Hybrid Therapy With Pilsicainide and Pulmonary Vein Isolation for Atrial Fibrillation

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Background Pulmonary vein (PV) isolation is commonly performed in patients with drug-refractory atrial fibrillation (AF) and in cases of unsuccessful ablation, antiarrhythmic agents that were ineffective before the ablation sometimes become effective afterward. Therefore, the effects and mechanisms of hybrid therapy with pilsicainide and PV isolation for AF were assessed in the present study.

Methods and Results Seventy-four patients with paroxysmal AF in whom pilsicainide was ineffective underwent PV isolation. If AF recurred, a second procedure was performed and if AF recurred again, pilsicainide was re-administered. After the first procedure, AF recurred in 42 patients, and a second procedure was performed in 31 patients, of whom 28 had recovery of left atrial (LA)-PV conduction and non-PV foci were identified in 3. After the second session, ablation eliminated AF without drugs in 53 (72%) patients. Pilsicainide suppressed the conduction properties at the LA-PV junction. In 21 patients with recurrence of AF, pilsicainide was re-administered and eliminated AF in 11 patients (success with pilsicainide: 86%).

Conclusions In cases of unsuccessful PV isolation, pilsicainide may prevent AF by modifying the LA-PV conduction properties. Hybrid therapy with pilsicainide and PV isolation may be an effective therapeutic approach for AF. (Circ J 2005; 69: 1503–1507)

Key Words: Antiarrhythmic agents; Atrium; Fibrillation; Pulmonary veins

Antiarrhythmic drugs, including Na⁺ channel blockers (Class I drugs), are widely used for pharmacologic cardioversion and prevention of atrial fibrillation (AF);^{1,2} however, if they are ineffective, radiofrequency catheter ablation targeting the pulmonary veins (PV) can be used to cure AF.^{3–5} It has been reported that PV isolation can result in a significant reduction in the severity of symptoms and can improve the QOL of patients with drug-refractory paroxysmal AF (PAF);⁶ however, in prior studies of PV isolation, the recurrence rate has been relatively high and a repeat ablation procedure is sometimes required.^{3–5,7} In some cases of unsuccessful ablation, antiarrhythmic agents that were ineffective before the ablation may become effective, but the mechanisms of hybrid therapy with antiarrhythmic agents and PV isolation are unclear. Therefore, we assessed the efficacy of hybrid therapy with a pure Na⁺ channel blocker, pilsicainide, and PV isolation for PAF.

Methods

Patients

The study population consisted of 74 patients (54 men, 20 women; mean age, 56±6 years) with symptomatic drug-refractory PAF who were referred for an electrophysiological study and catheter ablation. A mean of 3.0±1.0 antiarrhythmic drugs, including pilsicainide, had been

administered unsuccessfully. None had been treated with amiodarone during the preceding 6 months. The patients had frequent episodes of PAF, frequent atrial premature beats documented by 24-h Holter monitoring, or spontaneous re-initiation of AF after defibrillation. Fifteen patients had additional cardiovascular diagnoses, including systemic hypertension in 13 and ischemic heart disease in 2.

Electrophysiological Study

Written informed consent was given by all patients. Antiarrhythmic drugs were discontinued 5 half-lives before ablation. Treatment with anticoagulants, which were taken by all of the patients, was stopped on admission. Three 6-French quadripolar electrode catheters (Daig) were placed in the right atrial appendage, His bundle area and coronary sinus. A transseptal approach was performed with an 8.5Fr long sheath, both for the puncture and to introduce a 31 mm, 64-pole basket catheter (EP Technologies) dedicated to PV mapping. A 4-mm-tip conventional ablation catheter (EP Technologies) was also introduced into the left atrial (LA) for ablation. PV angiography was performed with an angiocatheter (6-Fr, Baxter) to determine the position of the basket catheter relative to the ostium of the PV. The proximal electrode (bipoles 7–8) of the basket catheter was located at the PV-LA junction. The proximal part of the PV was defined as the ostial side of the veins, and the distal was referred to as the lung side.

In patients with recurrence of AF, a second session was performed. The electrophysiological study was performed to assess the effect of pilsicainide on the electrophysiological properties of PV before ablation. PV pacing was performed from the distal (bipoles 1–2) electrode pair of all splines of the basket catheter. A programmed stimulator

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Fig 2. Changes in the electrograms of the pulmonary vein (PV) by pilsicainide in a representative patient. Electrograms from one spline of the basket catheter placed in the right superior PV are shown. (Left) During the first session, the PV and atrial potentials closely approach each other. (Middle) During the second session, recovery of left atrial (LA)-PV conduction occurs, but the conduction time from the LA to PV is prolonged to 55 ms. (Right) After the infusion of pilsicainide (PLS), conduction from the LA to the PV is blocked. A, atrial potential.

distal PV potentials.

Radiofrequency energy was delivered with a temperature-controlled, 4-mm-tip, deflectable catheter (EP Technologies, Inc) at a target temperature of 50°C and a maximum output of 30 W for 30–60 s at each ostial site. If the activation sequence around the PV-LA junction was changed, the bipole that showed the new earliest atrial potentials was targeted. After PV isolation, if premature atrial contractions were present or could be provoked by isoproterenol or by pacing maneuvers (incremental pacing or programmed stimulation), the origin of the premature atrial contractions was localized by activation mapping, and ablation was performed at this site.

Follow-up

Warfarin was re-administered and continued for 3 months with an international normalized ratio level of approximately 2.0. Follow-up was performed at 1 week and then at 1 month intervals. Clinical examination, ECG and 24-h Holter recordings were made every month or when symptoms suggested the recurrence of arrhythmia.

Success of the procedure was defined as the absence of clinical symptoms of AF without antiarrhythmic drugs and the documentation of stable sinus rhythm on 24-h Holter monitoring.

Second Session

After the electrophysiological studies, a second attempt at PV isolation was made. Follow-up was performed at 1 week and then at 1-month intervals. Clinical examination, ECG and 24-h Holter recordings were made every 3 months or when symptoms suggested the recurrence of arrhythmia. If AF recurred even after the second session or patient did not desire a second session, pilsicainide was re-administered (150 mg/day).

Three-dimensional (D) computed tomography (CT) was performed at 6 and 12 months after ablation to assess stenosis of the PVs. A change in the PV diameter as measured by 3D-CT between before and 12 months after ablation that showed a decrease in PV diameter of more than 25% was considered significant.

Statistical Analysis

Continuous variables are expressed as the mean $\pm$ SD. Differences in electrophysiological parameters between

before and after pilsicainide were evaluated using a paired Student's t-test. Statistical significance was set at $p < 0.05$.

Results

First Session of PV Isolation

PV isolation was performed in 281 targeted PVs (mean 3.8 per patient), which were isolated successfully. Segmental ablation at the exit breakthrough points during distal PV pacing blocked conduction from the PV to LA. Bidirectional conduction block between the PV and LA was confirmed by PV-LA dissociation in all PVs. The mean total duration of the procedure was 210 ± 72 min and the mean total fluoroscopy time was 62 ± 29 min. During follow-up, 32 patients (43%) were successfully treated without requiring antiarrhythmic drugs.

Recurrence of AF

After the first ablation procedure, PAF recurred in 42 of the 74 patients (57%) and a second procedure was performed 59 ± 9 days after the initial procedure in 31 patients. During the second procedure, the recovery of LA-PV conduction was noted in 56 PVs in 28 patients (90%), and non-PV foci (LA posterior wall in 2, superior vena cava in 1) were identified in 3 patients (10%). All recovered PVs were re-isolated.

Electrophysiological Effects of Pilsicainide on PVs

Twenty-eight PVs, including 19 left superior PVs and 9 right superior PVs, were studied at 76 pacing sites in 28 patients who showed recovery of LA-PV conduction.

Pilsicainide significantly prolonged the ERP of the distal PV, PV-LA junction and right and LA appendages (Table 1). Pilsicainide significantly prolonged the maximum conduction time during the drive cycle from the distal PV to PV-LA junction (S₁-A₁) (Table 1, Fig 1). In 2 patients pilsicainide blocked the conduction from the LA to the PV that had recovered after the first session (Fig 2).

During a single extrastimulus, nonsustained AF that spontaneously terminated within 10 min was induced in 7 patients and sustained AF (>10 min) was induced in 5 patients. Pilsicainide was administered during AF in the 5 patients with sustained AF, and terminated it in 3 patients; the other 2 patients were electrically cardioverted. Of 12 patients in whom AF was induced before pilsicainide, AF

could not be induced after pilsicainide in 8 patients, non-sustained AF was induced in 2 patients, and sustained AF could still be induced in 2 patients.

Follow-up

After 105 procedures in 74 patients, 53 patients (72%) who underwent ablation were free of AF at the 12-month follow-up (after the most recent ablation) without the need for antiarrhythmic drug treatment. In 21 patients with a recurrence of AF, pilsicainide was re-administered and eliminated the AF in 11 patients (success with pilsicainide: 86%). These 11 patients had a significantly longer ERP of the PV-LA junction (262 ± 47 ms vs 227 ± 50 ms, $p < 0.01$) and a longer conduction time from the distal PV to PV-LA junction (S1-A1) (160 ± 51 ms vs 126 ± 25 ms, $p < 0.01$) after pilsicainide than the 10 patients with recurrence of AF. However, there were no significant differences between patients with and without recurrence of AF in the ERPs of the distal PVs after pilsicainide.

Complications

One patient developed pericardial effusion, which was drained percutaneously. No significant PV stenosis was detected by 3D-CT at 12 months after the procedure.

Discussion

In the present study, we assessed the effects and mechanisms of hybrid therapy with pilsicainide and PV isolation for AF. In summary, in cases of unsuccessful PV isolation, pilsicainide, which had been ineffective before ablation, was effective afterward, probably because of a modification of the LA-PV conduction properties.

Effects of Pilsicainide on Electrophysiological Properties of PVs

Previous studies have suggested that the antiarrhythmic effects of Class I drugs on AF can be explained by prolongation of atrial refractoriness and intra-atrial conduction block caused by a decrease in the conduction velocity.⁸⁻¹¹ Pilsicainide is a Class Ic antiarrhythmic drug that was originally developed in Japan and has a pure Na⁺ channel-blocking action with slow recovery kinetics.¹² In animal studies, pilsicainide has a potent depressant effect on intra-atrial conduction and a slight but significant prolongation of the atrial ERP.¹² Clinical studies have reported that this drug is highly effective at terminating AF.^{13,14} In the dog, it has been reported that sodium-channel blocker suppresses focal discharges in the PV.^{15,16} Moreover, in humans, Kumagai et al¹⁷ demonstrated that pilsicainide prolonged the PV ERP and PV-LA conduction time and created pharmacological PV isolation just before the termination of AF because of the suppression of conductivity within the PVs and at the PV-LA junction. The antiarrhythmic effect of pilsicainide on AF appeared to occur not only at the atria but also at the PV and the PV-LA junction. Because pilsicainide can prolong the PV ERP and shorten the conduction delay by a short coupled premature beat, it may prevent the initiation and maintenance of AF by preventing the formation of reentry within the PVs or at the PV-LA junction by PV foci.

Hybrid Therapy With Pilsicainide and PV Isolation

It is known that successful cavotricuspid isthmus ablation of typical atrial flutter combined with AF^{18,19} or flutter

converted from AF by antiarrhythmic drugs²⁰ sometimes influences the preablation history of PAF. Also, antiarrhythmic agents that were ineffective before PV isolation are sometimes effective afterward. Although PV isolation is an effective therapy, in prior studies a large percentage of patients required additional ablation procedures.^{3-5,7} In the present patients who underwent a second procedure, recovery of conduction through the surrounding PVs was the most common reason for recurrent AF after PV isolation. As the recovered LA-PV conduction is weak, antiarrhythmic drugs with a depressant effect on conduction properties may create a LA-PV conduction block. Therefore, pharmacological PV isolation by pilsicainide may be by the mechanism of an additional effect after ineffective ablation. Additionally, another reason for the recurrence of AF after successful PV isolation is non-PV foci. Because pilsicainide can suppress focal discharges from atrial tissue, it may prevent AF after unsuccessful ablation. Thus, hybrid therapy with pilsicainide and PV isolation appears to be an effective therapeutic approach for AF.

Study Limitations

Pilsicainide may have many other electrophysiologic effects. We have no data to support our assertion that its effect is not caused by increasing atrial refractoriness, the creation of a conduction block at the wavefront turn-around points, or other electrophysiological effects. In addition, we provide no evidence in the present study that pilsicainide suppresses non-PV foci. Therefore, at most we can say that the creation of pharmacologic block in partially isolated PVs may contribute to the hybrid effect of pilsicainide after PV isolation.

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