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Pilsicainide for Atrial Fibrillation

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Abstract

Pilsicainide is a class IC antiarrhythmic drug, which has a pure sodium channel blocking action with slow recovery pharmacokinetics. In experimental studies, pilsicainide has a depressant effect on intra-atrial conduction and a prolonging effect on the atrial effective refractory period (ERP). In patients with paroxysmal atrial fibrillation (AF), pilsicainide significantly prolonged the ERP of the distal pulmonary vein (PV), PV-left atrium (LA) junction and LA, and the conduction time from the distal PV to the PV-LA junction. In some patients, PV-LA conduction block has been observed just before pilsicainide-induced termination of AF; this isolation of the PV may provide a new insight into the mechanism of pharmacological conversion of AF. Hybrid therapy with pilsicainide and PV isolation (by radiofrequency catheter ablation) appears to be an effective therapeutic approach for AF. The pharmacological PV isolation by pilsicainide and its suppression of focal discharges from atrial tissue may prevent the development of AF after unsuccessful ablation.

The effects of sodium channel antagonists (class I antiarrhythmics) on the pharmacological cardioversion and prevention of atrial fibrillation (AF) are well established, and these drugs are widely used.[1,2] Previous studies have suggested that these effects are explained by prolongation of atrial refractoriness and an intra-atrial conduction block both due to a decrease in conduction velocity.[3-6]

Pilsicainide is a class IC antiarrhythmic drug originally developed in Japan, which has a pure sodium channel blocking action with slow recovery pharmacokinetics.[7] Its mechanism of action appears to provide new insight into the pharmacological conversion of AF and makes it suitable for hybrid therapy with catheter ablation of the pulmonary veins (PVs).

1. Electrophysiological Effects of Pilsicainide on the Atria

In animal studies, pilsicainide has a potent depressant effect on intra-atrial conduction, and a slight but significant prolonging effect on the atrial effective refractory period (ERP).[7] Theoretically, the suppression of conduction velocity minimises the prolongation of wavelength induced by the increase in the ERP and may thus serve to allow the continuation of multiple re-entrant wavelets.

Iwasa et al.[5] demonstrated that pilsicainide was more effective at terminating vagally induced AF than propafenone, despite the greater effect of propafenone on wavelength, suggesting that suppression of conduction velocity may play an important role in terminating AF. Moreover, Wijffels et al.[8] reported that the pharmacological cardioversion of AF cannot be explained by the prolongation of wavelength.

An alternative explanation for the antifibrillatory effect of class I agents may be widening of the temporal excitable gap.[8] Kneller et al.[9] described three mechanisms that contributed to sodium channel block-induced AF termination in an experimental model: (i) enlargement of the centre of rotation beyond the capacity of the computational substrate; (ii) decreased anchoring to functional obstacles, increasing meander and extinction at boundaries; and (iii) reduction in the number of secondary wavelets that could provide new primary rotors.

2. Pharmacological Cardioversion by Pilsicainide

Restoration of sinus rhythm can usually be obtained by antiarrhythmic drugs or direct-current cardioversion. Class IA drugs, including disopyramide, have been used for many years, and their success rate in terminating AF is reported as 43–88%, depending on the AF duration, the dose of drugs and the endpoint.[10-12] Atarashi et al.[13] reported that a single oral administration of pilsicainide successfully restored the sinus rhythm in 45% of patients with recent-onset (<7 days) AF, with a mean conversion time of 37 minutes, reflecting its favourable pharmacokinetics. However, pharmacological cardioversion by oral administration generally takes several days; therefore, intravenous administration is widely used because of its faster effects.

The effects of a single oral treatment of pilsicainide were compared with that of a disopyramide infusion in a multicentre trial.[14] Seventy-two patients with symptomatic paroxysmal AF (<48 hours duration) identified by ECG were randomised to receive either a single oral dose of pilsicainide (100–150mg) or an infusion of disopyramide (2 mg/kg; maximum dose = 100mg).[14] In the pilsicainide group, the cumulative percentage of conversion to sinus rhythm within 120 minutes was 73% (higher than that of a previous study[12] because the AF was of more recent onset). Thus, a single oral dose of pilsicainide was as effective in restoring sinus rhythm in patients with recent-onset AF as the infusion of disopyramide (56% within 120 minutes).[14] The mean conversion time to sinus rhythm was 60 minutes in the pilsicainide group and 23 minutes in the disopyramide group ($p < 0.01$).

Moreover, the conversion time of pilsicainide in this study[14] is shorter than that of other class IC antiarrhythmics, including flecainide and propafenone, in patients with recent-onset AF.[15] This seems likely to be due to the favorable pharmacokinetics of pilsicainide, including its rapid absorption from the gastrointestinal tract, the absence of changes from a first-pass effect, and a short elimination half-life.[16] Disopyramide was especially effective in terminating AF occurring at night, whereas pilsicainide had a stable effect in terminating AF all day;[14] this may have resulted from the anticholinergic effects of disopyramide.

There were no adverse effects in either group during the study.[14] However, it has been reported that the use of class IC antiarrhythmics in AF introduces a risk of atrial flutter with 1 **:** 1 conduction, sinus pause on conversion and ventricular arrhythmias.[10,11] Therefore, once the safety and efficacy of a single oral dose of pilsicainide has been confirmed in the individual, patients with paroxysmal AF can cure themselves without hospitalisation, whenever AF occurs.

3. Effects of Pilsicainide on the Electrophysiological Properties of Pulmonary Veins (PVs)

AF can be initiated by triggers predominantly clustered within thoracic veins, particularly PVs, and radiofrequency ablation of these foci can eliminate AF.[17,18] Moreover, in patients with chronic AF and structural heart disease, after electrical cardioversion, the PVs are also the dominant trigger reinitiating AF.[19] Therefore, the PVs may have an important role not only in the onset but also the maintenance of AF.[20]

In dogs, sodium channel antagonists suppressed focal discharges in the PV.[21,22] Moreover, Jais et al.[23] showed that the PVs of patients with AF exhibited short ERPs and long conduction times. The conduction abnormality in PVs could be related to anisotropic conduction,[24] with the fractionated PV potentials and associated changes in activation

sequence and exits probably correlating with the complex arrangement of PV muscular sleeves.[25] Thus, the significant differences in the electrophysiological properties between the PV and PV-left atrium (LA) junction provide a very favourable characteristic for re-entry within or around the PVs, which may perpetuate arrhythmia and thus act as a substrate for AF maintenance.

In animal studies, Arora et al.[26] demonstrated that nonsustained re-entrant beats were induced with a single extrastimulus, and the complete re-entrant loop was visualised using high-resolution optical mapping. This re-entry was consistent with the classic 'leading-circle' model in that it seemed to occur in the absence of an anatomic obstacle (i.e. functional re-entry).[26] In the study by Hamabe et al.,[27] histological sections at the canine PV-LA junction with conduction block showed the presence of abrupt changes in myocardial fibre orientation. The complex arrangement of myocardial fibres at the PV-LA junction is a possible reason for conduction delay or block in the PV-LA junction.[28-30] The presence of anisotropic structures at the PV-LA junction may be critical to form re-entry.

The effects of pilsicainide on the electrophysiological properties within the PV and at the PV-LA junction have been evaluated using multielectrode basket catheter mapping in patients with paroxysmal AF[31] (figure 1). The programmed stimulation was performed in the distal PV and PV-LA junction before and after infusion of pilsicainide 1 mg/kg.

Pilsicainide significantly prolonged the ERP of the distal PV, PV-LA junction and LA.[31] Pilsicainide significantly shortened the ERP dispersion, defined as the difference between minimum and maximum ERP within the same PV. Pilsicainide also significantly prolonged the conduction time from the distal PV to PV-LA junction. Therefore, the antiarrhythmic effect of pilsicainide on AF appeared to be not only on the atria but also on the PV and PV-LA junction.

Since pilsicainide can prolong the ERP of the PVs 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 re-entry within the PVs or at the PV-LA junction by PV foci. In 3 of 5 patients who had AF termination with pilsicainide, PV-LA conduction block was observed just before termination of AF.[31] Before pilsicainide, the disorganised PV potentials were observed in all bipoles during AF and the mean AF cycle length was 158ms. At 8 minutes after infusion of pilsicainide, the mean AF cycle length was prolonged to 212ms and partial LA-PV conduction block and intra-PV conduction block occurred in some splines during AF. After 10 minutes, all PV

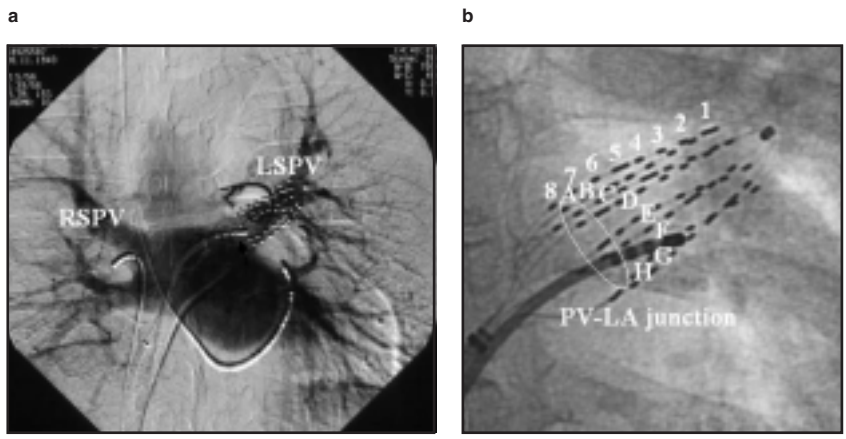

Fig. 1. Basket catheter guided pulmonary vein (PV) mapping. A basket catheter (A to H identify basket splines) is positioned in the PV (**a**). Distal PV pacing is performed from the distal electrode pair (bipoles 1–2), and the proximal electrode (bipoles 7–8) is located at the PV-left atrium (LA) junction (**b**). **LSPV** = left superior pulmonary vein; **RSPV** = right superior pulmonary vein.

potentials abruptly disappeared from all bipoles, i.e. a pharmacological PV isolation was created and then, AF was terminated. After that, in this patient, AF could no longer be induced by a single extrastimulus.

Oral et al.[32] reported that persistent AF was often terminated during isolation of the PVs by catheter ablation and that persistent AF became inducible less often as more PVs were isolated; this demonstrated that the PVs are not only a source of the triggers that initiate AF but also may play an important role in the maintenance of AF. Thus, in some patients with AF, PVs and the PV-LA junction may play important roles as substrates for AF maintenance. Although the precise mechanism for termination of AF by class IC antiarrhythmics was not identified in previous studies, pharmacological PV isolation by pilsicainide may provide a new insight into the mechanism for pharmacological conversion of AF (figure 2).

Thus, pilsicainide can modify the ERP heterogeneity and the conduction properties in the PV and at the PV-LA junction. Therefore, when the PV and PV-LA junction play important roles as substrates for the maintenance of AF, pilsicainide may terminate AF by pharmacological PV isolation.

4. Hybrid Therapy with Pilsicainide and PV Isolation for Atrial Fibrillation

Successful cavotricuspid isthmus ablation of typical atrial flutter combined with AF,[33,34] or flutter converted from AF by antiarrhythmic drugs,[35] sometimes influences the preablation history of paroxysmal AF. When antiarrhythmic drugs are ineffective, radiofrequency catheter ablation targeting PV can cure AF.[17,18,36] PV isolation resulted in a significant reduction in symptom severity and an improvement in quality of life with drug refractory paroxysmal AF.[37] However, in earlier studies of PV isolation, the recurrence rate is relatively high and a repeated ablation procedure is sometimes required.[17,18,36,38] In the case of an unsuccessful ablation, antiarrhythmic agents that were ineffective before the ablation are sometimes effective. However, the mechanisms of hybrid therapy with antiarrhythmic agents and PV isolation are unclear.

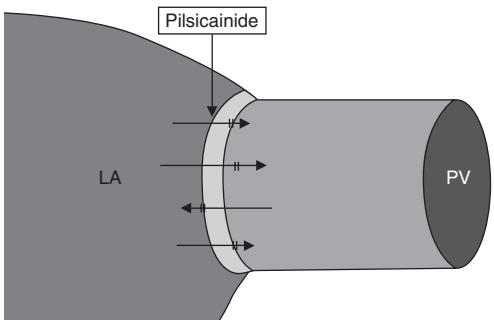

Fig. 2. Schema of mechanism of pharmacological pulmonary vein (PV) isolation by pilsicainide. Pilsicainide can block the entrance and exit conduction at the left atrium (LA)-PV junction.

The effects and mechanisms of hybrid therapy with pilsicainide and PV isolation for AF have been assessed.[39] Seventy-four patients with paroxysmal AF in whom pilsicainide was ineffective underwent PV isolation. If AF recurred, a second PV isolation was performed. If AF recurred even after the second session, pilsicainide was re-administered. After a first procedure, AF recurred in 42 patients (57%). A second PV isolation was performed in 31 patients. In these patients, recovery of LA-PV conduction was found in 56 PVs in 28 patients (90%), and non-PV foci were identified in 3 patients (10%). All recovered PVs were re-isolated. After the second session, ablation eliminated AF without drugs in 53 of the 74 (72%) patients. In 21 patients with recurrence of AF, pilsicainide was re-administered and eliminated AF in 11 patients (i.e. success with hybrid therapy was 86%).

5. Mechanism of Action of Hybrid Therapy

An electrophysiological study was performed to assess the effect of pilsicainide on the electrophysiological properties of PV before second ablation.[39] Twenty-eight PVs, including 19 left superior PVs and nine right superior PVs, were studied at 76 pacing sites in the 28 patients who had recovered LA-PV conduction after the second ablation.

Pilsicainide significantly prolonged the ERP of the distal PV, the PV-LA junction and the right and left atrial appendages. Pilsicainide significantly pro-

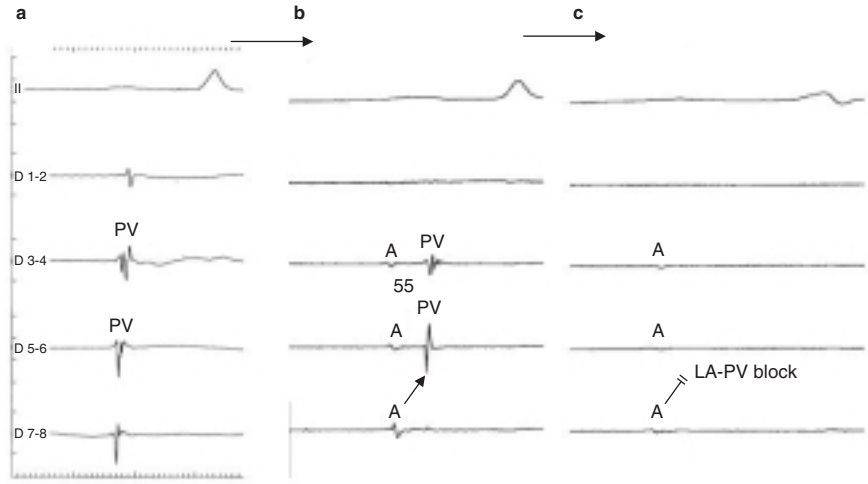

Fig. 3. Changes in electrograms of pulmonary vein (PV) by pilsicainide in a representative patient. Electrograms from one spline of the basket catheter placed in the right superior PV are shown. During the first session, PV and atrial potentials closely approach each other (**a**). During the second session, recovery of left atrium (LA)-PV conduction is observed, but the conduction time from LA to PV is prolonged to 55ms (**b**). After infusion of pilsicainide, conduction from LA to PV blocked (**c**) [reproduced from Tojo et al.,[39] with permission].

longed the maximum conduction time during the drive cycle from the distal PV to the PV-LA junction. Figure 3 shows that pilsicainide blocked the conduction from LA to PV that had recovered after the first PV isolation.

During a single extrastimulus, nonsustained AF that spontaneously terminated within 10 minutes was induced in seven patients and sustained AF (>10 minutes) was induced in five patients. Pilsicainide was administered during AF in five patients with sustained AF and terminated AF in three patients. Two patients who did not have AF termination with pilsicainide were electrically cardioverted. After administration of pilsicainide to the 12 patients in whom AF had been induced prior to receiving pilsicainide, AF became uninducible in eight patients, nonsustained AF was induced in two patients, and sustained AF could be still induced in two patients.

In the patients who underwent a second procedure, recovery of conduction through surrounding the PVs was the most common reason for recurrent AF after PV isolation. Since the recovered LA-PV conduction is weak, antiarrhythmic drugs with depressant effect on conduction property may create the LA-PV conduction block. Therefore, pharmacological PV isolation by pilsicainide may explain the mechanism for additional effect after ineffective ablation. Additionally, another reason for recurrence of AF after successful PV isolation is non-PV foci. Since pilsicainide can suppress focal discharges from atrial tissue, it may be effective for preventing AF after unsuccessful ablation. Thus, hybrid therapy with pilsicainide and PV isolation is an effective therapeutic approach for AF.

6. Conclusion

Pilsicainide is a class IC antiarrhythmic drug, which has a pure sodium channel blocking action with slow recovery pharmacokinetics, thereby having a depressant effect on intra-atrial conduction and a prolonging effect on the ERP. The antiarrhythmic effect of pilsicainide on AF appears to be not only on the atria but also on the PV and PV-LA junction. The pharmacological PV isolation by pilsicainide may provide a new insight into the mechanism for pharmacological conversion of AF. Moreover, in the case of an unsuccessful PV isolation, antiarrhythmic agents that were ineffective before the ablation are sometimes effective. Recovery of LA-PV conduction is the most common reason for re-

current AF after PV isolation; therefore, re-isolation of PVs by pilsicainide may explain the mechanism for the additional effect after ineffective ablation. Thus, hybrid therapy with pilsicainide and PV isolation is an effective therapeutic approach for AF.

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