Left Atrial Appendage Outflow Velocity is Superior to Conventional Criteria for Predicting of Maintenance of Sinus Rhythm After Simple Cryoablation of Pulmonary Vein Orifices

Naoki Isobe, MD; Koichi Taniguchi, MD; Shigeru Oshima, MD; Hiroshi Kamiyama, MD*; Masahiko Ezure, MD**; Tatsuo Kaneko, MD**; Hiroshi Tada, MD; Hitoshi Adachi, MD; Takuji Toyama, MD; Shigeto Naito, MD; Hiroshi Hoshizaki, MD

Background We sought to identify factors favoring long-term restoration of sinus rhythm (SR) in patients with atrial fibrillation (AF) who underwent a simple cryoablation of pulmonary vein orifices (PV-cryo) as part of their cardiac surgery.

Methods and Results Of 101 patients with AF undergoing PV-cryo, the 71 in SR at discharge were grouped according to whether they maintained or lost SR (group SR, n=61, and group AF, n=10) after an average of 2.3 years. Atrial fibrillation present at discharge (n=30) persisted during follow up. Comparisons were made to identify preoperative predictive factors, including transthoracic and transesophageal echocardiographic parameters. Of patients discharged from the hospital with SR, 92% (46 of 50) of those with AF duration of 3 years or less were in group SR, as were 92% (23 of 25) of those with left atrial dimension of 50mm or less, and 93% (37 of 40) of those with average peak left atrial appendage outflow velocities (LAA-V) of at least 30cm/s. Of 25 patients in group SR who had no paroxysmal AF and did not require antiarrhythmic drugs, all had LAA-V over 20cm/s. Patients in group AF all had LAA-V under 40cm/s.

Conclusions Left atrial appendage outflow velocities was the best predictor of whether SR was maintained long-term after PV-cryo. (Circ J 2005; 69: 446–451)

Key Words: Atrial fibrillation; Cryoablation of pulmonary vein; Left atrial appendage outflow velocity

Since Haissaguerre et al reported that most atrial premature beats that initiate atrial fibrillation (AF) originate in the pulmonary veins (PV), various surgical techniques have been devised to isolated PV by incision and/or cryoablation.1–5 In this context, we have used simple surgical cryoablation confined to the 4 PV orifices (PV-cryo) to eliminate chronic AF in appropriate patients undergoing cardiac surgery since 1999. We previously reported initial results in which 70% of patients showed sinus rhythm (SR) at discharge from the hospital6. Furthermore, we found that the duration of AF (AF-D), left atrial dimension (LAD), and the mean of peak left atrial appendage outflow velocities (LAA-V) before operation were important factors in assessing the likelihood of successful conversion from AF to SR.6 In this study, the patients were followed up for a relatively long period of time to determine whether maintenance of SR was related to these variables as well as which of the variables was the best long-term predictor of SR.

Methods

Patients

We carried out PV-cryo as part of a cardiac operation at our hospital in 101 patients with a history of chronic AF.

Table 1 Characteristics of 71 Patients Who Were Able to Maintain Sinus Rhythm After Cryoablation of Pulmonary Vein Orifices at Hospital Discharge

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group SR</th>
<th>Group AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>35/36</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63±12</td>
<td></td>
</tr>
<tr>
<td>Underlying heart disease (no. patients, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reumatic valve disease</td>
<td>32 (45)</td>
<td></td>
</tr>
<tr>
<td>MR (Not-reumatic)</td>
<td>26 (37)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>13 (18)</td>
<td></td>
</tr>
<tr>
<td>AF-D (years)</td>
<td>3.4±3.3</td>
<td></td>
</tr>
<tr>
<td>Transthoracic echocardiographic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>53±7</td>
<td></td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>53±9</td>
<td></td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>36±8</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59±12</td>
<td></td>
</tr>
<tr>
<td>Transesophageal echocardiographic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAA-V (cm/s)</td>
<td>33±15</td>
<td></td>
</tr>
</tbody>
</table>

M. male; F. female; MR. mitral regurgitation; AF-D. duration of atrial fibrillation; LAD, left atrial diameter; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LAA-V, average of the peak left atrial appendage outflow velocities.

Data are presented as the mean value±SD.
Measurement of LAA Doppler velocity profiles, especially LAA-V, is a recently described approach towards the assessment of LAA function by transesophageal echocardiography.8–12 Left atrial appendage-V profiles were inspected closely for the presence of thrombus and spontaneous echo contrast.

Patients were enrolled in the present study after giving written informed consent. Before operation, AF had resisted all antiarrhythmic drugs and persisted for at least 3 months (mean AF-D, 3.4±3.3 years). We divided the 71 patients discharged with SR into 2 groups according to rhythm maintained during follow up after discharge; a group in SR and a group in AF. Patients in group SR were divided further into subgroups according to whether paroxysmal AF (PAF) occurred, and whether antiarrhythmic drugs were required; those who remained as having long-term rhythm of SR had no PAF and did not require antiarrhythmic drugs unless the medication was discontinued (group SR-B); and those taking antiarrhythmic drugs but still developed PAF (group SR-C) (Table 1).

Echocardiography

Before the operation, transesophageal echocardiography was performed using an ultrasonic sector scanner with 2.5-MHz transducers (SONOS 2000, Hewlett Packard, Boston, MA, USA or SONOS 5500, Philips Technology, Andover, MA, USA). Standard parasternal long- and short-axis views and apical 2- and 4-chamber views were obtained in all patients. M-mode echocardiograms were derived from the 2-dimensional images, and left ventricular dimension and LAD were measured. Left ventricular ejection fraction was calculated by using the modified Simpson method. Measurements were carried out at end-expiration.

Transesophageal echocardiography was performed before operation with a multiplane 7.5-MHz transducer. Patients were studied in a fasted state after topical anesthesia of the hypopharynx with 2% viscous lidocaine and 10% lidocaine spray. The left atrium (LA) and left atrial appendage (LAA) were inspected closely for the presence of thrombus and spontaneous echo contrast.

Measurement of LAA Doppler velocity profiles, especially LAA-V, is a recently described approach towards the assessment of LAA function by transesophageal echocardiography.8–12 Left atrial appendage-V profiles were obtained by pulse Doppler interrogation at the orifice of the LAA. Peak outflow velocity signals within each RR interval were averaged over a minimum of 6 cardiac cycles for patients studied during atrial fibrillation. In all patients, interobserver differences in the measurement of LAA-V were determined from values obtained by 2 observers.

Surgical Procedure and Cryoablation of the Pulmonary Vein

The operation was performed by using standard cardiopulmonary bypass techniques with mild hypothermia and cold-blood cardioplegia. After initiation of cardiopulmonary bypass, a left-sided vertical atriotomy was extended to the left margin of the left pulmonary veins. Cryoablation (−60°C for 2 min) was performed with a spherical cryo-probe, which was 20mm in diameter. The orifices of the 4 pulmonary veins were encircled by the cryo-probe. No further atriotomy was performed for the atrial septum or right atrium. After completion of these procedures, the principal surgical procedure was performed. All patients in this series were operated on by the same surgical team.

Postoperative Management

Antiarrhythmic agents in the class I or IV from the Vaughan Williams classification13 as well as digitalis, were given to all patients postoperatively. These were discontinued at 3–6 months after the operation, with the exception of patients in atrial arrhythmia, who continued taking the medication.

Statistical Analysis

Data are expressed as the mean±SD. Comparisons of mean values between the SR and AF groups were performed by using the Wilcoxon rank-sum test. Categorical variables were compared by using the chi-squared test or the Fisher exact test, as appropriate. Results were considered statistically significant at a p<0.05.

Results

Long-Term Course of Patients

During the follow-up period, 2 patients who were in AF at hospital discharge died, one of heart failure and the other of gallbladder disease. Of 71 patients in SR at hospital discharge, 61 continued to be in SR (group SR), while 10 had a relapse of persistent AF (group AF, Table 2). The 30 patients in AF at hospital discharge, all had persistent AF

Table 2 Individual Data for Group AF Patients

<table>
<thead>
<tr>
<th>Patients no.</th>
<th>Age (years), sex</th>
<th>Underlying heart disease</th>
<th>Operation</th>
<th>History of DC</th>
<th>AF-D (years)</th>
<th>LAD (mm)</th>
<th>LVEF (%)</th>
<th>LAA-V (cm/s)</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63/M</td>
<td>MS + AS + TR</td>
<td>DVR + TAP</td>
<td>+</td>
<td>3.0</td>
<td>54</td>
<td>62</td>
<td>12</td>
<td>4.3</td>
</tr>
<tr>
<td>2</td>
<td>63/F</td>
<td>MR (MVP)</td>
<td>MVR</td>
<td>−</td>
<td>3.0</td>
<td>60</td>
<td>73</td>
<td>35</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>30/F</td>
<td>MR (MVP)</td>
<td>MVR</td>
<td>+</td>
<td>7.0</td>
<td>62</td>
<td>56</td>
<td>21</td>
<td>3.9</td>
</tr>
<tr>
<td>4</td>
<td>59/F</td>
<td>MSR</td>
<td>MVR</td>
<td>+</td>
<td>6.0</td>
<td>56</td>
<td>40</td>
<td>25</td>
<td>3.7</td>
</tr>
<tr>
<td>5</td>
<td>65/F</td>
<td>MS + TR</td>
<td>MVR + TAP</td>
<td>+</td>
<td>3.0</td>
<td>50</td>
<td>54</td>
<td>35</td>
<td>3.1</td>
</tr>
<tr>
<td>6</td>
<td>63/M</td>
<td>AR + MS</td>
<td>DVR</td>
<td>+</td>
<td>5.0</td>
<td>54</td>
<td>44</td>
<td>10</td>
<td>2.0</td>
</tr>
<tr>
<td>7</td>
<td>57/M</td>
<td>AAE + AR</td>
<td>modified Bentall</td>
<td>+</td>
<td>10.0</td>
<td>56</td>
<td>82</td>
<td>12</td>
<td>2.0</td>
</tr>
<tr>
<td>8</td>
<td>53/M</td>
<td>MSR</td>
<td>MVR</td>
<td>+</td>
<td>1.5</td>
<td>37</td>
<td>40</td>
<td>31</td>
<td>1.5</td>
</tr>
<tr>
<td>9</td>
<td>71/M</td>
<td>FS</td>
<td>MVR</td>
<td>+</td>
<td>9.0</td>
<td>60</td>
<td>50</td>
<td>18</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>55/M</td>
<td>MSR (MVP)</td>
<td>MVR</td>
<td>+</td>
<td>6.0</td>
<td>54</td>
<td>78</td>
<td>19</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean</td>
<td>58±11</td>
<td></td>
<td></td>
<td></td>
<td>5.3±2.8</td>
<td>54±7</td>
<td>58±15</td>
<td>22±9</td>
<td>2.6±1.4</td>
</tr>
</tbody>
</table>

M, male; F, female; MS, mitral stenosis; MR, mitral regurgitation; MVP, mitral valve prolapse; MSR, mitral stenosis and regurgitation; AS, aortic stenosis; AR, aortic regurgitation; MVR, mitral valve replacement; DVR, mitral and aortic valve replacement; TAP, tricuspid annuloplasty; History of DC, history of direct current cardioversion after cryoablation of pulmonary vein orifices in hospital; AF-D, duration of atrial fibrillation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LAA-V, average of the peak left atrial appendage outflow velocities.

Data are presented as the mean value±SD.

No intra- or perioperative complications were noted. At the time of hospital discharge, 71 patients were able to maintain SR. Patients were enrolled in the present study after giving written informed consent. Before operation, AF had resisted all antiarrhythmic drugs and persisted for at least 3 months (mean AF-D, 3.4±3.3 years). We divided the 71 patients discharged with SR into 2 groups according to rhythm maintained during follow up after discharge; a group in SR and a group in AF. Patients in group SR were divided further into subgroups according to whether paroxysmal AF (PAF) occurred, and whether antiarrhythmic drugs were required; those who remained as having long-term rhythm of SR had no PAF and did not require antiarrhythmic drugs unless the medication was discontinued (group SR-B); and those taking antiarrhythmic drugs but still developed PAF (group SR-C) (Table 1).
during their long-term course. In the SR group, 25 had no PAF and required no antiarrhythmic drugs (group SR-A); 28 had no PAF but needed antiarrhythmic drugs (group SR-B); and 8 had PAF and took antiarrhythmic drugs (group SR-C) (Fig 1).

Preoperative Predictors and Surgical Data in the Restoration and Maintenance of Sinus Rhythm

No statistically significant differences were found in terms of gender, age, underlying heart disease, LAD, LV ejection fraction, or surgical data between the SR and AF groups. However, AF-D was significantly longer and LAA-V was slower in the AF group than in the SR group (Tables 3 and 4).

Late Postoperative Rhythm

AF (n = 10)  
SR (n = 61)  
Antiarrhythmic drug (-) and PAF(-): 25 (25%)  
Antiarrhythmic drug (+): 36  
Persistent AF: 10 (10%)  
AF (n = 10)  
SR, sinus rhythm; AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation.

Relationship Between Late Postoperative Rhythm and Preoperative Factors

Among patients with AF-D of 3 years or less, 92% (46 of 50) were in group SR while 71% (15 of 21) of patients with AF-D exceeding 3 years were in group SR. This was not a statistically significant difference.

Of 25 patients with LAD of 50 mm or less, 23 (92%) were in group SR, while 83% (38 of 46) of patients with LAD exceeding 50 mm were in group SR, but this represented no significant differences.

In contrast, patients with LAA-V of at least 40 cm/s (n=21) all were in group SR, while 80% (40 of 50) patients with LAA-V less than 40 cm/s were in group SR; a significant difference was found between the 2 groups (p<0.05). In patients with LAA-V of at least 30 cm/s, 93% (37 of 40) were in group SR. Thirty-eight percent (5 of 14) of patients with LAA-V of 20 cm/s or less were in group AF, while 9% (5 of 57) of patients with LAA-V exceeding 20 cm/s were in group AF. Patients with LAA-V of 20 cm/s or less were more likely to be in the AF group than patients with LAA-V exceeding 20 cm/s (p<0.05; Fig 2).

Long-Term Results and Perioperative Factors for Patients in Sinus Rhythm at Hospital Discharge

No statistically significant differences were found for age or LAD, but AF-D was significantly longer in group AF.
than group SR-A; LAA-V was slower in group AF than in groups SR-A and SR-B; and the percentage of patients undergoing direct current cardioversion after the operation was significantly higher in group AF than in groups SR-A and SR-B. The relationship between LAA-V and late postoperative results is presented in Fig 3. Left atrial appendage outflow velocities in group SR-A were consistently above 20 cm/s. Among patients with LAA-V of at least 30 cm/s, 85% (34 of 40) did not experience even PAF. The LAA-V in group SR-A was significantly higher compared with groups SR-B (p<0.05), SR-C (p<0.05), and AF (p<0.001). The LAA-V in group SR-B was significantly higher than it was in group AF (p<0.05; Table 5).

Discussion

Comparison With Previous Studies
Since the study by Haissaguerre et al, simple surgical
isolation of the pulmonary veins has been developed as an anti-AF procedure. Results have been described by several investigators.\textsuperscript{2–5} Gaia et al performed limited posterior left atrial cryoablation in patients with chronic AF during valvular heart surgery, successfully restoring SR in only 69% of 29 survivors after 9 months of follow up\textsuperscript{1} Imai et al described outcomes following 32 simple left atrial procedures for chronic AF associated with mitral valve disease, with 74% of patients maintaining SR after an average follow-up period of 37 months\textsuperscript{2} Kallil et al reported that 92.3% of 15 patients with mitral valve disease had returned to SR after simple surgical isolation of the pulmonary veins and remained in SR at 6 months of follow up\textsuperscript{1} However, these reports involved fewer patients or less follow-up time than our investigation.

The outcomes of the present study, with 61 of 101 patients remaining in SR (60%), were somewhat poorer than those described above. However, our subjects included some with a long AF-D (>10 years; n=18, 18% of all patients), large LAD (=60 mm; n=28, 28% of all patients), or low LAA-V (=20 cm/s; n=38, 38% of all patients). Long-standing AF\textsuperscript{14,15} a large left atrium\textsuperscript{14,15} and low LAA-V\textsuperscript{16–20} are all considered negative predictive factors for both recovery and maintenance of SR.

Simple Cryoablation of Pulmonary Vein Orifices

In our center, we limited ablation to the orifice of the 4 pulmonary veins and used only cryoablation to produce the lesions, aiming to reduce time required for the procedure (<15 min) and also to preserve atrial contractility. This procedure was compatible with requirements for the open-heart surgery that immediately followed. Thus, patients with AF-D for 3 years or less, LAD not exceeding 50 mm, and/or LAA-V of at least 30 cm would be likely to benefit from PV-cryo.

Relation Between the LAA-V and Long-Term Results

We recognized that many patients with AF have a small LA contraction, representing a limited degree of residual LA function. Measurement of LAA-V is a recently described technique for assessing the LA function by transesophageal echocardiography.\textsuperscript{8–12} The relationship between the LAA-V and cardiac rhythm has been described in patients who underwent cardioversion of persistent AF\textsuperscript{16–20} if LA function was maintained at a certain level, patients were more easily kept in SR after PV-cryo. However, we sometimes encountered patients with AF in which an LA contraction could hardly be recognized. In pathologic studies, advanced structural changes in the atria have been reported in patients with chronic AF\textsuperscript{21} Larger numbers of patients with AF who underwent the maze procedure did not exhibit an effective atrial contraction, possibly because of fibrotic and calcified degeneration of the LA myocardium.\textsuperscript{22,23} Pathologic degenerative change would be irreversible; advanced LA dysfunction would persist after the PV-cryo. We considered that they were closely related to the recurrence of AF.

We found LAA-V to be superior to conventional criteria in predicting the maintenance of SR after simple cryoablation of the pulmonary vein orifices. An LAA-V below a certain level indicates failure to restore the LAA function. Left atrial appendage outflow velocities, which can be measured easily by using transesophageal echocardiography, was the most valuable predictor of whether SR could be maintained after PV-cryo and also whether patients would be free of PAF or would require antiarrhythmic drugs. The LAA-V data can determine whether anticoagulation and antiarrhythmic drugs are indicated for preventing thromboembolism resulting from PAF.

Study Limitations

As almost all patients referred to our hospital returned to their previous hospitals 3 months after the operation, they were then treated by their previous doctors. Had some group AF patients continued or resumed medications against atrial arrhythmia, they might not be in persistent AF. From the results of the present study, patients whose LAA-V was slow before the operation (especially <20 cm/s) might not exhibit an effective atrial contraction, possibly because of fibrotic and calcified degeneration of the LA myocardium.\textsuperscript{22,23} Pathologic degenerative change would be irreversible; advanced LA dysfunction would persist after the PV-cryo. We considered that they were closely related to the recurrence of AF.

Conclusion

Patients with AF undergoing PV-cryo who had AF-D for not more than 3 years, or LAD not exceeding 50 mm, or LAA-V of at least 30 cm/s often would show good results after an average follow-up period of 2.3 years. Left atrial appendage outflow velocities were related whether antiarrhythmic drugs were required, and whether PAF occurred after PV-cryo. Left atrial appendage outflow velocities were the most valuable predictor of whether SR would be

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**Table 5 Long-Term Results and Perioperative Factors for Patients in Sinus Rhythm at Hospital Discharge**

<table>
<thead>
<tr>
<th>Late postoperative rhythm</th>
<th>SR (Group SR-A)</th>
<th>SR (Group SR-B)</th>
<th>SR (Group SR-C)</th>
<th>Persist-AF (Group AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAF</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>n</td>
<td>25</td>
<td>28</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63±13</td>
<td>64±13</td>
<td>62±12</td>
<td>58±11</td>
</tr>
<tr>
<td>AF-D (years)</td>
<td>1.8±1.4*</td>
<td>3.8±1.7</td>
<td>4.6±2.5</td>
<td>5.4±2.8</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>50±7</td>
<td>54±7</td>
<td>52±7</td>
<td>54±7</td>
</tr>
<tr>
<td>LAA-V (cm/s)</td>
<td>41±14*</td>
<td>31±14*</td>
<td>29±14</td>
<td>22±9</td>
</tr>
<tr>
<td>No. of patients received DC</td>
<td>8 (32)*</td>
<td>6 (21)*</td>
<td>3 (38)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>2.0±1.3</td>
<td>2.4±1.3</td>
<td>2.2±1.2</td>
<td>2.6±1.4</td>
</tr>
</tbody>
</table>

SR, sinus rhythm; AF, atrial fibrillation; Persist-AF, persistent atrial fibrillation; PAF, paroxysmal atrial fibrillation; AF-D, duration of atrial fibrillation; LAD, left atrial diameter; LAA-V, average of the peak left atrial appendage outflow velocities; No. of patients received DC, number of patients received direct current cardioversion after cryoablation of pulmonary vein orifices in hospital.

Data are presented as the mean value ± SD.

\*p<0.05 vs Group AF.
maintained after PV-cryo.

References