Effect of Pilsicainide on Atrial Electrophysiologic Properties in the Canine Rapid Atrial Stimulation Model

— A Possible Suppressive Effect on Atrial Electrical Remodeling —

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The heterogeneous process of atrial electrical remodeling (AER) in the canine rapid atrial stimulation model has been previously reported although it has been reported that a sodium channel blocker might suppress the shortening of the atrial effective refractory period (AERP), its effect on long-term electrical remodeling is unknown. In the present study, the effect of pilsicainide on AER was evaluated. The right atrial appendage (RAA) was paced at 400 beats/min for 2 weeks. In the RAA, Bachmann's bundle (BB), the right atrium near the inferior vena cava (IVC) and in the left atrium (LA), AERP, AERP dispersion (AERPd) and the inducibility of atrial fibrillation (AF) were evaluated at several time points of the pacing phase and the recovery phase (1 week). The same protocol was performed during the administration of pilsicainide (4.5 mg/kg per day) and the parameters were compared with the controls. In the control dogs, the AERP was significantly shortened by rapid pacing at all atrial sites studied and the AERP shortening (ΔAERP) was larger at the RAA and LA sites ($p < 0.03$). However, pilsicainide decreased these ΔAERPs at all 4 atrial sites. AERPd was increased during the pacing phase whereas it was decreased during the recovery phase in the control dogs. In contrast, this pacing-induced AERPd was attenuated by the administration of pilsicainide. The AF inducibility was highest at the LA site in both groups, and the inducibility was lower in the pilsicainide group than the control group at all atrial sites. During the rapid pacing phase, the ventricular heart rate was significantly lower in the pilsicainide group than the control because of intra-atrial conduction block. In a canine rapid right atrial stimulation model, pilsicainide suppressed the shortening of the AERP at all atrial sites, possibly through the improvement of the hemodynamics as well as the action of the Na–Ca exchanger. (Circ J 2003; 67: 340–346)

Key Words: Atrial fibrillation; Electrical remodeling; Pilsicainide

It has been reported that continuous rapid atrial pacing caused shortening of the atrial effective refractory period (AERP); in other words, electrical remodeling, which might play an arrhythmogenic role in causing atrial fibrillation (AF) through the shortening of the atrial wave length.^{1–10} Although suppressive effect of a calcium channel blocker on electrical remodeling was expected, its effect was relatively short term^{1,7,11,12} and the outcome of long term electrical remodeling varied depending on the anatomical site in the atria.¹³ It has also been reported that sodium channel blockers might suppress the shortening of the AERP,^{14–16} possibly through the action of the Na–Ca exchanger, but its effect on long-term electrical remodeling is unknown. In the present study, the effect of pilsicainide, a pure sodium channel blocker, on long-term electrical remodeling was evaluated in the canine rapid atrial stimulation model mimicking right atrial focal fibrillation.

Methods

Subjects and Surgical Procedure

In 9 adult beagle dogs weighing 10–15 kg, the cardiac surface was exposed via a right thoracotomy under pentobarbital anesthesia (30 mg/kg body weight, iv) and mechanical ventilation (Model SN-480-5, Shinano Manufacturing, Tokyo, Japan) with oxygen (2 L/min).^{17–19} Four pairs of stainless steel wire electrodes were sutured onto the epicardial surface of the right atrial appendage (RAA), Bachmann's bundle (BB), the right atrium close to the inferior vena cava (IVC) and the center of the left atrial free wall (LA) (Fig 1A). The other ends of the wire electrodes were tunneled subcutaneously and exposed at the back of the neck for the electrophysiological measurements in the later studies. For continuous atrial rapid pacing, a screw-in pacing electrode (CapSureFix 5568, Medtronic Inc, USA) was introduced through the right external jugular vein and fixed to the endocardial surface of the RAA. The distal end of this pacing electrode was connected to a rapid pulse generator (customized Thera SR, Medtronic Inc), which was implanted subcutaneously in a right cervical pocket.¹³ All studies were performed in accordance with the guidelines specified by the Animal Experimentation and Ethics Committee of the Kitasato University School of Medicine.

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Evaluation of the Electrophysiological Properties

To achieve a stable baseline state, each dog was allowed to recover for 7 days after the initial surgical procedure without any pacing. Rapid atrial pacing (400 beats/min) was begun (day 0 in Fig 1B) and was continued for 2 weeks (rapid pacing phase) at 4 times the diastolic threshold (4.3 ± 0.6 V) and with a pulse width of 2 ms. After this continuous rapid pacing, the pacing was stopped, and each dog was allowed to recover for 1 week (recovery phase). On days 0, 3, 7, 10 and 14 during the rapid pacing phase, the rapid pacing was stopped temporarily to evaluate the atrial electrophysiological properties at the 4 atrial sites (ie, RAA, BB, IVC and LA). On days 1, 3 and 7 during the recovery phase after the rapid pacing phase (ie, days 15, 17 and 21 from the start of the rapid pacing), the electrophysiological properties were reevaluated (Fig 1B). All electrograms were recorded through a polygraph system (Bioelectric AMPL, NEC, Tokyo, Japan). The analogue signals were converted to digital signals and stored on a computer hard-disk (Power Lab, ADInstrument, USA) and subsequently used for analysis. At the time of each electrophysiological measurement, the autonomic nervous system was blocked pharmacologically by infusing atropine of 0.04 mg/kg and propranolol of 0.2 mg/kg while the animal was conscious.

Atrial Diastolic Threshold At each evaluation of the electrophysiological parameters, the atrial diastolic threshold was measured at the 4 atrial pacing sites by delivering 300 ms cycle length pacing with a pulse width of 2 ms.

Atrial Electrical Capture by the Rapid Stimulation In the rapid pacing phase, atrial electrocardiograms at all 4 atrial recording sites were recorded continuously for 5 min before and after each electrophysiological evaluation to confirm the atrial capture by the rapid atrial stimulation from the RAA.

Atrial Effective Refractory Period The AERP was measured at the 4 atrial pacing sites with basic cycle lengths (BCL) of 300, 200 and 150 ms. The electrical stimulation was delivered at twice the diastolic threshold at each pacing site at each evaluation time point. The coupling interval of the premature stimulus was shortened in 2-ms steps. The longest coupling interval of the premature beat that failed to capture the atrium was determined as the local AERP.

Dispersion of the AERP The AERPd was evaluated as an index of the inhomogeneity of atrial refractoriness during the progression and/or recovery of atrial electrical remodeling. It was calculated as the difference between the longest and shortest AERPs among the 4 atrial pacing sites, and was evaluated with each BCL at each evaluation time during the whole study protocol.

Inducibility of AF The inducibility of transient AF was evaluated with atrial burst pacing for 3 s at the minimal pacing cycle length that achieved a 1:1 atrial capture at each atrial pacing site. The transient AF was defined as the episode of the rapid irregular atrial activity lasting more than 1 s. This pacing was delivered at 4 times the diastolic threshold with a pulse width of 2 ms. Atrial burst pacing for AF induction was delivered 5 times at each pacing site at each evaluation point during the whole protocol. The incidence of AF induction was evaluated. At each episode of AF, spontaneous termination was allowed to occur and the next burst pacing for AF induction was performed 30 s after the termination of AF.

Ventricular and Atrial Heart Rate To evaluate approx-

Fig 1. Schematic of the positions of the atrial electrodes and the time course of the experimental protocol. Panel A shows the positions of the 4 epicardial pacing wires (●) and the endocardial pacing lead for continuous rapid atrial pacing (○). Panel B shows the time course of the study protocol. The initial surgery for implantation of the device and electrodes was performed 7 days before starting the rapid atrial pacing. Rapid pacing was continued for 2 weeks, and then normal sinus rhythm was resumed. The electrophysiological parameters were measured on days 0, 3, 7, 10, 14, 15, 17 and 21. The 9 dogs were divided into 2 groups with and without pilsicainide administration (4.5 mg/kg per day). The administration of pilsicainide was started 3 days before the start of the rapid pacing. See text for details. RAA, right atrial appendage; LA, left atrium; PV, pulmonary vein; SVC, superior vena cava; IVC, inferior vena cava; BB, Bachmann's bundle.

imately the hemodynamics during the rapid pacing, the ventricular heart rate (V-HR) was measured before each evaluation of the electrophysiological properties (ie, before stopping the rapid pacing and pharmacological autonomic blocking). The mean V-HR was measured from a 30 s recording during rapid atrial pacing. At the same time, the atrial heart rate (A-HR) at each atrial recording site was evaluated to confirm the capture of each atrial site by the rapid pacing.

Administration of Pilsicainide

In 4 of 9 dogs, pilsicainide was administered orally as a single capsule (4.5 mg/kg per day). The administration of pilsicainide was started 3 days before the start of the rapid atrial pacing protocol. The same evaluation protocol as the control was performed for the dogs treated with pilsicainide (Fig 1B). The blood concentration of pilsicainide was measured at each electrophysiological evaluation session.

Statistical Analysis

Values are expressed as means $\pm$ SD. Basic comparative statistics were analyzed with a Kruskal-Wallis-H-test, Student-Newmann-Keuls test or Mann-Whitney-U-test. A $p < 0.05$ was considered significant.

Results

Atrial Diastolic Threshold

In the pilsicainide group, the mean plasma concentration of pilsicainide was 1.3 ± 0.5 mg/L, which was within the therapeutic range of the drug. The atrial diastolic threshold was measured at the 4 atrial pacing sites at each electrophysiologic evaluation. In the control group at day 0, it was 0.9 ± 0.2 V at RAA, 1.3 ± 0.1 V at BB, 0.9 ± 0.1 V at IVC and 0.9 ± 0.2 V at LA site. In the pilsicainide group, the respec-

Fig 2. Representative atrial electrogram during rapid pacing from the RAA site in a pilsicainide dog. Although the RAA site showed 1:1 capture, the other 3 sites sometimes showed capture failure. Stimulation artifact (S), atrial electrogram (A) and ventricular electrogram (V far-field potential) are indicated. See text for details. RAA, right atrial appendage; BB, Bachmann's bundle; IVC, right atrium close to the inferior vena cava; LA, left atrium.

Fig 3. AERP at each atrial site on day 0, before the start of rapid pacing. Each white bar indicates the mean AERP at each atrial site in the control group and each shaded bar marks the data in the pilsicainide group. Thin horizontal lines indicate the range of the standard deviation. There was no significant difference between the control and pilsicainide groups at day 0. Among the 4 atrial sites, the AERP was shorter at the LA site than the other sites for all 3 basic drive cycle length. See text for details. BCL, basic cycle length; RAA, right atrial appendage; IVC, right atrium close to the inferior vena cava; BB, Bachmann's bundle; LA, left atrium.

tive values at day 0 were 0.9 ± 0.04 V at RAA, 1.1 ± 0.2 V at BB, 1.3 ± 0.1 V at IVC and 1.0 ± 0.1 V at LA site. There was no significant difference between the 2 groups and they did not show any significant changes throughout the study protocol.

Atrial Electrical Capture by the Rapid Stimulation

In the control group, all 4 atrial sites showed 1:1 capture during the rapid atrial pacing throughout the study. In contrast, in pilsicainide group, although the RAA site always showed 1:1 capture, the other sites sometimes showed capture failure (ie, intra-atrial dissociation, indicating the occurrence of intra-atrial conduction block). Fig 2 shows a representative example of the atrial electrograms during rapid pacing from RAA in a pilsicainide dog. In this case, intra-atrial conduction block was suspected between RAA and BB, or RAA and IVC because of the dissociation of the atrial electrograms.

Atrial Effective Refractory Period (AERP)

Fig 3 shows the AERPs at the 4 atrial sites on day 0 (ie, before the start of the rapid RA pacing protocol). Although the LA site showed a significantly shorter AERP than the other atrial sites with all BCL ($p < 0.05$), there was no significant difference between the control and pilsicainide groups.

Fig 4 shows the changes in AERPs at each atrial site over the time course of the pacing protocol. The vertical axis

indicates AERP expressed in AERP change with the data at day 0 at each site. In the control group, AERPs showed relatively quick shortening by day 3 then continued to shorten until day 14. During the recovery phase, after the cessation of the continuous rapid atrial pacing, AERPs showed quick recovery within the first day and recovered to pre-pacing levels by day 15. The AERP at RAA site was larger than those at IVC and BB sites with the basic cycle lengths of 200 and 150 ms. The AERP at LA site was larger than the 2 sites with all BCL. In contrast, in the pilsicainide group, although the basic properties of the changes in AERPs were similar to the control group, the shortening of the AERP during the rapid pacing phase was suppressed at all 4 sites especially with the BCL of 200 and 150 ms. There was no significant difference among 4 atrial sites with the cycle lengths of 200 and 300 ms.

Dispersion of AERP

Fig 5 shows the changes in AERPd among the 4 atrial sites with 3 BCL. AERPd was expressed as percent with the data at day 0 being 100%. In the control group, the AERPd increased quickly by day 3 and then reached a plateau. However, in the recovery phase, the AERPd decreased quickly and became temporarily smaller than the baseline state. The increase in the AERPd was most prominent with a BCL of 200 ms in the control group. In contrast, in the pilsicainide group, the increase in the AERPd during the rapid pacing phase was obviously suppressed and was

Fig 4. Changes in AERP (Δ AERP) at the 4 atrial sites with 3 basic cycle lengths. The vertical axis indicates the increase in AERP and the horizontal axis shows the time course during the protocol. In the control group (left 3 panels), the RAA and LA sites showed greater shortening in AERP than the other sites. This shortening was suppressed by pilsicainide at all 4 sites. During the recovery phase, the changes in AERPs were not significantly different between the control and pilsicainide groups. See text for details. AERP=[AERP]–[AERP on day 0], BCL, basic cycle length; RAA, right atrial appendage; IVC, right atrium close to the inferior vena cava; BB, Bachmann's bundle; LA, left atrium.

Fig 5. Changes in AERPd (ie, the maximal differences in AERPs among the 4 atrial sites with 3 basic cycle lengths) are plotted with the time course. The vertical axis indicates AERPd as a percentage by setting the value on day 0 at 100 %. By day 3 increased the control group, the AERPd showed a rapid increase that was maintained during the rapid pacing. In the recovery phase, AERPd recovered quickly and was temporarily less than that at day 0. In the pilsicainide group, the increase in the AERPd during the rapid pacing phase was suppressed in comparison with the control group. See text for details. BCL, basic cycle length.

rather decreased in comparison with the control findings with 150 ms BCL.

Inducibility of AF

Fig 6 shows the incidence of AF induction at the 4 atrial sites at each evaluation point. In the control group, the incidence of AF induction increased in accordance with the continuation of the rapid pacing. The incidence of AF induction at the LA pacing site was higher than at the other

sites. In the pilsicainide group, the incidence of AF induction was totally suppressed at all sites except the LA site during the rapid pacing phase, but it was rather higher at the BB site during the recovery phase.

V-HR and A-HR

Fig 7 shows the change in V-HR during rapid atrial pacing before pharmacological autonomic blocking. In the control group, a higher V-HR was maintained during the rapid

Fig7. Changes in ventricular HR (V-HR) with time during rapid atrial pacing before pharmacological autonomic blocking. In the control group, a higher V-HR was maintained during the rapid pacing, then there was a return to a lower V-HR because the sinus rhythm recovered during the recovery phase. In the pilsicainide group, V-HR was significantly lower than the control during the rapid pacing. The difference between the control and the pilsicainide groups was not significant during the recovery phase. See text for details.

pacing because of rapid atrial activation and relatively frequent conduction through the AV node. In the recovery phase, the V-HR returned to a lower level because the sinus rhythm recovered. In contrast in the pilsicainide group, V-HR was significantly lower than in the control during the rapid pacing. The difference between the control and the pilsicainide groups was not significant during the recovery phase. Fig 8 shows the change in the rate of atrial electrograms at each recording site during the rapid pacing. In the control group, all atrial sites were captured completely by the rapid pacing of 400beats/min. In contrast in the pilsicainide group, each atrial site showed relatively lower A-HR than 400beats/min, probably because of the conduction block between the pacing and the recording sites. The difference between the 2 groups was significant at the LA site.

Discussion

This study has several unique and interesting findings. In the control group, consistent with previous studies,¹³⁻¹⁷ the progression of atrial pacing induced electrical remodeling

Fig6. Incidence of AF induction at each evaluation point is shown for the 4 atrial pacing sites. Atrial burst pacing for AF induction was delivered 5 times at each pacing site at each evaluation time point. In the control group, AF inducibility increased gradually in accordance with the time course of the rapid pacing phase. Among the 4 atrial sites, the incidence of AF induction was highest at the LA site. Pilsicainide suppressed the AF induction during both the rapid pacing phase and the recovery phase. The total incidence of AF induction was less in the pilsicainide group than the control group. See text for details. RAA, right atrial appendage; IVC, right atrium close to the inferior vena cava; BB, Bachmann's bundle; LA, left atrium.

was inhomogeneous, depending on the atrial site assessed. Shortening of the AERP was larger at the RAA and LA sites than at the other sites and as a result, the AERPd was increased early during the rapid pacing phase and then decreased during the recovery phase. The AF inducibility gradually increased concordant with the shortening of AERP and the increase of AERPd. In the pilsicainide group, although the changes in AERPs caused by rapid atrial pacing were inhomogeneous, the degree of shortening of the AERPds were significantly less than in the control group. In contrast to the control group, the pilsicainide group did not show an increase in AERPd during the rapid pacing phase. The V-HR during rapid pacing phase was significantly lower in the pilsicainide group than the control group. Intra-atrial conduction block was observed in the pilsicainide group whereas the control group showed complete 1:1 atrial capture throughout the rapid pacing phase.

Inhomogeneity of Electrical Remodeling

Atrial electrical remodeling has been evaluated in several animal models of rapid atrial pacing,^{1,2,4,7,9,10,20-23} which have documented the shortening of the AERP and prolongation in atrial conduction time, but few have reported the inhomogeneity in the process of atrial electrical remodeling. We previously reported that the shortening of the AERP was larger at the RAA and LA sites than at the other atrial sites when the rapid pacing was performed from the RAA site for 2 weeks.¹³ The AERP dispersion was temporally increased during the rapid pacing phase as a result of the inhomogeneity of the shortening of the AERPs. The mechanism of this inhomogeneity was unclear. The distance between the pacing and recording sites probably does not play a role in this inhomogeneity because all atrial sites in the control group showed complete 1:1 capture during the rapid pacing phase. The difference in the mechanical stretch during rapid pacing may play a role, especially in causing a larger AERP shortening at the LA site than the other sites. In addition, as Feng et al reported, the basic electrophysiological characteristics of the atrial cells might differ in the LA compared with the right atrium on the basis of the difference in the profiles of ionic current densities.²¹ Our model of rapid atrial stimulation for the evaluation of the atrial electrical remodeling has some limitations: (1) a

Fig 8. Atrial heart rate (A-HR) at each recording site during the rapid pacing. In the control group, all atrial sites were captured completely by the rapid pacing of 400 beats/min. In the pilsicainide group, each atrial site showed relatively lower A-HR, probably because of conduction block between the pacing and recording sites. The difference between 2 groups was significant at the LA site. See text for details. RAA: right atrial appendage, BB: Bachmann's bundle, IVC: right atrium close the inferior vena cava, LA: left atrium.

change in the hemodynamics because of higher V-HR during rapid pacing and (2) possible inhomogeneity in atrial activations. However, our model can evaluate the physiologic phenomenon that might appear in a clinical case, such as focal atrial tachycardia.

Effect of Antiarrhythmic Drugs on Atrial Electrical Remodeling

Many studies have reported the effects of antiarrhythmic drugs on atrial electrical remodeling caused by rapid atrial excitement. Because intracellular calcium overload is thought to play an important role in atrial electrical remodeling, an L-type Ca channel blockade was expected to prevent it. Tieleman et al demonstrated in a goat model that the shortening of the AERP caused by rapid atrial pacing was significantly attenuated by verapamil, but only during short-term pacing.⁷ Several studies have similarly reported that verapamil might suppress the shortening of AERP in the relatively short term (<24 h).^{11,12,15} Lee et al demonstrated that verapamil did not suppress the shortening of AERP in a relatively long-term model (1 and 6 weeks), although they did not evaluate the progression of the atrial electrical remodeling.²⁴ We previously reported that verapamil might suppress the shortening of the AERP in a rapid atrial stimulation model for 2 weeks, but this suppressive effect was observed only at the LA site, not at the other right atrial sites studied.²⁵ The mechanism of this difference between the left and right atria was unclear, but it appeared that the effect of verapamil on electrical remodeling was inhomogeneous, in addition to the progression of the electrical remodeling.

The effect of sodium channel blockade on atrial remodeling is uncertain. Daoud et al reported that procainamide suppressed the shortening of the AERP during induced atrial fibrillation for 5–10 min in a clinical electrophysiologic study although the degree of suppression was significantly less than that of verapamil.¹¹ Kumagai et al reported that pilsicainide, a pure sodium channel blocker, might suppress the shortening of the AERP in a canine model of rapid atrial stimulation for 3 h;²⁶ and in the present study, which is the first systematic evaluation of the effect of a relatively pure sodium channel blocker on atrial electrical remodeling, we evaluated the effect of pilsicainide in a

relatively long-term atrial stimulation model. The result was that the shortening of the AERP was suppressed at all atrial sites studied and the AERPd was relatively decreased even during the rapid pacing phase. The mechanism of suppression of the shortening of the AERP by sodium channel blockers is unclear, but there are 3 possible mechanisms. First, a direct action on atrial muscle (ie, increase of the outward Ca current caused by the action of the Na–Ca exchanger). Sodium channel blockers suppress the inward sodium current and increase the extra-intracellular sodium gradient. The larger the sodium gradient, the more the Na–Ca exchanger works, then the outward calcium current through the Na–Ca exchanger increases and results in suppressing intracellular calcium overload. Second, a lower A-HR caused by intra-atrial conduction block. As shown in Fig 8, pilsicainide reduced the A-HR during rapid pacing at all atrial sites, probably caused by intra-atrial conduction block as a result of suppression of the sodium current, and the difference was significant at the LA site. The lower the frequency of the atrial activation, smaller the degree of the AERP shortening caused by rapid atrial pacing, especially in the present model of 'focal' atrial tachycardia. This mechanism explains well the decrease in AERPd in the pilsicainide group. Because the shortening of the AERP in the LA site plays an important role in increasing the AERPd in the control group, pilsicainide decreased the AERPd at least in this model of rapid atrial stimulation at the RAA site. Third, improvement of the hemodynamics during the rapid pacing. In the present study, the V-HR during rapid pacing was monitored. Although the intra-cardiac pressure could not be monitored in the present model, the hemodynamics during the rapid pacing were considered to be reflected approximately by the V-HR, and it was significantly lower in the pilsicainide group than the control group. It is unlikely that pilsicainide suppressed conduction through atrioventricular (AV) node because this drug is a pure sodium channel blocker. Although the atrial activation around the AV node could not be monitored, intra-atrial conduction block may reduce the frequency of the input to the AV node, which then may result in a reduction of the V-HR. The first mechanism is a direct action and the latter 2 would be indirect effects on electrical remodeling. In particular, intra-atrial conduction block may reduce the

atrial activation frequency itself at a site distal to the pacing site. This might be an important factor in suppressing the AERP shortening at the LA site because the atrial activation frequency at the LA was significantly lower than at the RAA, which can not be considered a direct action of pilsicainide on atrial electrical remodeling, but might be a phenomenon that could appear in a clinical case affecting the whole body. Our canine model of rapid atrial pacing can not evaluate these factors separately; however, it indicates the action of pilsicainide on electrical remodeling in clinical cases of focal AF or atrial tachycardia. In the present study, pilsicainide suppressed the AF induction at all atrial sites throughout the study protocol, which may reflect the effect of pilsicainide (ie, the suppression of the shortening of AERP or the suppression of the increase in the AERPd), but it is unclear because pilsicainide itself has an antiarrhythmic effect through its sodium channel blocking action.

Study Limitations

There are several important limitations. First, the time and spatial resolution of the evaluating points were limited. Second, because a His-bundle ablation was not performed, the influence of hemodynamic changes during rapid atrial pacing was not eliminated. Third, hemodynamic factors (eg, atrial pressure and atrial wall stress) were not monitored. Fourth, the role of the changes in electrophysiological parameters (ie, the AERP shortening and the AERPd) in provoking the appearance of AF was unclear. Finally, the action of pilsicainide on atrial activation frequency or hemodynamics could not be evaluated. These parameters should be evaluated separately in future studies with a larger number of dogs.

Conclusions

- (1) The shortening of the AERP was suppressed by pilsicainide at all atrial sites.
- (2) The increase in AERPd during the rapid pacing phase was suppressed by pilsicainide.
- (3) The incidence of AF induction was suppressed by pilsicainide at all atrial sites.
- (4) These effects of pilsicainide might be explained by changes in the atrial and ventricular HR as well as by the direct action of pilsicainide on the atrial muscle.

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