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Effects of pilsicainide and propafenone on vagally induced atrial fibrillation: role of suppressant effect in conductivity

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Abstract

The effects of pilsicainide on vagally induced atrial fibrillation and on electrophysiological parameters were compared with those of propafenone in α-chloralose-anesthetized dogs. Conduction velocity, effective refractory period, wavelength, averaged atrial fibrillation cycle length and activation sequence in the right atrial free wall were determined before and after drug administration. Pilsicainide (2 mg/kg/5 min and 3 mg/kg/h)($n = 10$) or propafenone (2 mg/kg/15 min and 4 mg/kg/h)($n = 10$) was intravenously infused during stable atrial fibrillation sustaining > 30 min. Pilsicainide terminated atrial fibrillation in nine dogs, while propafenone did so in three ($p < 0.01$). After the drug, conduction velocity was suppressed more in the pilsicainide than in the propafenone group($p < 0.01$). There was no difference in effective refractory period after drug between the two groups. Mean wavelength was prolonged from 46.0 to 70.4 mm in the pilsicainide group and from 45.0 to 110.8 mm in the propafenone ($p < 0.01$ vs. pilsicainide). Activation mapping during atrial fibrillation showed Type II or III atrial fibrillation as previously defined [Konings, K.T.S., Kirchhof, C.J.H.J., Smeets, J.R.L.M., Wellens, H.J.J., Penn, O.C., Allessie, M.A., 1994. High-density mapping of electrically induced atrial fibrillation in humans. Circulation. Vol. 89, pp. 511–521.] before the drug, and changed to Type I before atrial fibrillation termination. Thus, pilsicainide was more effective to terminate vagally induced atrial fibrillation than was propafenone despite a greater effect of propafenone than of pilsicainide on wavelength. In this canine atrial fibrillation model, the suppression of conduction velocity may play an important role in changing the activation pattern of atrial fibrillation and thus, terminating atrial fibrillation.

Keywords: Pilsicainide; Propafenone; Atrial fibrillation; Wavelength; Conduction velocity

1. Introduction

Although the nature of atrial fibrillation is not fully understood, random re-entry of coexisting multiple wavelets in the atria is the most likely mechanism for maintenance of the arrhythmia. Allessie et al. (1985) extensively studied the nature of atrial fibrillation and suggested that shortening of the atrial wavelength, a product of the atrial effective refractory period and conduction velocity, is the most important electrophysiological substrate related to the occurrence and maintenance of atrial fibrillation. Atrial fibrillation, especially its paroxysmal form, is generally treated with class Ia anti-arrhythmic drugs. Experimental results have suggested the efficacy of classes Ic and III anti-arrhythmic drugs to terminate atrial fibrillation and possible mechanisms have been discussed (Rensma et al., 1988; Wang et al., 1992; Wang et al., 1993).

Pilsicainide (Fig. 1A) is a new class Ic anti-arrhythmic drug originally developed in Japan with a relatively mild effect on effective refractory period (Sasaki et al., 1995) and a mildly negative inotropic effect (Kihara et al., 1996; Ino et al., 1998). A preliminary clinical study in Japanese patients with atrial fibrillation has demonstrated the high efficacy of the drug to terminate the arrhythmia (Atarashi et al., 1996). However, it is not clear what change in the electrophysiological parameters induced by pilsicainide is related to its effect on atrial fibrillation. In the present

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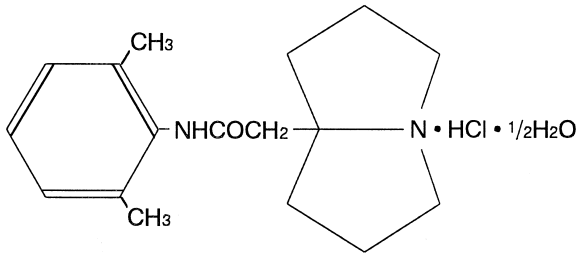
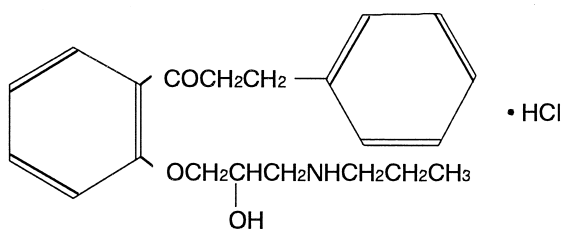


A: Pilsicainide hydrochloride



B: Propafenone hydrochloride

Fig. 1. Chemical structure of pilsicainide and propafenone.

study, we examined the effect of pilsicainide on vagally induced atrial fibrillation induced in a canine model and compared it with that of propafenone (Fig. 1B). The effects of these drugs on the electrophysiological characteristics were also compared.

2. Methods

2.1. Surgical preparation

All experiments were done in accordance with the guidelines on experimental animals issued by Kumamoto University School of Medicine and were approved by the Center of Laboratory Animals. Adult mongrel dogs of either sex weighing from 16 to 27 kg were anesthetized with intravenous α-chloralose (100 mg/kg followed by an hourly dose of 10 mg/kg) and ventilated with room air supplemented with oxygen. After a right thoracotomy, the heart was exposed and suspended in a pericardial cradle. Bipolar electrodes were sutured at the high and low right atrium to stimulate the atrium and record the atrial electrograms, and at the right ventricle to pace the ventricle at a rate of 100 beats/min when the ventricular rate was decreased during vagal stimulation. The tip of a Ag–AgCl-tipped Franz catheter (EP Technologies) was placed at a site adjacent to the high right atrial electrode to record monophasic action potential. A plaque electrode (20 mm × 28 mm) containing 48 electrodes with an interelectrode distance of 4 mm was attached on the right atrial free wall and was used to record simultaneously multiple unipolar electrograms from the right atrium.

The bipolar electrograms, monophasic action potential and arterial pressure were recorded with an electrocardiographic lead II (RM-6000, Nohon Kohden, Japan). The unipolar electrograms from a plaque electrode were recorded with a mapping system (HPM-7100, Fukuda Denshi, Japan). All pacing procedures were done with an output twice the diastolic threshold and with a 2-ms pulse width, with a cardiac stimulator (SEC-2102, Nihon Koden, Japan).

2.2. Bilateral vagal stimulation and measurements of electrophysiological properties

Bilateral cervical vagal trunks were isolated and decentralized. Bipolar needle electrodes were inserted into the middle of each nerve with the electrodes running parallel to vagal fibers for about 1 cm. After propranolol was administered intravenously at an initial dose of 0.5 mg/kg and an hourly dose of 0.25 mg/kg, and ventricular demand pacing at 100 beats/min was initiated, bilateral vagal nerves were stimulated with rectangular pulses with a pulse width of 200 μs and at an output of 6 V with the use of a stimulator (SEN-3201, Nohon Kohden, Japan). Stimulation frequency was set at 2, 5, and 10 Hz.

Effective refractory period at the high right atrium was measured with a train of 10 basic stimuli (S1)(cycle length: 300 and 200 ms) followed by a premature stimulus (S2) in the absence and presence of vagal stimulation at 2, 5, and 10 Hz. Effective refractory period was defined as the longest S1S2 interval failing to produce a propagated response. During S1 stimulation, the conduction time from the high to the low right atrium was determined by measuring the time interval from the onset of monophasic action potential at the high right atrium to the first major deflection of the electrogram at the low right atrium. The distance between the Franz monophasic action potential electrode and the electrode at the low right atrium was divided by the conduction time, and the conduction velocity between the high and low right atrium was determined. The wavelength was calculated as effective refractory period multiplied by conduction velocity.

2.3. Induction of atrial fibrillation

At baseline and during vagal stimulation, a short burst of atrial pacing (cycle length: 100–130 ms) was performed to induce atrial fibrillation. When atrial fibrillation lasted for > 10 s, 48 unipolar electrograms in the right atrial free wall were recorded. Of the 48 electrograms, five with discrete atrial potentials (one from the high right atrium, two from the middle atrium and two from the low atrium) were selected and the cycle lengths of atrial potentials at each electrogram were measured during a 1-s period and were averaged (atrial fibrillation cycle length). In the case that the induced atrial fibrillation persisted for longer than

30 min especially during vagal stimulation at a frequency of 10 Hz, sinus rhythm was restored by the discontinuation of vagal stimulation and the experiment was continued according to the study protocol described below. If the induced atrial fibrillation did not persist for longer than 30 min even in the presence of vagal stimulation at 10 Hz, the experiment was terminated.

2.4. Study protocol

The following protocols for the effects of drugs were applied during vagal stimulation at 10 Hz. After re-induction of atrial fibrillation by burst pacing and verification of its stability (lasting > 15 min), pilsicainide hydrochloride (Suntory, Osaka, Japan) ($n = 10$) or propafenone hydrochloride (Yamanouchi, Tokyo, Japan) ($n = 10$) was administered intravenously. Pilsicainide was administered as a loading dose of 2 mg/kg over 5 min followed by a maintenance dose of 3 mg/kg/h. Propafenone was administered as a loading dose of 2 mg/kg over 15 min followed by a maintenance dose of 4 mg/kg/h. The duration of administration of the loading dose of each drug was derived from that used in clinical cases. Our preliminary study showed that loading propafenone over a shorter period, such as a 5-min period resulted in a marked fall in blood pressure. The negative inotropic effect of pilsicainide is significantly smaller than that of flecainide (Kihara et al., 1996), allowing relatively rapid injection of pilsicainide. When atrial fibrillation was interrupted after drug administration, the measurements of effective refractory period and conduction velocity were then repeated while vagal stimulation (10 Hz) was continued. Also, the measurements were done in the absence and presence of vagal stimulation at 2 and 5 Hz. If atrial fibrillation was not interrupted within 30 min after drug administration, vagal stimulation was terminated and sinus rhythm was restored. The measurements of effective refractory period and conduction velocity were repeated in the absence and presence of vagal stimulation at 2, 5, and 10 Hz.

A blood sample for the measurement of the serum drug level was obtained just after atrial fibrillation was interrupted or at 30 min after drug administration. Pilsicainide and propafenone levels were measured by high performance liquid chromatography.

2.5. Data analysis

All data are shown as means $\pm$ 1 S.E. A two-tailed paired *t*-test was used for the comparison of the effective refractory period, conduction velocities and wavelengths before and after drug administration. Comparison of the atrial fibrillation cycle lengths, effective refractory period, conduction velocities and wavelengths measured at baseline and during vagal stimulation at 2, 5, and 10 Hz between pilsicainide and propafenone groups was done with a two-tailed unpaired *t*-test. The incidences of the interruption of atrial fibrillation by the two drugs were compared using a chi-square test. A *p*-value of less than 0.05 was considered significant.

3. Results

3.1. Correlation between the wavelength and averaged atrial fibrillation cycle length

In seven dogs each from the pilsicainide and propafenone groups, the averaged cycle length of atrial

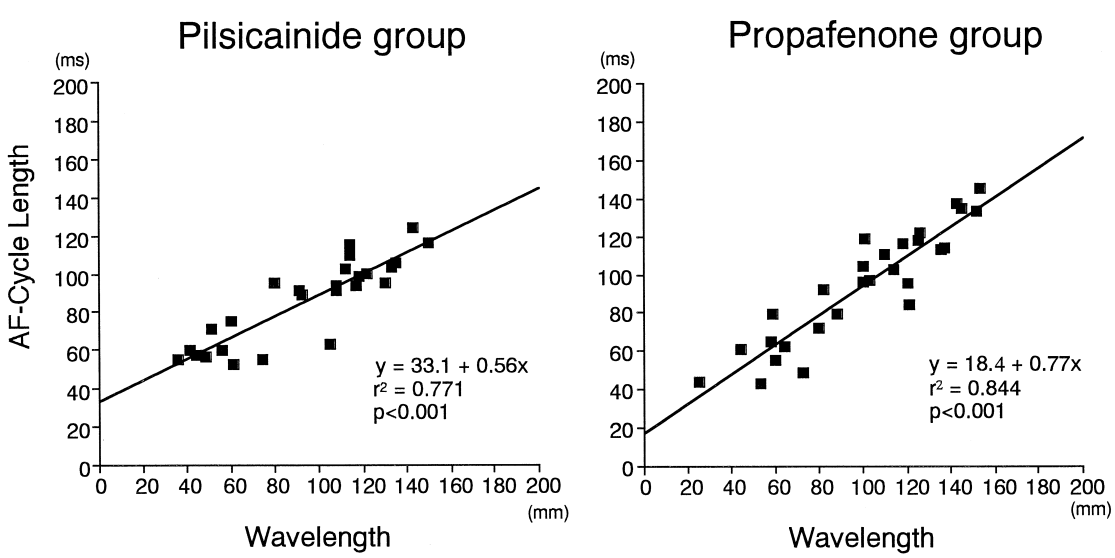


Fig. 2. Correlation between wavelength and averaged atrial fibrillation cycle length (AF-cycle length) determined at baseline and during vagal stimulation at 2, 5, and 10 Hz in the pilsicainide and propafenone groups. There was a significant linear correlation in both groups.

fibrillation (lasting > 10 s) induced at baseline and during vagal stimulation at 2, 5, and 10 Hz was correlated with the wavelength measured under each set of conditions. As shown in Fig. 2, there was a significant linear correlation between the wavelength and the averaged atrial fibrillation cycle length in both pilsicainide ($p < 0.001$) and propafenone groups ($p < 0.001$). Atrial fibrillation induced during vagal stimulation at 10 Hz was sustained for > 30 min in all 10 dogs of each group, while that at baseline and during vagal stimulation at 2 Hz was terminated within 2 min after initiation in all dogs. Fibrillation induced during vagal stimulation at 5 Hz was sustained for > 3 min in all dogs.

3.2. Effects of pilsicainide and propafenone on the electrophysiological properties determined at baseline and during vagal stimulation

Atrial pacing at a cycle length of 200 ms for the measurement of conduction velocity and effective refractory period was done in seven dogs of each group and resulted in the failure of one-to-one atrial capture in one dog of the pilsicainide group and in four of the propafenone group after drug administration. The data obtained during atrial pacing at a cycle length of 300 ms were, therefore, analyzed ($n = 10$ in each group). Table 1 shows the conduction velocities, effective refractory period and wavelengths at baseline and during vagal stimulation at 2, 5, and 10 Hz before drug administration, for the pilsicainide and the propafenone groups. There were no differences in values for any of the parameters between the two groups.

Fig. 3 shows the changes in the electrophysiological parameters after pilsicainide and propafenone administration. After pilsicainide, the conduction velocities at baseline and during vagal stimulation were all significantly decreased and effective refractory period at baseline and during vagal stimulation at 5 and 10 Hz were significantly prolonged. The wavelengths at baseline and during vagal stimulation at 2 Hz were significantly shortened after pilsicainide, while the wavelength during vagal stimulation at 10 Hz was slightly but significantly prolonged to 70.4 ± 4.9 mm from the control of 46.0 ± 3.7 ($p < 0.01$). After propafenone, the conduction velocities at baseline and during vagal stimulation were all significantly decreased and effective refractory period at baseline and during vagal stimulation were all significantly prolonged. The wavelength during vagal stimulation at 10 Hz was significantly prolonged to 110.8 ± 10.2 mm from the control of 45.0 ± 6.1 ($p < 0.01$). When the parameters after drug administration were compared between the two groups, the conduction velocities at baseline and during vagal stimulation in pilsicainide group were all significantly smaller than those in propafenone (all $p < 0.05$), while the effective refractory period were not different. As a result, the wavelengths measured in each case in the pilsicainide group were all significantly shorter than those in the propafenone group (all $p < 0.01$).

3.3. Effects of pilsicainide and propafenone on atrial fibrillation induced during vagal stimulation at 10 Hz

The averaged atrial fibrillation cycle length before drug was 55.5 ± 2.4 ms in the pilsicainide group and 53.4 ± 2.2 ms in the propafenone group ($P = NS$, between two groups). After drug administration, the averaged atrial fibrillation cycle length was increased in all dogs of both groups. In the pilsicainide group, atrial fibrillation was interrupted in nine of the 10 dogs (90%) at a mean time of 8.9 min (range: 4.5–16 min) after drug administration. In the propafenone group, it was interrupted in three of the 10 dogs (30%) ($p < 0.01$ vs. pilsicainide) at 12, 14.5, and 15 min after the drug. The averaged cycle length of atrial fibrillation just before termination of the arrhythmia or at 15 min after drug administration in the dogs in which atrial fibrillation was not interrupted was 147.1 ± 6.8 ms in the pilsicainide group and 124.4 ± 10.7 ms in the propafenone group ($P = NS$ between the two groups).

The relationships between the wavelength and the averaged atrial fibrillation cycle length before and after drug administration were analyzed for each dog. As shown in Fig. 4, the point determined by the wavelength (X-axis) and the averaged atrial fibrillation cycle length (Y-axis)

Table 1
Electrophysiological parameters determined at baseline and during vagal stimulation at 2, 5, and 10 Hz before drug administration

	Pilsicainide group				Propafenone group			
	Baseline ($n = 10$)	2 Hz ($n = 7$)	5 Hz ($n = 7$)	10 Hz ($n = 10$)	Baseline ($n = 10$)	2 Hz ($n = 7$)	5 Hz ($n = 7$)	10 Hz ($n = 10$)
CV (m/s)	1.01 ± 0.02	0.99 ± 0.04	1.01 ± 0.05	1.01 ± 0.04	1.02 ± 0.03	1.04 ± 0.04	1.03 ± 0.04	1.08 ± 0.04
ERP (ms)	135.0 ± 6.4	121.4 ± 6.7	90.0 ± 9.8	46.7 ± 3.3	126.0 ± 7.5	115.7 ± 4.3	90.0 ± 7.9	43.0 ± 5.8
WL (mm)	134.2 ± 6.1	118.3 ± 4.3	89.0 ± 9.4	46.0 ± 3.7	127.4 ± 7.4	119.0 ± 6.4	92.9 ± 8.5	45.0 ± 6.1

ERP: effective refractory period.
CV: conduction velocity.
WL: wavelength.
Data indicated are means ± S.E.

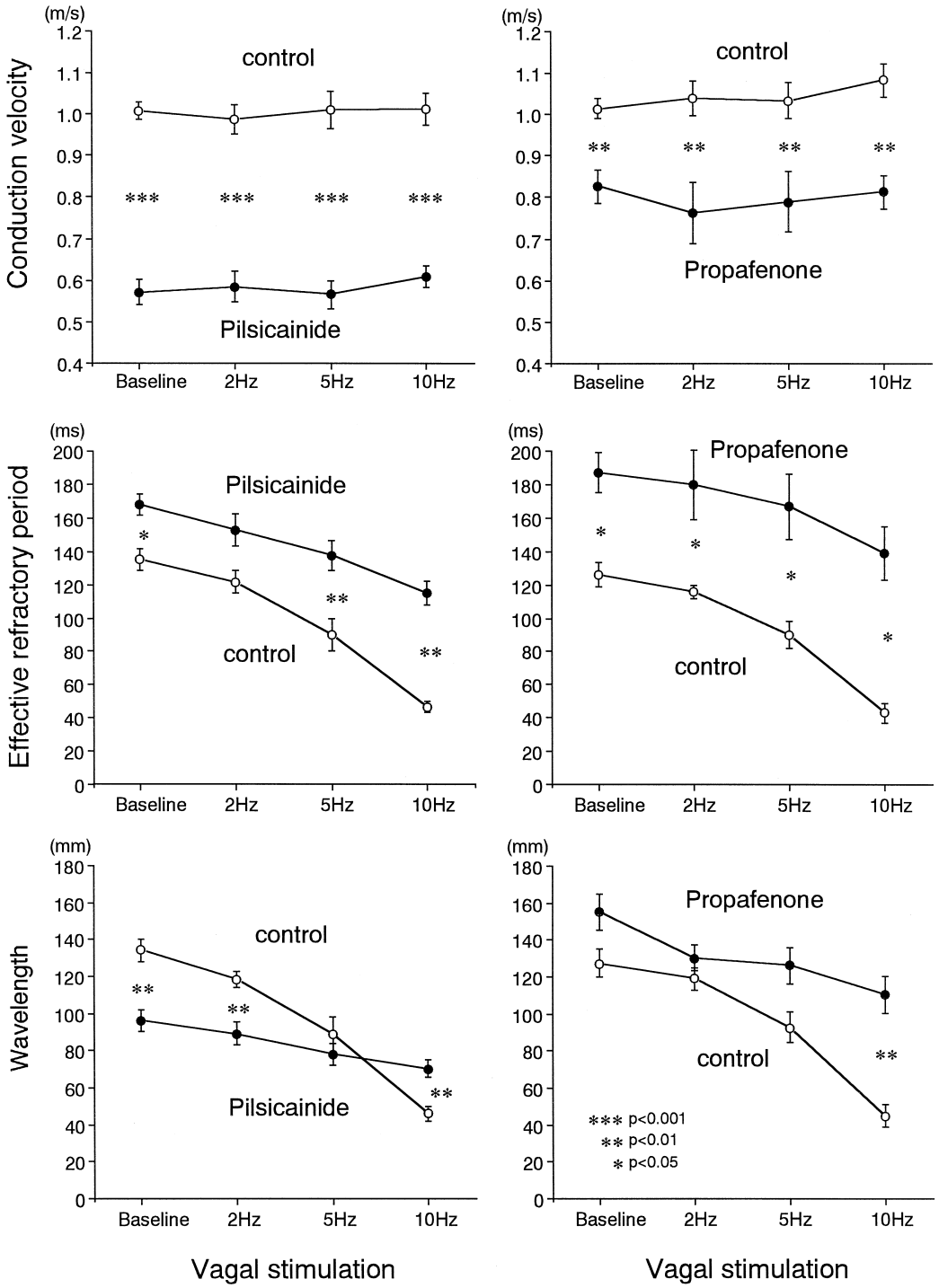


Fig. 3. The effects of pilsicainide (left panel) and propafenone (right panel) on the electrophysiological properties determined at baseline and during vagal stimulation at 2, 5, and 10 Hz. In each panel, open and closed circles indicate measurements before and after drug administration, respectively. When the values of the parameters after drug administration were compared between the two groups, the conduction velocities at baseline and during vagal stimulation in the pilsicainide group were all significantly smaller than those in the propafenone group (all $p < 0.05$), and the wavelengths measured in each case in the pilsicainide group were all significantly shorter than those in the propafenone group (all $p < 0.01$). See text for discussion.

shifted to a right-upper site on the X–Y plane for every dog in both groups. In the propafenone group, the relationship shifted almost along the regression line obtained during vagal stimulation at different frequencies before the drug (Fig. 2), while in the pilsicainide group, it shifted away from the regression line.

Systolic arterial pressures before and after pilsicainide were 120 ± 5 and 108 ± 5 mm Hg, respectively ($P =$

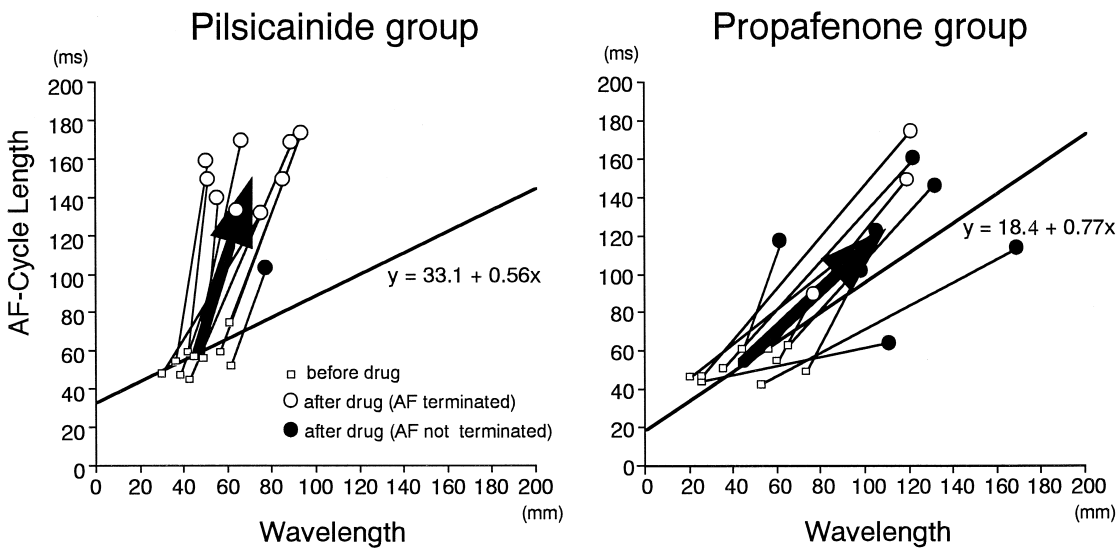


Fig. 4. Changes in the relationships between wavelength and the averaged atrial fibrillation cycle length (AF-cycle length) after the administration of pilsicainide and propafenone. In the propafenone group, the relationship shifted almost along the regression line obtained during vagal stimulation at different frequencies before the drug (Fig. 2), while in the pilsicainide group, it shifted away from the regression line. A large arrow in each panel indicates the changes in mean values of the wavelength and AF-cycle length after drug administration.

0.004), while those before and after propafenone were 129 ± 8.6 and 109 ± 9.0 mm Hg, respectively ($P = 0.013$). The mean plasma concentration of pilsicainide immediately after bolus infusion, i.e., at 5 min after administration, was 5.5 ± 0.7 μg/ml (range: 3.0–8.0 μg/ml). That of propafenone immediately after bolus infusion, i.e., at 15 min after administration, was 2.0 ± 0.25 μg/ml (range: 1.28–2.65 μg/ml).

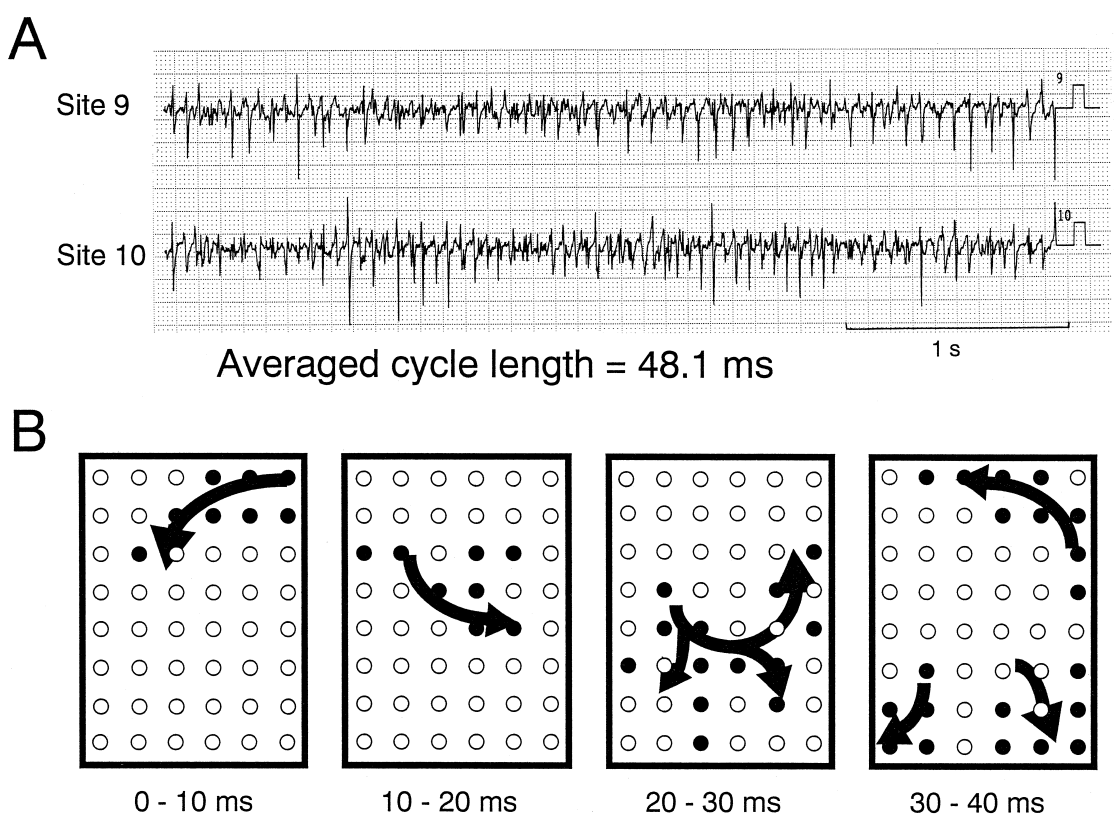


Fig. 5. An example of the recording of the electrograms during atrial fibrillation with an averaged cycle length of 48.1 ms (Panel A) and the activation maps during four successive 10-ms periods in the right atrial free wall (Panel B) before drug administration obtained from one dog in the pilsicainide group. The closed circles in each map indicate the sites activated during a 10-ms period among the 48 recording sites. See text for discussion.

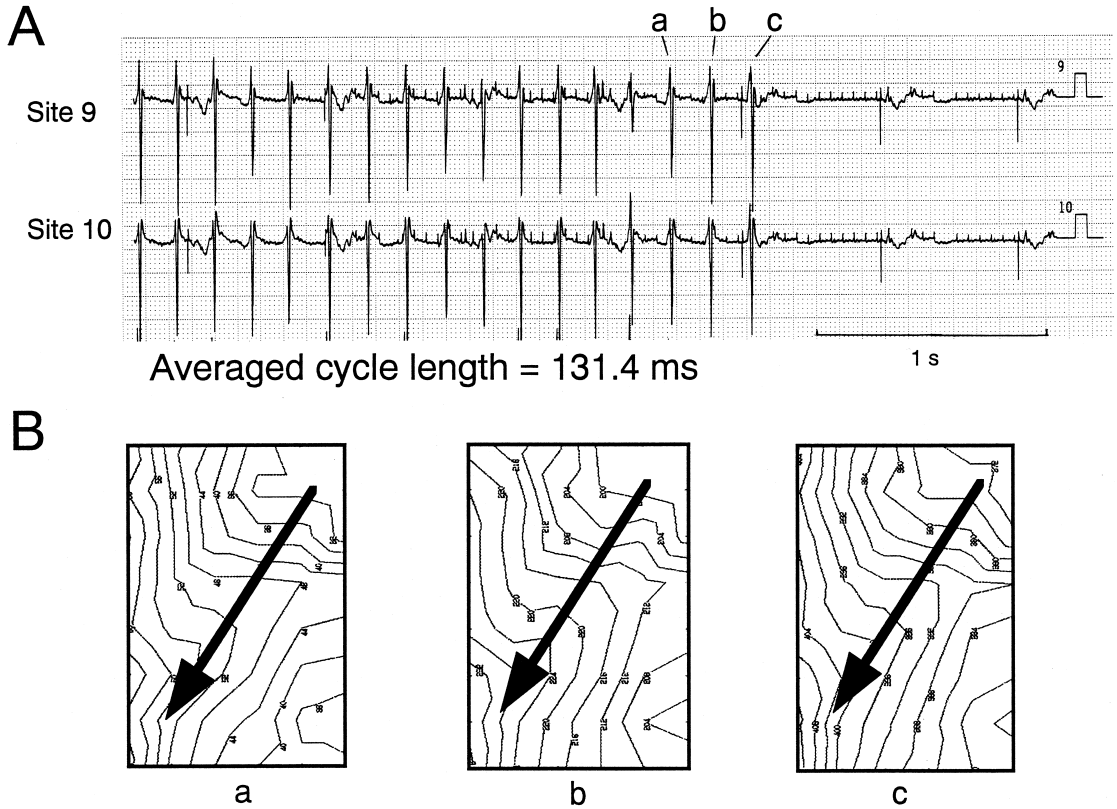


Fig. 6. Recording of the electrograms at the moment of termination of atrial fibrillation (Panel A) and activation maps (Panel B) of the last three beats indicated by a, b, and c in Panel A obtained from the same dog as in Fig. 5. The electrograms are those recorded at the same sites as in the Panel A of Fig. 5 and the averaged atrial fibrillation cycle length was 131.4 ms. The isochrones in Panel B are drawn at a 4-ms interval. It is noted that the atrial excitation was relatively regular (Panel A) and the last three beats showed almost the same activation pattern (Panel B).

3.4. Activation mapping in the right atrial free wall during atrial fibrillation induced during vagal stimulation at 10 Hz

When the activation pattern in the right atrial free wall during atrial fibrillation was analyzed according to the criteria proposed by Konings et al. (1994), Type I activation pattern was never observed before drug administration in any of the dogs, but Type II or III was. Fig. 5 shows an example of the recording of electrograms during atrial fibrillation (Panel A) and the activation maps during four successive 10-ms periods in the right atrial free wall (Panel B) before drug administration, obtained from one dog in pilsicainide group. A markedly disorganized excitation with an averaged cycle length of 48.1 ms (Panel A) and a single re-entry with a revolution time of approximately 40 ms supplying at least two daughter wavelets (Panel B) were noted. Atrial fibrillation was interrupted 4.5 min after pilsicainide in this dog.

Fig. 6 shows the electrograms at the moment of termination of atrial fibrillation (Panel A) and activation maps of the last three beats (Panel B) in the same dog as in Fig. 5. The atrial electrograms showed organized excitation with an averaged cycle length of 131.4 ms and a beat-to-beat variation $\leq$ 10 ms. The activation patterns of the last 3 beats were similar to each other and were comparable to Type I as defined by Konings et al. (1994). A similar observation was made in the other two pilsicainide group dogs and in one propafenone group dog in which atrial activation pattern at the moment of termination of atrial fibrillation could be determined.

4. Discussion

4.1. Mechanism of vagally induced atrial fibrillation

As demonstrated in the previous study (Rensma et al., 1988; Wang et al., 1992; Wang et al., 1993), the inducibility of atrial fibrillation and its stability were found to depend on the shortening of the wavelength. The present study further showed that the averaged atrial fibrillation cycle length measured in the right atrial free wall was also shortened progressively with the increase in the frequency of vagal stimulation. There was a highly significant, positive linear correlation between the atrial fibrillation cycle length and wavelength. Furthermore, fickle re-entrant excitation, defined as Type III atrial fibrillation by Konings et

al. (1994) with a revolution time approximately equal to the atrial fibrillation cycle length was demonstrated in the small area in which no anatomical obstacle was present. Although the recording system in the present study allowed us to analyze the activation sequence only in a localized area in the right atrium and not in the entire atria, multiple re-entrant wavelets were likely to be present simultaneously in the atria. This possibility was strengthened by the fact that the wavelength became as short as 40 to 50 mm during vagal stimulation. Thus, the present vagally induced atrial fibrillation was most likely to be due to random re-entry of multiple wavelets in the setting of critically shortened wavelength as shown in the previous studies (Rensma et al., 1988; Wang et al., 1992; Wang et al., 1993).

4.2. Comparison of the electrophysiological effects of pilsicainide and propafenone

Wang et al. (1993) reported that in the absence of vagal stimulation, propafenone showed little effect on wavelength because of its balanced effects of slowing conduction and prolonging refractoriness, while in the presence of vagal stimulation, it markedly prolonged the wavelength because of its augmented effect of prolonging refractoriness (during atrial pacing at a cycle length of 300 ms, the wavelength measured changed from about 80 mm to 120 mm after the drug). In the present study, propafenone depressed conduction and prolonged the refractory period at baseline and during vagal stimulation. Since the degree of suppression of conductivity and of prolongation of refractoriness was similar at baseline and during vagal stimulation at 2 and 5 Hz, the wavelength remained unchanged after propafenone. However, the wavelength determined during vagal stimulation at 10 Hz was increased from 45 mm to 110.8 mm after propafenone. These results are consistent with those reported by Wang et al. (1993), and propafenone was considered to show an electrophysiological effect similar to that of class III drug especially at high atrial rates.

Pilsicainide, originally developed in Japan, is classified as a class Ic anti-arrhythmic drug and, in the present canine model, it showed a potent depressant effect on intra-atrial conduction and a slight but significant prolonging effect on the atrial refractory period. These effects of pilsicainide are consistent with those previously reported (Sasaki et al., 1995). Since the effect on conductivity was greater than that on refractoriness at baseline and during vagal stimulation at 2 Hz, the wavelength was somewhat shortened after pilsicainide under these conditions. During vagal stimulation at 10 Hz, the effect on refractoriness became more apparent, so that the wavelength was slightly but significantly increased after the drug. Thus, the electrophysiological effects of pilsicainide and propafenone in the present canine model were similar. However, the depressant effect of pilsicainide on conductivity was greater than that of propafenone and, therefore, the increasing effect of the former on wavelength was significantly smaller than the effect of the latter. It should be noted that the mean wavelengths determined during vagal stimulation at 10 Hz after pilsicainide and propafenone were 70.4 mm and 110.8 mm, respectively.

4.3. Effects of pilsicainide and propafenone on atrial fibrillation

The vulnerable parameter of atrial fibrillation is the refractory period, as clearly delineated in the Sicilian Gambit (Task force of the working group on arrhythmias of the European Society of Cardiology, 1991) and also demonstrated in this study, and the prolongation of the refractory period, and thus the wavelength, has been believed to be a key measure for the termination of atrial fibrillation. Rensma et al. (1988) examined the relationship between the electrophysiological parameters and electrically induced atrial arrhythmia in normal conscious dogs and stressed the short wavelength < 78 mm as a determinant of atrial fibrillation. Wang et al. (1993) showed that propafenone, procainamide and *d*-sotalol all effectively terminated vagally induced atrial fibrillation by prolonging the wavelength. Thus, as the wavelength was prolonged, the number of wavelets in the atria was decreased and atrial fibrillation was terminated. Propafenone was shown to prolong the wavelength, especially at a rapid atrial rate, reflecting its use-dependent effect on refractoriness. The same group of authors also reported on the effectiveness of flecainide, another class Ic anti-arrhythmic drug, on the same model of atrial fibrillation and stressed the tachycardia-dependent increase in the refractory period induced by the drug (Wang et al., 1992).

In the present study, propafenone prolonged the wavelength measured during vagal stimulation at 10 Hz to a mean value of 110.8 mm, as described above. Nevertheless, atrial fibrillation was terminated by propafenone in only 30% of the dogs. The disparity in propafenone's effect found in the present study and that found in the previous study by Wang et al. (1993) can be explained by the differences in the strength of vagal stimulation and plasma concentration of the drug. In the study by Wang et al., the mean wavelength during vagal stimulation was about 80 mm, while that in the present study was < 50 mm, suggesting that the atrial fibrillation induced in the present model was more stable and, therefore, more refractory to anti-arrhythmic drugs than that induced in the previous study. The plasma concentration of propafenone in the present study was two-thirds of that shown in the previous study (Wang et al., 1993). It is to be noted that after propafenone administration, the relationship between the wavelength and the averaged atrial fibrillation cycle length shifted almost along the regression line obtained

during vagal stimulation at different frequencies and before the drug (Fig. 4). Thus, propafenone increased the atrial fibrillation cycle length by prolonging the wavelength. However, it remains unclear why atrial fibrillation was not terminated after propafenone in most dogs even though the wavelength and the averaged atrial fibrillation cycle length were both prolonged to the values at which atrial fibrillation was expected to be unsustained, as observed at baseline and during vagal stimulation at 2 Hz before drug administration.

Despite a low effectiveness of propafenone to terminate the present vagally induced atrial fibrillation, pilsicainide terminated the arrhythmia in 90% of the dogs. It was noted that the prolongation of the wavelength induced by pilsicainide was only moderate (that after the drug was 70.4 mm) as compared to that by propafenone. Thus, pilsicainide is suggested to have terminated atrial fibrillation by a mechanism other than prolongation of the refractory period. The precise mechanism for pilsicainide-induced termination of atrial fibrillation could not be identified in the present study, but the effect on conductivity might have been involved because the difference between pilsicainide's and propafenone's effects induced by the present doses of the drugs was the degree of the suppression of conduction velocity. This possibility is made more likely by the fact that the relationship between the wavelength and the averaged atrial fibrillation cycle length after pilsicainide apparently shifted away from the regression line obtained before drug administration (Fig. 4). Theoretically, the suppression of conduction velocity minimizes the prolongation of the wavelength induced by the increase in the refractory period and may thus serve to allow the continuation of multiple re-entrant wavelets. However, as suggested by Brugada et al. (1993) based on the study on the effect of cibenzoline, if the depressant effect on conduction velocity is large enough, it might lead to conduction block of the impulse, reducing the number of wavelets present. Hayashi et al. (1998) recently reported on a comparison of the effect of pilsicainide on vagally induced atrial fibrillation with that of class III drugs MS-551. They concluded that vagally induced atrial fibrillation could be terminated by either prolongation of effective refractory period or suppression of conduction. The present findings for the effects of pilsicainide are consistent with these recent reports and further confirmed the role of suppression of conductivity in terminating atrial fibrillation induced in the experimental model with a much shorter atrial effective refractory period and thus a more stable arrhythmia. Recently, Kumagai et al. showed that unstable re-entrant circuits of very short cycle length, principally involving the atrial septum, appear to be critical for the maintenance of atrial fibrillation induced in a sterile pericarditis model and some re-entrant circuits disappear as others reform, so that at least one re-entrant circuit is always present (Kumagai et al., 1997). If an anti-arrhythmic drug with a predominantly suppressant effect on conductivity enhances the disappearance of unstable re-entrant circuits by causing conduction block, the number of circulating wavelets may be decreased.

4.4. Limitations of the study

We measured the atrial electrophysiological parameters during atrial pacing at a cycle length of 300 ms and not during atrial fibrillation. The changes in the parameters after drugs may not necessarily be representative of those during atrial fibrillation. Furthermore, effective refractory period was measured only at one atrial site (high right atrium). In our present study, the effects of pilsicainide and propafenone were examined under the same conditions and compared with each other. The difference in the effects demonstrated appears to be related to the difference in the rate of the termination of atrial fibrillation between the drugs. Although the role of the suppression of conductivity seems to be important in the effect of pilsicainide shown in this study, the role of the prolongation of refractoriness, especially at very rapid rates, still remains to be elucidated.

We used a mapping system which allowed us to observe the atrial activation sequence in only a small area in the right atrium. The study clearly demonstrated the efficacy of pilsicainide to terminate the present vagally induced atrial fibrillation. Analysis of the mechanism by which pilsicainide terminated the arrhythmia, however, may require mapping of the entire atria as done in the previous study.

Finally, the mechanism of atrial fibrillation induced in the present canine model may be different from that involved in clinical cases. A marked shortening of atrial effective refractory period induced by vagal stimulation especially contributed to the perpetuation of atrial fibrillation in this model. Recent experimental and clinical studies showed that atrial fibrillation per se shortens atrial effective refractory period and begets the arrhythmia (electrical remodeling) (Wijffels et al., 1995; Daoud et al., 1996). Thus, the present findings obtained from a canine model may suggest at least a part of the mechanism of termination of atrial fibrillation with anti-arrhythmic drugs in clinical cases.

References

Allessie, M.A., Lammers, W.J.E.P., Bonke, F.I.M., Hollen, J., 1985. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes, D.P., Jalife, J. (Eds.), Cardiac Electrophysiology and Arrhythmias. Grune and Stratton, Orlando, FL, pp. 265–275.

PSTAF investigators, Atarashi, H., Inoue, H., Hiejima, K., Hayakawa, H., 1996. Conversion of recent-onset atrial fibrillation by a single oral dose of pilsicainide (pilsicainide suppression trial on atrial fibrillation). Am. J. Cardiol. 78, 694–696.

Brugada, J., Gursoy, S., Brugada, P., Atie, J., Guiraudon, G., Andries, E., 1993. Cibenzoline transforms random re-entry into ordered re-entry in the atria. Eur. Heart J. 14, 267–272.

Daoud, E.G., Bogun, F., Goyal, R., Harvey, M., Man, K.C., Strickberger, S.A., Morady, F., 1996. Effect of atrial fibrillation on atrial refractoriness in humans. Circulation 94, 1600–1606.

Hayashi, H., Fujiki, A., Tani, M., Usui, M., Inoue, H., 1998. Different effects of class Ic and III antiarrhythmic drugs on vagotonic atrial fibrillation in the canine heart. J. Cardiovasc. Pharmacol. 31, 101–107.

Ino, K., Atarashi, H., Kuruma, A., Onodera, T., Saitoh, H., Hayakawa, H., 1998. Electrophysiologic and hemodynamic effects of a single oral dose of pilsicainide hydrochloride, a new class Ic antiarrhythmic agent. J. Cardiovasc. Pharmacol. 31, 157–164.

Kihara, Y., Inoko, M., Hatakeyama, N., Momose, Y., Sasayama, S., 1996. Mechanism of negative inotropic effects of class Ic antiarrhythmic agents: comparative study of the effects of flecainide and pilsicainide on intracellular calcium handling in dog ventricular myocardium. J. Cardiovasc. Pharmacol. 27, 42–51.

Konings, K.T.S., Kirchhof, C.J.H.J., Smeets, J.R.L.M., Wellens, H.J.J., Penn, O.C., Allessie, M.A., 1994. High-density mapping of electrically induced atrial fibrillation in humans. Circulation 89, 1665–1680.

Kumagai, K., Khrestian, C., Waldo, A.L., 1997. Simultaneous multisite mapping studies during induced atrial fibrillation in the sterile pericarditis model. Insights into the mechanism of its maintenance. Circulation 95, 511–521.

Rensma, P.L., Allessie, M.A., Lammers, W.J.E.P., Bonke, F.I.M., Schalij, M.J., 1988. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ. Res. 62, 395–410.

Sasaki, R., Inoue, D., Ishibashi, K., Inoue, M., Shirayama, T., Yamahara, Y., Asayama, J., Nakagawa, M., 1995. Kinetics of frequency-dependent conduction delay by class I antiarrhythmic drugs in human atrium. J. Cardiovasc. Pharmacol. 25, 953–960.

Task force of the working group on arrhythmias of the European Society of Cardiology, 1991. The sicilian gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Circulation 84, 1831–1851.

Wang, Z., Page, P., Nattel, S., 1992. Mechanism of flecainide's antiarrhythmic action in experimental atrial fibrillation. Circ. Res. 71, 271–287.

Wang, J., Bourne, G.W., Wang, Z., Villemaire, C., Talajic, M., Nattel, S., 1993. Comparative mechanisms of antiarrhythmic drug action in experimental atrial fibrillation. Importance of use-dependent effects on refractoriness. Circulation 88, 1030–1044.

Wijffels, M.C.E.F., Kirchhof, C.J.H.J., Dorland, R., Allessie, M.A., 1995. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. Circulation 92, 1954–1968.