 patients, ischemic heart disease in 1 patient, and cerebrovascular disease in 4 patients. All patients gave written informed consent to participate in the study and the study protocol was approved by the institutional ethic committee for clinical trials.
Circulation Journal  Vol.72, February 2008

Fig 1.  (A) Transesophageal echocardiographic view (90 degree) of left atrial appendage (LAA) in which LAA velocities were measured.  (B) Representative pulsed wave Doppler flows of sinus rhythm in LAA.

Echocardiography
Transthoracic echocardiography (TTE) with a 2.5-MHz transducer (Sonos 5500, Phillips, Andover, MA, USA) was performed in all patients at baseline, 1 week after CV, 1 month after CV, 3–6 months after CV and 1 year after CV. The left ventricular end-diastolic dimension, left ventricular end-systolic dimension, diastolic interventricular septal wall thickness, posterior wall thickness and left atrial dimension (LAD) were measured by M-mode echocardiography. The left ventricular volume and ejection fraction (LVEF) were calculated by Simpson’s method using 2-dimensional echocardiography. After CV, mitral E and A wave velocities and deceleration time were also assessed with Doppler echocardiography.

Transesophageal echocardiography was performed with a 4- to 7-MHz phased-array multiplane probe (Sonos 5500, Phillips) before CV, immediately after CV and after isoproterenol infusion with gradually increasing doses in all patients.

The presence of a thrombus and spontaneous echo contrast in the LAA were assessed. To measure the LAA emptying and filling velocities (LAAEV, LAAFV), sample volumes were placed 1 cm into the mouth of the LAA and LAA flow velocities were measured with pulsed-wave Doppler echocardiography (Fig 1).

Protocol
Cardioversion was performed by the transthoracic direct current method with a step-up protocol (70 J, 100 J, 150 J) of a biphasic wave form cardioverter under anesthesia with sodium pentothal and diazepam. Immediately after the attainment of SR, the mitral inflow velocities, LAAEV and LAAFV were measured by TEE. After a baseline Doppler examination, intravenous isoproterenol was initiated at a rate of 2 mg/min and maintained for 5 min, after which the dose of isoproterenol infusion was titrated (to a maximum of 5 mg/min) until achievement of the target heart rate (110–120 beats/min) with monitoring of SaO2, ECG and blood pressure. LAAEV and LAAFV were continuously assessed during isoproterenol infusion. After CV, anticoagulant and antiarrhythmic (amiodarone or flecainide) medications were maintained. Patients were divided into 2 groups according to the recurrence of AF at a 1-year follow up. The patients who maintained SR during the 1-year follow up were assigned to Group 1, and those with AF recurrence were assigned to Group 2.

Follow-up
Patients were examined at the outpatient clinic at 1 week, 1 month, 3–6 months, and 1 year after CV. At each visit, electrocardiogram (ECG) and TTE were performed and the cardiac rhythm of the patient was evaluated. During the follow-up period, when AF was documented on ECG or during an outpatient clinic visit, the patient was assigned to the recurred AF group.

Statistical Analysis
Data were analyzed using SPSS 10.0 (SPSS 10.0 for Windows; SPSS; Chicago, IL, USA) and SAS. Continuous variables are reported as the mean ± SD and compared with the use of the t-test and paired t-test. Categorical variables were compared with the use of chi-square analysis. Receiver-operating characteristics (ROC) analysis was used to determine the optimal cut-off value for the prediction of maintenance of SR with respect to the peak increase of LAAEV.

Table 1 Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=53)</th>
<th>Group 1 (n=27)</th>
<th>Group 2 (n=26)</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (76%)</td>
<td>22 (82%)</td>
<td>18 (69%)</td>
<td>0.352</td>
</tr>
<tr>
<td>Female</td>
<td>13 (24%)</td>
<td>5 (18%)</td>
<td>8 (31%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.7±3.0</td>
<td>59±2.9</td>
<td>58.3±3.2</td>
<td>0.82</td>
</tr>
<tr>
<td>Duration of AF (months)</td>
<td>23.6±4.5</td>
<td>18.8±3.9</td>
<td>28.3±4.8</td>
<td>0.185</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Antiarrhythmics</td>
<td>19 (36%)</td>
<td>13 (48%)</td>
<td>6 (23%)</td>
<td>0.086</td>
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<tr>
<td>CCB</td>
<td>16 (30%)</td>
<td>9 (33%)</td>
<td>7 (27%)</td>
<td>0.766</td>
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<tr>
<td>β-blocker</td>
<td>24 (45%)</td>
<td>11 (41%)</td>
<td>13 (50%)</td>
<td>0.586</td>
</tr>
<tr>
<td>Digoxin</td>
<td>14 (27%)</td>
<td>5 (19%)</td>
<td>9 (35%)</td>
<td>0.224</td>
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<tr>
<td>ACEI</td>
<td>7 (13%)</td>
<td>5 (19%)</td>
<td>2 (8%)</td>
<td>0.420</td>
</tr>
<tr>
<td>ARB</td>
<td>23 (43%)</td>
<td>13 (48%)</td>
<td>10 (39%)</td>
<td>0.583</td>
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<tr>
<td>Associated conditions</td>
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<td></td>
<td></td>
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<tr>
<td>HTN</td>
<td>26 (49.1%)</td>
<td>18 (66.7%)</td>
<td>8 (30.8%)</td>
<td>0.013</td>
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<tr>
<td>DM</td>
<td>3 (5.7%)</td>
<td>1 (3.7%)</td>
<td>2 (7.7%)</td>
<td>0.610</td>
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<tr>
<td>IHD</td>
<td>1 (1.9%)</td>
<td>0 (0%)</td>
<td>1 (3.8%)</td>
<td>0.491</td>
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<tr>
<td>CVA</td>
<td>4 (7.5%)</td>
<td>2 (7.4%)</td>
<td>2 (7.7%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CCB, calcium-channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HTN, hypertension; DM, diabetes mellitus; IHD, ischemic heart disease; CVA, cerebrovascular attack.

Table 2 Baseline TTE Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
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<tr>
<td>LVEDD (mm)</td>
<td>51.4±1.9</td>
<td>50.4±1.9</td>
<td>0.289</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>32.1±2.4</td>
<td>31.7±2.1</td>
<td>0.792</td>
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<tr>
<td>Septum (mm)</td>
<td>10.3±1.3</td>
<td>9.8±1.2</td>
<td>0.285</td>
</tr>
<tr>
<td>PW (mm)</td>
<td>10.4±1.2</td>
<td>9.7±1.2</td>
<td>0.090</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>46.2±2.4</td>
<td>46.5±2.4</td>
<td>0.852</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>47.9±3.1</td>
<td>50.3±2.4</td>
<td>0.284</td>
</tr>
</tbody>
</table>

TTE, transthoracic echocardiography; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PW, posterior wall thickness; LAD, left atrial dimension; LVEF, left ventricular ejection fraction.
Results

The mean cumulative dose of electrical shock to convert to SR was 98.4±5.6 J and there were no difference between the 2 groups (Group 1 vs Group 2 = 93.0±5.3 J vs 104.0±5.8 J, p=0.221). At 1 month after successful CV, AF recurred in 16 of 53 patients and AF recurred in 8 patients at 3–6 months after CV. On the 1-year follow-up visit, 27 of the 53 patients remained in SR (Group 1, n=27) and 26 patients had AF recurrence (Group 2). Of all of the recurrences, 92% occurred within 6 months of successful CV. As depicted in Table 1, age, gender, duration of AF and current use of cardiovascular medication did not differ between group 1 and group 2 patients. Only hypertensive disease was more common in group 1 than in group 2 (Table 1). Baseline echocardiographic parameters, such as left ventricular size, ejection fraction and left atrial size, were similar for both groups as shown in Table 2.

**Table 3 Changes of Mitral Inflow Pattern After Isoproterenol Infusion**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Isopro</th>
<th>Group 2</th>
<th>Isopro</th>
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<tbody>
<tr>
<td>Post CV</td>
<td>(n=26)</td>
<td>(n=24)</td>
<td>Post CV</td>
<td>(n=25)</td>
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<tr>
<td>E (cm/s)</td>
<td>59.0±3.7</td>
<td>57.8±3.7</td>
<td>69.1±4.6</td>
<td>80.1±4.4</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>30.6±3.6</td>
<td>50.4±4.4</td>
<td>23.2±3.0</td>
<td>44.6±4.3</td>
</tr>
<tr>
<td>E/A</td>
<td>2.2±1.0</td>
<td>1.3±0.7</td>
<td>3.3±1.2</td>
<td>2.1±1.0</td>
</tr>
</tbody>
</table>

*p<0.01, *Post CV vs Isopro, †Group 1 vs Group 2.

CV, cardioversion; Isopro, isoproterenol; E, mitral E wave velocity; A, mitral A wave velocity; E/A, E/A ratio.

Effects of Isoproterenol on LAA Function after CV

A target heart rate of 110–120 beats/min was successfully achieved by isoproterenol infusion after SR for both groups (Group 1 vs Group 2 = 115.8±2.6 vs 110.8±3.6).

With isoproterenol infusion, LAAEV and LAAFV increased in patients in both groups (Figs 3, 4). In group 1 patients, LAAEV increased from 15.6±3.0 cm/s to 23.8±3.5 cm/s (60% decrease, p<0.0001; Fig 2A) and LAAFV increased from 43.7±4.0 cm/s to 23.8±3.5 cm/s (43% decrease, p<0.0001; Fig 2B) after CV to SR. The AF recurrence group (Group 2) patients also showed a decreased LAAEV from 34.1±4.0 cm/s to 12.2±2.5 cm/s (60% decrease, p>0.0001; Fig 2) after CV to SR. The degree of decrement of LAAEV and LAAFV after CV was similar for both groups.

Mitrail inflow pattern was also assessed immediately after CV. Mitrail E wave velocity was lower and A wave velocity higher for Group 1 patients than for Group 2 (Group 1 vs Group 2, E velocity; 59.0±3.7 cm/s vs 69.1±4.6 cm/s, p=0.037; A velocity; 30.6±3.6 cm/s vs 23.2±3.0 cm/s, p=0.004; Table 3). The mitral inflow E/A ratio was lower in Group 1 patients than in Group 2 patients (Group 1 vs Group 2 = 2.2±1.0 vs 3.3±1.2, p=0.014; Table 3).

Prediction Model for the Maintenance of SR at 1 Year

The clinical and echocardiographic factors that predict...
maintenance of SR after electrical CV were analyzed. By univariate analysis, the peak increase of LAAEV after isoproterenol infusion, the E/A ratio immediately after CV, and the A velocity immediately after CV were significantly associated with maintenance of SR. By multivariate analysis, the peak increase of LAAEV after isoproterenol infusion was identified as an independent predictor for the maintenance of SR at 1 year (odds ratio 1.044, 95% confidence interval 1.014 to 1.075; p=0.0033).

According to the ROC analysis, the peak increase of LAAEV after isoproterenol infusion of more than 34.4 cm/s could predict the maintenance of SR at 1 year with 61.5% sensitivity and 81.5% specificity (Fig 5A, p<0.0001, area under the curve =0.766). An E/A ratio <2.5 immediately after CV could predict the maintenance of SR at 1 year with 72% sensitivity and 65.4% specificity (Fig 5B, p=0.0006, area under the curve =0.735).

For predicting the maintenance of SR at 1 year, we used a logistic regression model consisting of 2 variables, which...

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Fig 3. Representative of left atrial appendage (LAA) flow velocity changes after cardioversion (CV) and isoproterenol infusion in patient with maintained sinus rhythm (SR) at 1 year. (A) LAA emptying velocity (LAAEV) and LAA filling velocity (LAAFV) assessed immediately after SR restoration by CV decreased significantly. (B) After achieving target heart rate (110-120 beats/min) by isoproterenol infusion. LAAEV and LAAFV increased prominently.

Fig 4. Representative of left atrial appendage (LAA) flow velocity changes after cardioversion (CV) and isoproterenol infusion in patient with recurred atrial fibrillation at 1 year. (A) LAA emptying velocity (LAAEV) and LAA filling velocity (LAAFV) assessed immediately after sinus rhythm restoration by CV decreased significantly. (B) After achieving target heart rate (110-120 beats/min) by isoproterenol infusion. LAAEV and LAAFV appear increased, but not as much as in group 1.

Fig 5. (A) Receiver operating characteristics (ROC) of the peak increase in the left atrial appendage emptying velocity after isoproterenol infusion predict the maintenance of SR. (B) The ROC curve of the mitral E wave velocity/mitral A wave velocity ratio immediately after cardioversion predicts the maintenance of sinus rhythm.
were predicted by the following function:

\[ y = \exp(b_0 + b_1 \cdot X_1 + \ldots + b_n \cdot X_n) / \left(1 + \exp(b_0 + b_1 \cdot X_1 + \ldots + b_n \cdot X_n)\right) \]

where \( X_1 \) is the peak increase of LAAEV after isoproterenol infusion and \( X_2 \) is the E/A ratio immediately after CV \( (b_0=0.0827, b_1=0.0337, b_2=-0.5647) \). When both the peak increase of LAAEV after isoproterenol infusion >34.4 cm/s and E/A ratio <2.5 immediately after CV were considered together, this logistic regression model predicted the maintenance of SR with 69.8% correct ratio (sensitivity 66.7%, specificity 73.1%, positive predictive value =72%).

Complications

One patient experienced AF recurrence during isoproterenol infusion; however, SR was successfully restored after repeat electrical CV. Otherwise no significant complications developed with respect to electrical CV or isoproterenol infusion.

Discussion

The results of our study demonstrate that LAA mechanical function and its improvement, determined by the changes in the LAA flow velocities with isoproterenol infusion, can be used as a useful predictor for the maintenance of SR. Moreover, TEE with isoproterenol infusion was shown to be a feasible method of assessing LAA mechanical reserve after CV of AF.

Clinical Implications of LAA Function in AF

The LAA mechanical function has been studied as a predictor for thromboembolic events after CV of AF, and as a representative of atrial function or chronicity of AF. Whether the LAA mechanical function determined by flow velocities represents left atrial function or not, it is known to have important clinical value in the management of AF. In chronic AF, the left atrium undergoes remodeling processes that are believed to be pathophysiologic factors for the maintenance and recurrence of AF.24,25 The left atrium and appendage dysfunction caused by the remodeling processes in AF are reversible in part when SR is restored.15,18–20,22,23,26–30 Thus, it could be referred that impaired or incomplete reversal of the remodeling process is associated with recurrence of AF. To our knowledge, various factors that affect the reverse remodeling of the atrium, such as the LAD, AF duration, and the LVEF, have been suggested as predictors for AF recurrence, but no definite factors have been determined. Moreover, the relationship between the reversibility of LAA dysfunction and AF recurrence is uncertain. One might suggest that the potential reversibility of LAA mechanical function after CV of AF was satisfactory, so that SR could be maintained. On the other hand, others could also suggest that LAA mechanical dysfunction caused by chronic AF might be reversed because of the maintenance of SR. Thus, it would be useful if we could demonstrate the existence of the potential reversibility of LAA mechanical dysfunction after CV of AF and clarify its relationship to the recurrence of AF.

In this study, we successfully identified the predicted extent of LAA mechanical improvement in cardioverted AF, and determined its impact on the maintenance of SR. As seen in other studies, atrial stunning developed immediately after CV of AF and was restored with isoproterenol infusion in most patients examined in this study. However, the peak increase of LAAEV and the degree of LAA mechanical functional improvement after isoproterenol infusion were greater in the patients who had maintained SR at 1 year (Fig 2). The E/A ratio immediately after CV of AF was lower in group 1 than in group 2. Although multivariate analysis demonstrated only the peak increase of LAAEV after isoproterenol infusion as an independent predictor for SR maintenance, the E/A ratio immediately after CV might be considered as another predictor for the recurrence of AF, because it represents both diastolic heart function and atrial contractile function. When both the peak increase of LAAEV after isoproterenol infusion and E/A ratio after CV are considered together, there was good predictability for the maintenance of SR. These findings indicate that the potential reversibility of LAA mechanical dysfunction in AF can be predicted and its role in the recurrence of AF can be identified.

Validity of LAA Flow Velocities for Predicting LAA Mechanical Reserve

For the assessment of atrial mechanical function, the left atrial ejection fraction, mitral E and A velocities and the LAA flow velocities have been used in a number of studies.15,19,20,27–28 However, the precise assessment of atrial function with those parameters has been limited because of the effects of diverse hemodynamic and structural factors. Although there have been controversies with regards to their value, LAA flow velocities are less influenced by other hemodynamic factors, such as valvular regurgitations and thus, it has been suggested, to represent LAA contractile function. Recently, Date et al have reported that low-dose isoproterenol infusion improved LAA mechanical function after CV of AF by positive inotropic action through ß-adrenergic responsiveness of the atrial myocytes.22 Sanders et al have demonstrated the significant improvement of atrial mechanical stunning with increasing atrial pacing rates, treatment with isoproterenol, and with calcium.23 In addition, at the myocardial fiber level, atrial contractile function was shown to be reversible with isoproterenol and calcium treatment by Schotten et al.22

In our study, LAA flow velocities were successfully assessed by the use of TEE. Even after the infusion of isoproterenol, they were clearly delineated by Doppler echocardiography. LAAEV and LAAFV decreased significantly immediately after CV of AF and recovered transiently with infusion of isoproterenol. As presented by the changes of LAA flow velocities, the potential reversibility of atrial dysfunction after CV was different between the SR maintained group and the AF recurrence group (Figs 2–4). In conclusion, this study presents a valid and feasible method for assessing LAA mechanical reserve after CV of AF.

Study Limitations

One of the limitations of our study is that the definite functional relationship between the left atrium and the LAA could not be determined and remains to be elucidated. The other one is the limited evaluation of the mitral inflow pattern after isoproterenol infusion. Because the mitral E and A velocities are markedly influenced by heart rate and diverse hemodynamic factors, their measurement could not be completed in some patients at peak heart rate (Table 3). We also cannot exclude the effects of underlying cardiovascular conditions, such as hypertension and cardiovascular medications, on the maintenance of SR. Hypertension was more common in group 1 than in group 2 and more
patients in group 1 appeared to use antiarrhythmic drugs, although the statistical difference was not so significant (Table 1). Those findings need to be considered in-depth in a prospective large scale study because of the complexity of interpretation and the relatively small sample size of our study. Furthermore, the exact mechanism of the association between the reversibility of LAA dysfunction and the recurrence of AF need to be clarified at the molecular and cellular levels.

Conclusions

Our study has demonstrated a valid evaluation method for LAA mechanical reserve, and has proved that LAA mechanical reserve is responsible for the long-term maintenance of SR.

References