Mechanisms of the Preventive Effect of Pilsicainide on Atrial Fibrillation Originating From the Pulmonary Vein

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Background  It has been shown that pilsicainide terminates atrial fibrillation (AF) by pharmacologic pulmonary vein (PV) isolation. However, whether it can prevent AF induction originating from the PV by the same mechanism is still uncertain.

Methods and Results  Rapid pacing from the left superior PV (LSPV) and the right atrial free wall (RAF) was performed to induce AF during electrical stimulation of both cervical vagal nerves in 6 anesthetized dogs and during the infusion of acetylcholine (ACh) in 8 isolated atria. Rapid pacing induced AF in all dogs, regardless of the pacing site, before pilsicainide. Pilsicainide (1 mg/kg) prevented AF during rapid pacing from the LSPV, with an impulse conduction block between the LSPV and the left atrial free wall (LAF). However, the same dose of pilsicainide did not prevent AF when pacing was performed from the RAF. Pilsicainide partially restored the action potential duration shortened by ACh infusion and prevented AF with an impulse conduction block at the LSPV-left atrial junction in all isolated preparations tested.

Conclusion  The results suggest that (1) impulse conduction block at the LSPV-LA junction is the underlying mechanism of pilsicainide-induced prevention of vagally-induced AF originating from the LSPV and (2) pilsicainide is more effective at preventing AF originating from the LSPV than that from the RAF.  

Key Words: Atrial fibrillation; Impulse conduction block; Pilsicainide; Pulmonary veins

Clinical studies have shown that paroxysmal atrial fibrillation (AF) is initiated by focal discharges originating from the pulmonary veins (PVs).1,2 This important finding has led to the development of several radiofrequency catheter ablation techniques to eliminate paroxysmal and persistent AF.3–6 Recent studies have shown that complete isolation of the PV is important for preventing recurrence of AF.7,8 In addition, Pappone et al9 have demonstrated that vagal denervation around the ostia of the PVs during catheter ablation reduces recurrence of AF originating from that site. Those studies emphasize the importance of complete isolation of the PVs, plus vagal denervation, in the prevention of AF originating from the PVs. Pilsicainide, a class Ic antiarrhythmic drug with slow recovery kinetics,10 is frequently used in clinical practice in Japan to interrupt AF11,12 Several clinical and experimental studies have shown mechanisms of pilsicainide-induced termination of AF10,13–16 but the mechanisms of pilsicainide-induced prevention of AF originating from the PVs are still unclear. It has been reported that pilsicainide inhibits the muscarinic acetylcholine receptor-operated potassium current (IK,ACH).17 In addition, the IC50 of pilsicainide for IK,ACH is similar to that for the sodium current17,18 We hypothesized that pilsicainide prevents AF originating from the left superior PV (LSPV) by isolating the PV and reducing IK,ACH. First, the present study was designed to test whether pilsicainide could prevent AF originating from the LSPV during electrical stimulation of both cervical vagal nerves in anesthetized dogs. Then, to examine the mechanisms of pilsicainide-induced prevention of AF originating from the LSPV, a second study was performed using optical mapping techniques and pilsicainide treatment with constant ACh administration in isolated, arterially perfused, whole canine atria.

Methods  The experimental protocol was approved by the institutional animal experiments committee and complied with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication 85–23, revised 1996).

Anesthetized Dogs  Six male dogs (weight 10–12 kg) were anesthetized with sodium pentobarbital (30 mg/kg iv) with supplemental doses to maintain stable anesthesia. A tracheal cannula was inserted and intermittent positive-pressure ventilation with room air was delivered by a respirator (model 607, Harvard Apparatus, Millis, MA, USA). The chest was opened transversely at the fifth intercostal space and a pericardial cradle was created. The bilateral cervical vagal nerves were isolated via a midline neck incision and crushed with a tight ligature. Each stellate ganglion was isolated and crushed at its junction with the ansae subclaviae. These maneuvers
Three bipolar electrodes were placed on the epicardial surface of the left atrial free wall (LAF), the left inferior PV (LSPV) and the proximal site of LSPV (the site near the left atrial (LA)) to record atrial electrical activation. Electrocardiogram (ECG) lead II was also recorded and each of the 4 electrographic signals was filtered (0.1–300 Hz), digitized with 12-bit precision at a sampling rate of 1,000 Hz per channel (Microstar Laboratories Inc, Bellevue, WA, USA), transmitted to a microcomputer and saved to CD-ROM. To perform atrial pacing, an additional 2 bipolar electrodes were placed on the epicardial surface of the right atrial free wall (RAF) and the distal site of the LSPV (the site near the lung). To stimulate extracardiac parasympathetic nerves to the heart, bipolar stainless steel wire electrodes were inserted in the cardiac end of each cervical vagal nerve, and connected to an electrical stimulator (SEN 7103, Nihon Kohden, Tokyo, Japan). A catheter introductor was inserted into the left femoral artery to monitor arterial blood pressure. ECG lead II, heart rate, and femoral arterial blood pressure were monitored throughout the experiment.

**Isolated Canine Atria**

Eight male dogs (weighing 17–20 kg each) were treated with sodium heparin (500 USP units/kg iv) and anesthetized with sodium pentobarbital (30 mg/kg iv). After a right thoracotomy, the heart and surrounding lungs were quickly removed and placed in cold cardioplegic solution of the following composition (mmol/L): NaCl, 130; KCl, 8.0; CaCl2, 1.8; NaHCO3, 20.0; MgSO4, 1.0 and dextrose, 5.5. Next, the entire atrium was isolated from the heart, the right and left coronary arteries were cannulated and leaking arteries were ligated. Two or more centimeters of each PV were retained intact with the rest of the LA. The preparation was maintained for 2 h without signs of deterioration, and our experimental protocol typically lasted 1–1.5 h. After each experiment, tissue viability was confirmed by staining with 10 ml of the voltage sensitive dye, di-4-ANEPPS (Molecular Probes, Eugene, OR, USA) dissolved (14 mg/ml). ANEPPS was excited at 495 nm and the fluorescence emitted at 518 nm was recorded through a bandpass filter (509±3 nm). Tissue viability was confirmed by staining with 200 ml of 2,3,5-tetrazolium chloride (14 mg/ml).

**Optical Mapping System**

Perfused whole atria were immersed in a Tyrode filled customized Lexan chamber specifically designed for optical recordings. The epicardial surface of the PVs was exposed to the optical mapping camera by inverting the vein inside-out to visualize it from the ostium to the transition between myocardial and venous tissue. Gentle pressure was applied with a movable piston to the surface of the atria opposite to the mapping field, allowing the preparation to contract freely except within the mapping field. Electromechanical uncouplers were not used to reduce motion artifact. The optical mapping system used in this study has been described in detail previously. Briefly, excitation light (500 nm) obtained from a 250 W quartz tungsten halogen lamp (Oriel Co, Stratford, CT, USA) was directed at the heart using a liquid light guide. Light that was fluoresced from the heart was collected by a tandem lens assembly and directed to a long pass filter (>610 nm) that passes light of longer wavelengths to a 16×16 element photodiode array. The spatio-temporal resolution was 256,000 pixels/s. Signals recorded from each photodiode and the ECG signals were multiplexed and digitized with 12-bit precision at a sampling rate of 1,000 Hz per channel (Microstar Laboratories Inc, Bellevue, WA, USA). An optical magnification of ×0.81 was used, corresponding to a mapping field of 2.1×2.1 cm and 0.13 cm spatial resolution between recording pixels. To view, digitize, and store the anatomical features, a mirror was temporarily inserted between the lenses of the tandem lens assembly to direct reflected light to a digital video camera (DCR-PC120 Sony Co, Tokyo, Japan).

**Experimental Protocol**

Experiments using anesthetized canine hearts were performed 30 min after completion of the surgical procedures. To examine the effects of pilsicainide on the initiation of AF, rapid pacing at a pacing cycle length (PCL) of 150 and 100 ms was performed from the distal LSPV or the RAF during cervical vagal stimulation before and after treatment with pilsicainide (1–3 mg/kg) in 6 autonomically decentralized hearts of the open-chest, anesthetized dogs. In this study, the right and left cervical vagal nerves were stimulated with a voltage of 10 V, pulse duration of 0.03 ms, and frequency of 3–10 Hz. The stimulation intensity was adjusted to decrease the atrial rate by approximately 50–60% before each experiment started and the intensity was unchanged throughout the experiment. Pilsicainide was injected from the right femoral vein over 20 s. The protocol started 2 min after the injection and ended in 15 min at each dose of pilsicainide. In half of the experiments, the LSPV pacing was first performed and then the RAF pacing. In the other half, the RAF pacing was first performed. Atrial electrical activations from 3 atrial sites (LAF, proximal LSPV, and LIPV) were obtained during each cycle length (CL) of rapid pacing and during the initiation of AF. In addition, to examine the effects of pilsicainide on atrial impulse conduction, conduction time from the LSPV to the RAF and from the RAF to the LAF was measured during LSPV and RAF pacing at a CL of 250 ms, in the absence and during the vagal stimulation, respectively.

In the isolated arterially-perfused atrial preparations, a polytetrafluoroethylene-coated silver bipolar electrode with 1-mm interelectrode spacing was used to stimulate the endocardial surface of the LSPV at 4-fold the diastolic threshold current with a duration of 1 ms. Spontaneous activity was observed throughout the experiment. To examine the mechanisms of pilsicainide-induced prevention of cholinergically-induced AF originating from the LSPV, rapid pacing at a PCL of 400, 300, 200, 150, and 100 ms was performed.
from the LSPV during the infusion of ACh before and after treatment with pilsicainide (3 and 10 μmol/L) in isolated atria. Each dose of pilsicainide was continuously infused from the right and left coronary artery and rapid pacing was started 2 min after the infusion started. Optical action potentials were obtained during each CL of rapid pacing and during the initiation of AF.

In all experiments, the first rapid pacing at a given CL was performed for 10–15 s, followed by spontaneous activity, and the second rapid pacing at the same CL was then performed for 10–15 s (Fig 1A). AF initiation was defined as rapid (CL <180 ms) regular or irregular atrial rhythm persisting more than 10 beats after atrial pacing ended. When AF continued longer than 3 min, vagal stimulation or ACh infusion was stopped. All AF terminated within 1 min after vagal stimulation or ACh infusion was stopped. Recovery time between experiments was appropriate to allow for the effects of the previous interventions to resolve.

Data Analysis

In experiments using isolated atria, automated algorithms were used to determine depolarization time relative to a single fiducial point (ie, the stimulus). Depolarization time was defined as the point of maximum positive derivative in the action potential upstroke (dV/dtmax). Depolarization contour maps were computed for the entire mapping field. Repolarization time was defined as the time when repolarization reached a level of 80% of the APD. The APD was defined as the difference between repolarization time and depolarization time. Local optical APD at the LSPV, the LSPV-LA junction, and the PLA was calculated from the average of optical APDs at 10 sites from each of the 3 areas. The method of Bayly et al21 was modified for optically recorded action potential maps to accurately quantify the direction and magnitude of conduction velocity (CV) and the repolarization gradient at each recording site. Local CV was calculated from the average of conduction velocities at 12 sites from the LSPV-LA junction and from the PLA at each PCL. The local repolarization gradient was also calculated from the average of repolarization gradient at the same 12 sites from the LSPV-LA junction.

All data are shown as the mean ± SE. An analysis of variance with Bonferroni’s test was used for the statistical analysis of multiple comparisons of data. Student’s t-test for paired or unpaired data was used for comparisons between 2 groups. Fisher’s exact test was used to compare the incidence of AF between different conditions. P<0.05 was considered statistically significant.

Drugs

Pilsicainide was provided by Daiichi Pharmaceutical Co (Tokyo, Japan) and was dissolved and diluted in 0.9% NaCl. Acetylcholine chloride (Daiichi Pharmaceutical Co) was also dissolved and diluted in 0.9% NaCl. Kumagai et al13 have suggested that in patients with paroxysmal AF, the infusion of pilsicainide (1 mg/kg) may terminate AF by pharmacologic PV isolation. In addition, an effective plasma concentration of pilsicainide for treatment of arrhythmia is 2–10 μmol/L.18 Therefore, we used 1 and 3 mg/kg of pilsicainide in the anesthetized dogs and 3 and 10 μmol/L in the isolated preparations.

Results

Initiation and Duration of AF During Vagal Stimulation Before and After Pilsicainide Treatment in Anesthetized Dogs

The electrical stimulation of both cervical vagal nerves decreased the sinus rate from 104±3 beats/min to 38±2 beats/min in 6 anesthetized canine hearts. After treatment with pilsicainide (1 mg/kg), vagal stimulation decreased the sinus rate to 42±3 beats/min and the effect of vagal stimulation on the rate was similar to that before pilsicainide administration. In contrast, after treatment with pilsicainide (3 mg/kg), vagal stimulation decreased the sinus rate to 52±4 beats/min and the effect of vagal stimulation on the rate was inhibited compared with before pilsicainide (p<0.01). Fig 1B is a representative example of the initiation of AF by rapid atrial pacing during vagal stimulation. After 10s of rapid pacing from the distal LSPV, an atrial electrogram recorded from the LAF showed rapid irregular excitation at a CL of less than 100 ms. ECG lead II also demonstrated
disorganized, almost continuous activity (ie, f wave) and irregular R-R intervals, which are ECG features of AF. During vagal stimulation, rapid pacing at a PCL of 150 and/or 100 ms initiated AF and continued it for more than 3 min in all 6 canine hearts, regardless of the pacing site (Table 1). After treatment with pilsicainide (1 mg/kg), rapid pacing from the LSPV initiated AF in only 1 heart during vagal stimulation (Table 1). However, rapid pacing from the RAF initiated AF and continued it for longer than 15 s in 5 hearts.

**Table 2** Effects of PIL on Atrial Conduction Time Between 2 Sites in the Absence and During Cervical Vagal Stimulation (VS) in 6 Anesthetized Dogs

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Table 2: Effects of PIL on Atrial Conduction Time Between 2 Sites in the Absence and During Cervical Vagal Stimulation (VS) in 6 Anesthetized Dogs (Continued)

- **Distal LSPV pacing**

- **RAF pacing**

**Fig 2.** Representative example of atrial electrical activations recorded from the proximal left superior pulmonary vein (LSPV), left atrial free wall (LAF), and left inferior pulmonary vein (LIPV) during distal LSPV pacing before and after treatment with pilsicainide (PIL, 1.0 mg/kg) in the presence of vagal stimulation. P, pacing artifact; PCL, pacing cycle length. See text for details.

**Fig 3.** Representative example of atrial electrical activations recorded from the proximal left superior pulmonary vein (LSPV), left atrial free wall (LAF), and left inferior pulmonary vein (LIPV) during right atrial free wall (RAF) pacing before and after treatment with pilsicainide (PIL, 1.0 mg/kg) in the presence of vagal stimulation. P, pacing artifact; PCL, pacing cycle length. See text for details.
After treatment with pilsicainide (3 mg/kg), rapid pacing did not initiate AF, regardless of the pacing site and CL during vagal stimulation. In the absence of vagal stimulation, rapid pacing from the LSPV initiated and terminated AF in 10 s in 2 canine hearts before treatment with pilsicainide.

**Preventive Effect of Pilsicainide on AF During Vagal Stimulation in Anesthetized Dogs**

Figs 2 and 3 are representative examples of atrial electrical activation recorded from 3 sites (proximal LSPV, LAF and LIPV) during distal LSPV or RAF pacing, respectively. Before pilsicainide was administered, when rapid pacing was performed from the LSPV at CLs of 150 and 100 ms during vagal stimulation, the 3 sites were excited at almost the same CL as the PCL (Fig 2, Left). In contrast, when rapid pacing was performed at a PCL of 150 ms during vagal stimulation after treatment with pilsicainide (1 mg/kg), the LAF was excited at a longer CL than the PCL and a Wenckebach type of conduction between the LSPV and the LAF was observed (Fig 3, Right). In addition, when rapid pacing was performed at a PCL of 100 ms during vagal stimulation, the LAF and LIPV were excited at a 2-fold longer CL than the PCL and a 2:1 conduction block between the LSPV and the LAF was observed (Fig 2, Right). In this preparation, rapid pacing induced AF before, but not after, treatment with pilsicainide (not shown). After treatment with pilsicainide (1 mg/kg), a similar pattern of atrial activation was observed in 5 canine hearts in which AF was not induced during LSPV pacing. When rapid pacing was performed from the RAF during vagal stimulation, atrial electrograms from 3 sites showed beat-by-beat changes in excitation CL after pilsicainide treatment (1 mg/kg) and AF was initiated (Fig 3, Right). No conduction block between the LSPV and the LAF was observed during RAF pacing.

After treatment with 3 mg/kg of pilsicainide, rapid pacing from the RAF at a PCL of 100 ms caused atrial electrical excitation at a longer CL than the PCL at all 3 sites and did not induce AF in any preparation.

**Effects of Pilsicainide on Impulse Conduction Time in Anesthetized Canine Atria**

Pilsicainide at a dose of 1 mg/kg significantly increased mean impulse conduction time from the LSPV to the LAF, both in the absence and during vagal stimulation in 6 anesthetized canine atria (Table 2). However, the same dose of pilsicainide tended to increase the mean conduction time from the RAF to the LAF during RAF pacing, both in the absence and during the vagal stimulation, but it was not significant, indicating spatial differences in the effect of pilsicainide on impulse conduction in the atria. Moreover, the same dose of pilsicainide had little effect on atrial conduction time from the LSPV to the RAF in dog No. 4 in which the LSPV pacing induced AF during vagal stimulation (Table 2). In contrast, 3 mg/kg of pilsicainide significantly increased mean conduction time regardless of the pacing site. These results suggest differences in the threshold dose of pilsicainide causing impulse conduction slowing between the atrium and PV.

**Initiation of AF During ACh Infusion Before and After Pilsicainide Treatment in Isolated Canine Atria**

During the LSPV pacing at a PCL of 100 ms, AF was initiated and continued for longer than 3 min in all 8 preparations. After treatment with pilsicainide (3 μmol/L), AF was also initiated in all of 6 preparations tested, but continued longer than 3 min in 1 preparation. In contrast, after treatment with pilsicainide at a dose of 10 μmol/L, AF was not initiated in any of 6 preparations tested. In the absence of...
ACh, rapid pacing at a PCL of 100 ms from the LSPV initiated and terminated AF in 5 s in 1 preparation before treatment with pilsicainide.

**Effect of Pilsicainide on APD and LA Conduction During ACh Infusion in Isolated Canine Atria**

Fig 4 shows the effects of pilsicainide on atrial APD in the LA, including the LSPV, during ACh infusion. APD maps and local APD in each of the 3 areas revealed that pilsicainide homogenously prolonged the atrial optical APD in the LA, including the LSPV (Figs 4A,B). In addition, the local repolarization gradient at the LSPV-LA junction was less than 3 ms/mm in all 8 preparations after pilsicainide treatment. As we could not obtain authoritative APD data from the optical signals in the control condition because of motion artifact, a monophasic action potential was recorded from the epicardial surface of the PLA during LSPV pacing at a PCL of 400 ms in 6 isolated atria (Fig 4C). In the absence of ACh, pilsicainide (10 μmol/L) did not change the monophasic APD. In contrast, the same concentration of pilsicainide significantly increased the monophasic APD in the presence of ACh.

Fig 5 shows the effects of ACh on the LA CV. Activation maps in the control condition revealed marked conduction slowing at the LSPV-LA junction was less than 3 ms/mm in 8 preparations after pilsicainide treatment. As we could not obtain authoritative APD data from the optical signals in the control condition because of motion artifact, a monophasic action potential was recorded from the epicardial surface of the PLA during LSPV pacing at a PCL of 400 ms in 6 isolated atria (Fig 4C). In the absence of ACh, pilsicainide (10 μmol/L) did not change the monophasic APD. In contrast, the same concentration of pilsicainide significantly increased the monophasic APD in the presence of ACh.

Fig 5 shows the effects of ACh on the LA CV. Activation maps in the control condition revealed marked conduction slowing at the LSPV-LA junction during ACh infusion before and after treatment with pilsicainide. During ACh infusion, activation maps after pilsicainide (3 μmol/L) caused homogeneous conduction slowing in the mapping field compared with that before it (Fig 6A). Activation maps after pilsicainide (10 μmol/L) revealed marked conduction slowing and block at the LSPV-LA junction (Fig 6A). Pilsicainide dose-dependently decreased the local CV at the LSPV-LA junction and the PLA (Fig 6B). Because the impulse conduction block at the LSPV-LA junction occurred in the first 3–5 beats of LSPV pacing at shorter CLs (150 and 100 ms) after treatment with pilsicainide (10 μmol/L), we did not measure the local CV at the PCLs.
Mechanisms of AF Prevention by Pilsicainide (10 μmol/L) During ACh Infusion in Isolated Canine Atria

Fig 7 is an example of the prevention of AF by pilsicainide (10 μmol/L) during infusion of ACh (3 μmol/L). During LSPV pacing at a PCL of 200 ms, the amplitude of the optical action potential at the LSPV was less changed and atrial muscle in the LSPV was continuously activated (Fig 7B-a). In contrast, the amplitude of the action potential at the LSPV-LA junction markedly decreased after 5.5 s of rapid pacing. In addition, after 5.5 s of pacing, the optical signal at the PLA disappeared even if pacing continued (Fig 7B-c). Activation maps during the 3rd and 5th beat (shown in panel B) showed impulse conduction slowing and a block at the LSPV-LA junction, respectively (Figs 7C,D). Moreover, the map obtained from the photodiode array with action potentials obtained during the period marked on panel B revealed that atrial muscles in the LSPV were activated (Fig 7E), indicating that pilsicainide caused impulse conduction block at the junction. However, the activation map during the 14th beat in panel B showed that the beat originating outside the mapping field entered at the lower left of the field and then propagated toward the upper right including the LSPV (Fig 7E), suggesting that pilsicainide cannot cause impulse conduction block when the impulse propagates from the PLA toward the PVs. The impulse conduction block at the junction was observed in all of 6 preparations tested.

Discussion

Role of Autonomic Tone at the PV-LA Junction

It is well known that autonomic tone has an important role in the induction of AF. Recent experimental studies have demonstrated the importance of autonomic tone at the PVs and PV-LA junction in the induction of AF originating from the PVs. In addition, Pappone et al have demonstrated that vagal denervation around the ostia of the PVs reduces the recurrence of AF originating from the PVs. Moreover, Tritto et al have shown that adenosine restores impulse propagation between the LA and PVs after apparently successful ostial catheter ablation of the PVs. In the present study, we demonstrated that ACh increased the CV at the LSPV-LA junction, but not in the PLA. In addition, pilsicainide induced conduction slowing and conduction block at the junction in the presence of ACh and prevented AF induction and its maintenance. These results suggest that increased autonomic tone at the PV-LA junction contributes to AF induction and its maintenance via facilitation of impulse propagation between the PVs and the LA.

Mechanism of Pilsicainide-Induced AF Prevention

Iwasa et al showed that pilsicainide was more effective at terminating vagally-induced AF than propafenone, despite propafenone having increased the wavelength more than pilsicainide, suggesting that suppression of impulse propa-
pilsicainide may be important for terminating AF. In the present study, pilsicainide (1 mg/kg) significantly increased the conduction time between the LSPV and the LAF during LSPV pacing and prevented AF with a conduction block between the LSPV and the LAF during vagal stimulation in anesthetized canine atria (Table 2, Fig 2). In contrast, the same dose of pilsicainide tended to increase conduction time from the RAF to the LAF, but not significantly, and did not prevent AF during RAF pacing. Moreover, pilsicainide decreased the local CV at the LSPV-LA junction more effectively than at the PLA during infusion of ACh in isolated atrial preparations, and prevented AF with an impulse conduction block at the LSPV-LA junction. These results suggest that pilsicainide-induced suppression of the sodium current more effectively causes impulse conduction slowing and block in the atrial muscles of the LSPV-LA junction and prevents AF originating from the LSPV.

Several papers have reported that pilsicainide inhibits the Ik, ACh17,18 the potassium channel current of human ether-a-go-related gene (HERG)25 and the calcium current (ICa)26. In addition, the IC50 of pilsicainide for Ik,ACh was similar to that for sodium current17,18. In the present study, during vagal stimulation a higher, but not lower, dose of pilsicainide inhibited the effects of vagal stimulation on the sinus rate and prevented AF during RAF pacing in anesthetized canines. Moreover, pilsicainide partially restored the left monophasic APD shortened by the infusion of ACh and prevented AF with an impulse conduction block at the LSPV-LA junction in isolated atrial preparations, suggesting that, in addition to inhibiting the sodium current, pilsicainide may cause partial inhibition of Ik,ACh and prevent initiation of cholinergically-induced AF. In contrast, in the absence of ACh, pilsicainide neither increased nor decreased the monophasic APD compared with the control, suggesting that it did not inhibit the ICa or the potassium current of HERG.

It is well recognized that impulse propagation is highly dependent on the structural arrangement of the tissue.27,28 Recently, Hamabe et al29 have shown that tissue structure (segmental muscle disconnection and tissue expansion at the LSPV-LA junction) plays an important role in conduction disturbance at the LSPV-LA junction. Kumagai et al30 have shown that the effective refractory period of the PV-LA junction is significantly longer than that of the distal PV. Laurita et al31 have shown that the formation of an unidirectional conduction block is critically dependent on the source-sink mismatch imposed by tissue structure and spatial heterogeneity of repolarization. In the present study, pilsicainide (1 mg/kg) caused impulse conduction block between the LSPV and the LA during LSPV pacing, but not during the Raf pacing, in anesthetized canines. In addition, pilsicainide homogeneously prolonged the optical APD in the LA and the LSPV during ACh infusion. Thus, these results suggest that the tissue structure of the junction plays an important role in pilsicainide-induced prevention of AF. Nevertheless, pilsicainide is a Class IC antiarrhythmic drug and has a sodium-channel blocking action with...
slow recovery kinetics and, therefore, it decreases tissue excitability and increases the refractoriness of atrial muscles. In addition, Yoshizawa et al. have shown that a sodium-channel blocker increases the total inexcitability of local tissue for activation conduction and then post-repolarization refractoriness, suggesting that pilsicainide would potentiate a source-sink mismatch. Thus, the increased source-sink mismatch at the junction in the presence of pilsicainide may result in a unidirectional conduction block, even if the repolarization gradient is small.

Clinical Implications
Recent studies have shown that complete isolation of the PV is important for preventing recurrence of paroxysmal AF. Ouyang et al. have demonstrated that the recovery of conduction after complete circular isolation of the PV plays an important role in the recurrence of AF originating from the PVs. However, achieving complete isolation by ablation is technically challenging. We have demonstrated that pilsicainide in concentrations achievable in human plasma was more effective at preventing vagally-induced AF originating from the LSPV than from the RA. Moreover, a clinical study has indicated that in the case of the Pilsicainide Suppression Trial on atrial fibrillation (PSTAF): The PSTAF Investigators. Am J Cardiol 1996; 78: 694–697.


Pilsicainide-Induced Prevention of AF

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Conclusions
We found that pilsicainide prevented vagally-induced AF originating from the LSPV with an impulse conduction block between the LSPV and the LA in anesthetized canines. In addition, a lower dose of pilsicainide prevented vagally-induced AF originating from the LSPV but not from the RA. Our study using isolated atrial preparations demonstrated that pilsicainide caused impulse conduction block at the LSPV-LA junction during LSPV pacing. These results suggest that (1) impulse conduction block at the LSPV-LA junction is an underlying mechanism in pilsicainide-induced prevention of AF originating from the LSPV and (2) pilsicainide is more effective at preventing AF originating from the LSPV rather than the RA.

References


