Pharmacological cardioversion preceding left atrial ablation: bepridil predicts the clinical outcome following ablation in patients with persistent atrial fibrillation

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Aims
Bepridil is highly effective in terminating persistent atrial fibrillation (AF). Despite continued treatment, a high rate of AF recurrence after pharmacological cardioversion (PC) with bepridil has been reported. Bepridil therapy is also associated with significant adverse effects.

Methods and results
This retrospective case–control study included 82 patients with persistent AF (PEF). Group 1 (22 patients) comprised cases undergoing AF ablation following attempted PC with bepridil. Group 2 (60 patients) comprised control that underwent AF ablation without bepridil pre-treatment. In Group 1, 15 patients (68%) restored sinus rhythm (SR) with bepridil (SR group) and 7 continued to have AF (AF group). SR group underwent extensive pulmonary vein isolation (EPVI) alone. AF group and Group 2 underwent linear ablation after EPVI, if AF was inducible. At the end of 18 ± 5 months off antiarrhythmic drugs, the AF-free rate was 87% in SR group, 29% in AF group, and 72% in Group 2 (72 vs. 29%, \( P = 0.02 \)).

Conclusion
Following AF ablation in patients who successfully restored SR with bepridil pre-treatment, AF-free rate was significantly higher than in those who failed to do so. Conversion to SR with bepridil might help select the optimal patients with PEF for catheter ablation.

Keywords
Pharmacological cardioversion • Atrial fibrillation • Catheter ablation • Extensive pulmonary vein isolation • Bepridil

Introduction
Isolation of pulmonary veins is effective in curing paroxysmal atrial fibrillation (AF)1–3 and isolation of a large area including pulmonary vein (PV) antrum is more effective than individual PV isolation (PVI).4 Recently, a variety of techniques including linear ablation have been proposed to improve the outcome of AF ablation.5–7 However, such strategies are associated with limited success in patients with long-lasting AF making the catheter ablation of persistent AF (PEF), a controversial strategy.

On the other hand, the rate of successful pharmacological cardioversion (PC) of PEF by class I drugs is not very high compared with class III drugs.8 Bepridil was originally developed as an anti-anginal drug. Besides calcium channel blocking properties, it has multiple ion-channel blocking effects.9,10 Previous reports showed favourable drug effects on restoration of sinus rhythm (SR) and reverse atrial remodelling in patients with PEF.11–13 However, high rate of AF recurrence and substantial adverse effects were also observed with the use of bepridil in PEF.13

We investigated clinical outcome following AF ablation in PEF patients who were pre-treated with bepridil to attempt PC and

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compared its results to those who were not pre-treated with bepridil.

**Methods**

**Study population**

This retrospective case–control study included 82 patients with PEF. Group 1 comprised 22 consecutive cases undergoing AF ablation following attempted PC with bepridil. Group 2 comprised 60 consecutive controls that underwent AF ablation without preceding bepridil treatment. All patients underwent AF ablation between January 2006 and May 2007 and were followed up for at least 12 months. Persistent AF was defined as non-self-terminating AF lasting more than 7 days. The patients with a left atrial diameter (LAD) > 50 mm and/or left ventricular ejection fraction (LVEF) < 40% on echocardiography and/or period of AF lasting > 3 years were excluded from the study because previous reports showed that it was difficult to restore SR with bepridil in these subsets. All patients were effectively anticoagulated for at least 1 month before either the PC or catheter ablation. All the patients gave written informed consent to participate in the study.

**Study protocol**

In Group 1, oral bepridil (100–150 mg/day) was administered for 1 month. If it failed to restore SR and the QTc interval was not markedly prolonged, the dose of bepridil was increased up to 200 mg/day. The maximum period for attempting PC was 4 months and the drug was stopped if it failed to restore SR during that period. Regardless of the results of PC, all patients underwent extensive PVI (EPVI) more than 3 weeks after discontinuation of bepridil. The patients with successful PC (SR group) underwent EPVI without an LA linear ablation. Those with unsuccessful PC (AF group) underwent additional LA linear ablation if AF was inducible after EPVI.

In Group 2, all antiarrhythmic drugs (AAD) were discontinued for more than 7 days before ablation. All patients underwent AF ablation without attempting prior PC. Extensive PVI was performed in all patients, and LA linear ablation5–7 was added if AF was inducible.

**Ablation protocol**

Transoesophageal echocardiography was performed and atrial thrombi excluded before ablation in all patients. Surface electrocardiogram (ECG) and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recorder system (Cardiolab system, Prucka Engineering, Houston, TX, USA or LabSystem PRO, Bard Electrophysiology, Lowell, MA, USA). The bipolar electrograms were filtered from 30 to 500 Hz. After single transseptal puncture, two long sheaths (SR0, AF Division, St Jude Medical, Minnetonka, MN, USA and Mullins transeptal sheath, Medtronic Inc., Minneapolis, MN, USA) were introduced into the left superior and inferior PVs, respectively. Bolus dose (5000 units) of heparin was administered intravenously followed by continuous infusion at 1000 U/h to maintain an activated clotting time of 200–300 s. Left pulmonary venography and contrast esophagography were simultaneously performed to obtain the anatomical relationship between the area around the PV ostia and esophagus. Subsequently, right pulmonary venography was undertaken.

Patients presenting with AF were internally cardioverted before starting ablation. If cardioversion failed to restore SR, ablation was performed during AF. After achieving EPVI, cardioversion was repeated. Two circular mapping catheters (Lasso, Biosense Webster, Diamond Bar, CA, USA) were placed one each in the superior and inferior PVs during EPVI performed under fluoroscopic and electrophysiologic guidance.14,15 Left atrial posterior wall, at a distance of 1–3 cm from each of the left- and the right-PV ostia, was anatomically ablated to include an extensive region of the LA posterior wall within the isolated area. At the anterior aspect of PVs, distal edges of PVs with early PV potentials or continuous PV and LA potentials were targeted for ablation. Isolation of left and right PVs was performed during distal coronary sinus pacing and SR, respectively.

Radiofrequency (RF) energy was delivered using an 8 mm tip ablation catheter (Ablaze, Japan Lifeline, Tokyo, Japan), in temperature-control mode, with a target temperature of 55°C and maximum power of 35 W on LA posterior wall and 40 W on the anterior aspect of PVs. A steerable 4 mm tip ablation catheter, connected to a thermocouple thermometer (Delta Ohm, Italy), was used as an oesophageal temperature probe.14 It was advanced into the esophagus via an endogastric tube, and positioned as close as possible to the ablation electrode under fluoroscopic guidance during ablation. The delivery of RF energy did not exceed 40 s per site. When oesophageal temperature reached 42°C, the delivery of RF energy at a given site was stopped until the oesophageal temperature returned to the control value. The endpoint of the ablation was elimination of all PV potentials. After EPVI, cavo-tricuspid isthmus (CTI) was ablated to create bi-directional conduction block.16 If atrial premature contractions frequently occurred, we performed focal ablation.

After EPVI plus CTI in Group 2 and AF group, inducibility of AF was evaluated three times by burst atrial pacing at twice the diastolic threshold from high right atrium starting at a cycle length of 250 ms and reducing it by 10 ms intervals until atrial refractoriness was reached. If AF could be induced and sustained for more than 5 min, a LA roof line6 between the left and right PV isolation circles was added. If sustained AF was again inducible after performing the roof line ablation, an inferior line7 and/or mitral isthms line between left inferior PV and mitral annulus were added. The endpoint of inferior line ablation was absence or dissociation of any potential within the ablated zone. The endpoint of mitral line ablation was bi-directional conduction block.5 If sustained AF could be induced even after all of these procedures, no further ablation was attempted.

**Follow-up**

In absence of any AF recurrence, anticoagulant treatment was discontinued after 6 months, unless major risk factors were present. No AAD were prescribed after the procedure in Group 1 and 1 month post-ablation in Group 2. All patients were scheduled to visit our clinic at 2, 6, 10, 14, 24, 36, 48, 60, 72, 84 and 96 weeks after discharge. Recurrence of AF was determined according to patient’s symptoms, ECG and Holter recordings. Regular Holter monitoring was performed in the absence of symptoms. Blanking period of AF recurrence was 1 month.

**Statistical analysis**

Continuous variables are expressed as the mean ± SD. Continuous and categorical variables are compared using Student’s t-test and χ² test, respectively. A property value <0.05 is considered statistically significant.

**Results**

The characteristics of study population are described in Table 1. A successful EPVI and bidirectional CTI conduction block were achieved in all the patients. Transient air embolism of right
coronary artery was observed in one patient in Group 2. There were no other complications related to the procedure. Follow-up periods were 18 ± 4 and 18 ± 7 months in Groups 1 and 2, respectively.

In 15/22 (68%) patients in Group 1, AF was converted to SR after 48 ± 28 days of 160 ± 47 mg/day of bepridil therapy (SR group). These patients underwent EPVI after 54 ± 42 days of successful PC without any significant complication. At the beginning of the procedure, 3/15 (20%) patients demonstrated AF. Finally, 13/15 (87%) patients maintained SR without any AAD in SR group. Seven patients in Group 1 failed to restore SR on bepridil therapy (AF group). Among them, three patients received only EPVI since sustained AF could not be induced post-EPVI. Another four patients received LA linear ablation (roof line in four patients, mitral isthmus line in two patients, and inferior line in three patients) besides EPVI. Finally, 2/7 (29%) patients maintained SR without any AAD in AF group. Thus, in Group 1, 15/22 (68%) patients maintained SR without any AAD at follow-up. The positive and negative predictive values of achieving SR on bepridil pre-treatment were 87% and 71%, respectively. In the SR group, LAD and LVEF before PC did not change significantly from that obtained before ablation (LAD 41.1 ± 4.0 vs. 41.1 ± 3.7 mm, LVEF 62.1 ± 9.4 vs. 66.0 ± 6.5%).

In Group 2, 32/60 (53%) patients received only EPVI. Remaining 28/60 (47%) patients received EPVI plus LA linear ablation (roof line in 23 patients, mitral isthmus line in 18 patients, and inferior line in 17 patients). At follow-up, 43/60 (72%) patients maintained SR without any AAD. Regarding arrhythmia recurrence, no patients in SR group, 1/7 (14%) patients in AF group, and 5/60 (8%) patients in Group 2 experienced recurrence in the form of atrial tachycardia (AT). Except one patient in Group 2, all the patients with AT were previously subjected to LA linear ablation.

The AF-free survival rate without any AAD was significantly lower in AF group who failed to respond to bepridil pre-treatment than Group 2, who were not given the bepridil pre-treatment (29 vs. 72%, P = 0.02) in spite of the same ablation strategy. However, there were no significant differences in the baseline characteristics (Table 1).

### Table 1 Patient clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>SR group</th>
<th>AF group</th>
<th>Group 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>7</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.6 ± 7.8</td>
<td>63.4 ± 4.8</td>
<td>60.0 ± 11.3</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>13/2</td>
<td>5/2</td>
<td>52/8</td>
<td>NS</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>1 (7%)</td>
<td>1 (14%)</td>
<td>6 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
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<tr>
<td>Valvular heart disease</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Duration of AF (months)</td>
<td>24.9 ± 61.3</td>
<td>19.3 ± 4.3</td>
<td>31.0 ± 41.3</td>
<td>NS</td>
</tr>
<tr>
<td>Ineffective AAD</td>
<td>1.6 ± 1.1</td>
<td>0.7 ± 1.0</td>
<td>1.4 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>42.3 ± 3.3</td>
<td>39.1 ± 4.6</td>
<td>43.1 ± 6.6</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>62.5 ± 7.5</td>
<td>62.3 ± 13.3</td>
<td>63.2 ± 8.5</td>
<td>NS</td>
</tr>
<tr>
<td>LAA velocity (cm/s)</td>
<td>47.9 ± 26.2</td>
<td>50.4 ± 27.9</td>
<td>50.1 ± 26.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

AAD, antiarrhythmic drugs; LAD, left atrial diameter; LVEF, left ventricular ejection fraction, LAA, left atrial appendage.

### Discussion

#### Left atrial ablation

Previous studies identified PVs as the source of triggers initiating and perpetuating AF.1–3 Pulmonary vein isolation is recognized as an established therapy for curing paroxysmal AF. Recently, it has been shown that isolation of a large area around the PVs is more effective in treating AF than isolation of individual PV.4 Additional linear ablations, such as LA roof6 or mitral isthmus ablation,5 have also been proposed to improve the success rate. However, such strategies are associated with limited success in patients with long-lasting AF and the strategy for catheter ablation of PEF has not been established.

#### Pharmacological cardioversion preceding extensive pulmonary vein isolation

The precise mechanism of conversion to SR still remains unclear, but bepridil is considered to have a reverse remodelling effect on the atria.10,12 This study demonstrated two results. First, the AF-free rate following a relatively aggressive left atrial ablation was lower in the patients without successful PC than those in whom PC was not attempted. Second, the AF-free rate following EPVI alone in patients with successful PC was relatively high. It suggests that bepridil could be used to classify the patients with PEF before AF ablation.

We speculate two explanations for the outcomes observed. It could be stated that bepridil pre-treatment classified the patients with PEF into two groups based on the risk of arrhythmia recurrence following AF ablation. The fact that the patient characteristics and success rates of Groups 1 and 2 are similar supports this possibility. Secondly, it could be possible that additional linear ablation influenced the final outcome. Among the patients with recurrence manifested as AT, most of them had undergone linear ablation previously. The precise mechanism of those ATs was not evaluated in this study. Hence, we cannot disregard the...
possibility that previously performed linear ablation could be associated with recurrent macroreentrant AT and that additional linear ablation failed to improve the outcome of the procedure. Because our protocol was not uniform among the three groups, we cannot answer this question satisfactorily. However, our data showed that bepridil could help select the patients who would have a favourable AF ablation outcome with a limited AF ablation approach. Besides, the data also justified limited approach avoiding additional linear ablation in patients with a successful PC.

Furthermore, we speculated other possible mechanisms for a relatively high success rate in the SR group. First, the maintenance of SR preceding the procedure itself prevented further atrial remodelling. The perpetuation of AF has been reported to facilitate atrial remodelling. Second, bepridil itself caused reverse atrial remodelling. Nishida et al. reported that bepridil reversed the electrophysiological consequences of atrial remodelling to some extent and L-type Ca channel downregulation, using a canine atrial tachypacing model. In the SR group, the echocardiographic parameters did not change significantly between those obtained before and after conversion indicating that anatomical reverse remodelling, probably, did not influence the results on its own. Electrical reverse atrial remodelling could be attributed to combined effect of bepridil therapy and maintenance of restored SR. On the other hand, the AF group patients might have had advanced electrical atrial remodelling which would mandate more extensive ablation strategy to suppress the recurrence of AF.

Clinical implications
Many ablation strategies have been reported for PEF and therefore selecting appropriate patients for catheter ablation has been difficult. This study suggested that the PC response to bepridil was helpful in predicting the clinical outcome following ablation in patients with PEF.

Although the AF conversion rate with bepridil was high, it was shown that the recurrence rate after initial conversion was also high irrespective of continued treatment. A transition from continued treatment with bepridil to catheter ablation could be a reasonable choice of therapy for PEF in patients with successful PC.

Study limitations
The main limitation of this study was the non-uniform ablation protocol used in the three study groups. Atrial fibrillation inducibility was not evaluated in the SR group and we did not perform any further ablation after EPVI. The patients with AF lasting >3 years and/or LAD >50 mm were excluded from this study. Therefore, the results cannot be applied to the patients with advanced anatomical atrial remodelling.

Conclusions
Following AF ablation in patients who successfully restored SR with bepridil pre-treatment, the AF-free rate was significantly higher than those who failed to restore SR. Conversion to SR with bepridil might help select the optimal patients with PEF for catheter ablation.

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