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## Electrophysiologic Mechanism of Conversion of Atrial Fibrillation to Sinus Rhythm

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# Electrophysiologic Mechanism of Conversion of Atrial Fibrillation to Sinus Rhythm

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**MOROE, ET AL:** *Electrophysiologic Mechanism of Conversion of Atrial Fibrillation to Sinus Rhythm.* We investigated the validity of the circulating wavelet hypothesis as an explanation of the mechanism of termination of atrial fibrillation in 11 patients with atrial fibrillation. During the atrial fibrillation, 11 electrocardiograms of the right atrium and a left atrial electrocardiogram were recorded. The average interval of atrial potentials and the standard deviation of the intervals at 12 atrial sites, defined as the dispersion of the interval during atrial fibrillation, were determined. Pilsicainide resulted in successful conversion to sinus rhythm in 6 of 11 patients. Pilsicainide significantly reduced the dispersion of the interval in responders compared with non-responders. The minimal dispersion was observed just before termination of atrial fibrillation. These results suggest that the mechanism of pharmacologic conversion of atrial fibrillation to sinus rhythm may be related to a decrease in the dispersion of atrial fibrillation leading to synchronization of multiple reentrant wavelets in both atria. (*J HK Coll Cardiol* 1999; 7:87-95)

*atrial fibrillation, termination, antiarrhythmic agent, mechanism, synchronization*

## 摘要

在11例心房顫動〔房顫〕病例中，我們研究了循環子波假說作為一種房顫終止機制解釋的合理性。在房顫期間，記錄了11處的右心房電圖和1處的左心房電圖。在12個心房位置，我們確定了心房電位平均間期間期的標準差〔定義為房顫間期離散度〕。Pilsicainide將11房顫病例中的6例成功地轉為竇性心律。與對其無效者相比，在對其有效者Pilsicainide顯著減少間期離散度。在房顫剛終止前，觀察到最小的離散度。這些結果提示房顫為竇性心律的藥理機制可能與減少房顫的離散導致左右心房多重折返子波的同步化有關。

關鍵詞：心房顫動 終止 抗心律失常藥物 機制 同步化和

## Introduction

Atrial fibrillation, the most common symptom in sustained and non-sustained arrhythmia, occurs in 2% of the general population.<sup>1</sup> While its mechanisms have not been fully clarified in humans, the reentrant mechanism is generally accepted as an explanation of the development and maintenance of atrial

fibrillation.<sup>2-4</sup> Atrial fibrillation often terminates spontaneously<sup>5</sup> and can be terminated by the administration of antiarrhythmic drugs;<sup>1</sup> the mechanism of such termination is poorly understood. The circulating wavelet hypothesis suggests that atrial fibrillation is terminated by either the progressive fusion or the simultaneous blockade of all wavelets. We investigated the electrophysiologic effects of pilsicainide, a new class 1C antiarrhythmic drug on the conversion of atrial fibrillation to clarify the mechanism of termination.

## Methods

### Patient characteristics

We studied 11 consecutive patients with

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paroxysmal atrial fibrillation who were undergoing electrophysiologic studies at Chikushi Hospital of Fukuoka University (7 men and 4 women, mean age:  $64 \pm 16$  yr, range: 37 to 83 yr). The duration of atrial fibrillation was less than 6 months in all patients. Thyroid function was normal in all subjects. This investigation conformed with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Fukuoka University Committee on Human Studies. Informed consent was obtained from all subjects.

### Electrophysiologic studies

Electrophysiologic studies were performed during the spontaneous development of atrial fibrillation following the discontinuation of antiarrhythmic drugs for a period equal to 5 half-lives of the drug. Quadripolar electrode catheters (6 Fr) positioned at the high right atrium, at the right ventricular apex, in the coronary sinus, and across the tricuspid valve, were used to record intracardiac electrograms and for pacing. A deflectable 7-Fr Halo catheter (20 paired ring electrodes, HD-720-P10-MS, Webster, Watertown, MA, USA) with 10-mm spaces between pairs and 1-mm interelectrode spacing was positioned on the annulus of the tricuspid valve to record right atrial electrograms. The catheter was positioned under fluoroscopic guidance with the loop on the edge of the annulus from the 30 degree right anterior oblique projection and the 50 degree left anterior oblique projection to show the plane of the loop at a 90 degree angle. Atrial electrograms were recorded with the 10 paired electrodes from the right atrium and, from the coronary sinus for the left atrial electrogram during atrial fibrillation. Bipolar atrial electrograms and surface leads were amplified with a physiologic recorder (Nihon Koden, Tokyo, Japan). Filtered (30 to 600 Hz) intra-atrial data were continuously recorded before, during, and after the infusion of pilsicainide.

### Pilsicainide infusion

Pilsicainide, a class IC antiarrhythmic agent, was administered intravenously 0.1 mg/kg/min for 10 min through an infusion pump (total dosage: 1 mg/kg) until sinus rhythm was restored or the total dosage was infused.

### Measurements

During atrial fibrillation, 50 consecutive intervals between the intra-atrial potentials and the width of the

intra-atrial potentials were measured at 11 right atrial sites, (10 from the Halo catheter positioned at the tricuspid annulus and from the high right atrium) and at a distal pair of electrodes at the coronary sinus at 1-minute intervals. Measurements of the intervals and widths between intra-atrial potentials were obtained every minute until sinus rhythm was restored or until 15 minutes after the completion of the infusion of the total dose of pilsicainide. Measurements of atrial cycle length and width of atrial electrograms were made manually at a paper speed of 100mm/s to an estimated precision of 3 ms by two physicians. Actual data were taken as an average of data measured by two physicians.

### Definitions

- 1) AF interval: the mean of the intra-atrial intervals, which is the beat to beat changes from the 12 atrial sites.
- 2) AF 1 (the dispersion of the interval of atrial fibrillation): the mean of the standard deviation of the intra-atrial intervals among different atrial sites.
- 3) AF 2 (the dispersion of the interval of atrial fibrillation): the mean of the difference between the maximal and minimal atrial AF intervals among different atrial sites.
- 4) AF width: the mean width of the intra-atrial potentials, which is the beat to beat changes from the 12 atrial sites.
- 5) AF width dispersion 1: the mean width of the standard deviation of the intra-atrial potentials among different atrial sites.
- 6) AF width dispersion 2: the mean of the difference between the maximal and minimal atrial AF width among different atrial sites.

### Statistics

The differences in variables between two groups were determined by a paired or nonpaired t test. The differences in variables among groups and repeated measurements within groups were investigated by ANOVA. Probability levels of less than 0.05 were considered statistically significant. All data are presented as mean  $\pm$  standard deviation.

### Results

Spontaneous atrial fibrillation was terminated by infusion of pilsicainide during the electrophysiologic study in 6 of 11 patients (responders). Pilsicainide failed

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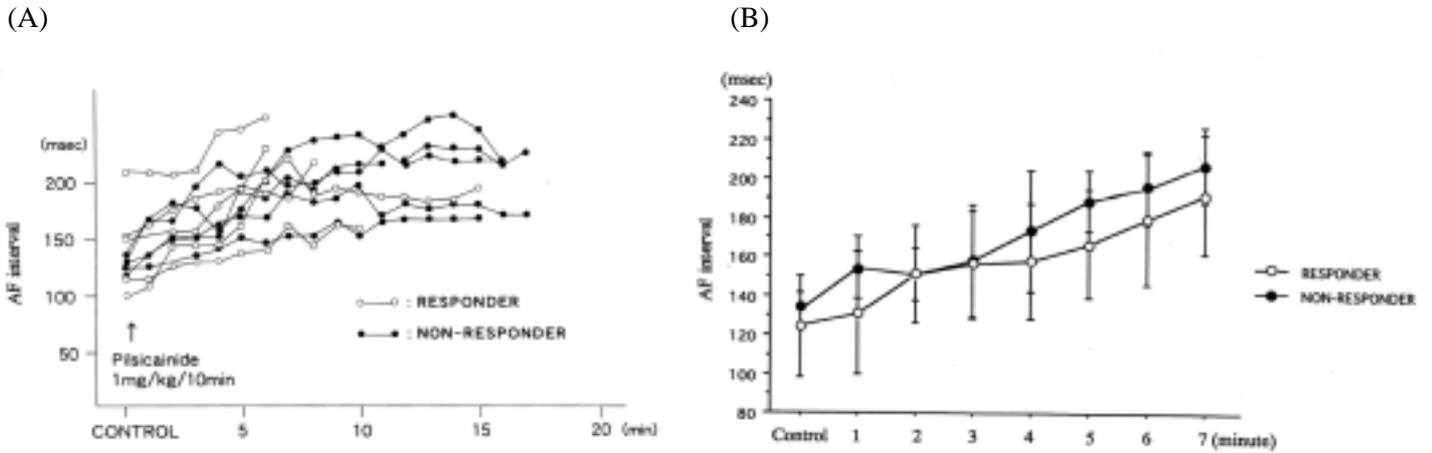
to induce a conversion to sinus rhythm in 5 patients (non-responders). There were no significant differences between groups in mean age, sex or echocardiographic parameters (Table 1). In responders, atrial fibrillation was terminated 5 to 10 minutes (means 9 minutes) after the start of pilsicainide infusion. The AF interval increased significantly in both responders (from  $147 \pm 28$  ms on control to  $224 \pm 34$  ms immediately before termination) and non-responders (from  $132 \pm 41$  ms on control to  $206 \pm 20$  ms on the completion of the infusion of the total dose of pilsicainide). There was no significant difference in the pilsicainide - induced prolongation of the AF interval between groups (responders:  $71 \pm 25$  ms; non-responders:  $87 \pm 41$  ms). The AF interval increased during pilsicainide infusion in both groups (Fig.1A). The AF interval just prior to termination of atrial fibrillation was significantly greater than those of previous AF interval in both groups. Figure 1B shows AF interval during the last 6 cycles just before termination (0) of atrial fibrillation in responders and on the completion of the infusion of the total dose of pilsicainide (0) in non-responders. The AF interval just prior to termination of atrial fibrillation was significantly greater than those of previous AF interval in responders, but not in non-responders ( $P < 0.05$  by ANOVA). The baseline AF dispersion was similar in both groups (responders:  $11 \pm 2$  ms; non-responders:  $10 \pm 9$  ms). Pilsicainide significantly increased the AF dispersion in non-responders compared with responders (non-responders  $19 \pm 6$  ms vs responders  $9 \pm 3$  ms;  $p < 0.05$ ). The ratio of the AF dispersion to the AF interval significantly decreased in responders ( $7.2 \pm 1.2$  on

control to  $3.9 \pm 1.7$  immediately before termination;  $p = 0.0076$ ), but no significantly different in non-responders (from  $8.8 \pm 8.2$  on control to  $11.0 \pm 4.2$  on the completion of the infusion of the total dosage of pilsicainide). The pilsicainide - induced changes in the AF dispersion were observed before the termination of atrial fibrillation, which occurred at the minimal AF dispersion (Fig. 2A). Figure 2B shows AF dispersion during the last 6 cycles just before termination (0) of atrial fibrillation in responders and on the completion of the infusion of the total dose of pilsicainide (0) in non-responders. The AF dispersion alternately increased and decreased at all atrial potentials just prior to termination in responders, but not in non-responders. AF dispersion at 8 minutes after infusion of pilsicainide in non-responder were apt to increase than base line ( $P < 0.05$  by ANOVA). The AF interval just prior to termination was greater than the interval at the beginning of AF in responders and increased suddenly just before conversion to sinus rhythm in 5 out of 6 cases in responders (Fig.3). The dispersion of AF interval alternately increased and decreased just prior to termination. Atrial fibrillation was terminated at the relatively lower rate of AF dispersion. The AF widths just prior to termination increased when compared with those observed at the beginning of atrial fibrillation (Fig. 4). The AF width dispersion 1 and the AF width dispersion 2 alternately increased and decreased at all atrial potentials just prior to termination. Figure 5 illustrates a representative example of the electrophysiologic presentation of termination of atrial fibrillation. Upper panel demonstrates the change of

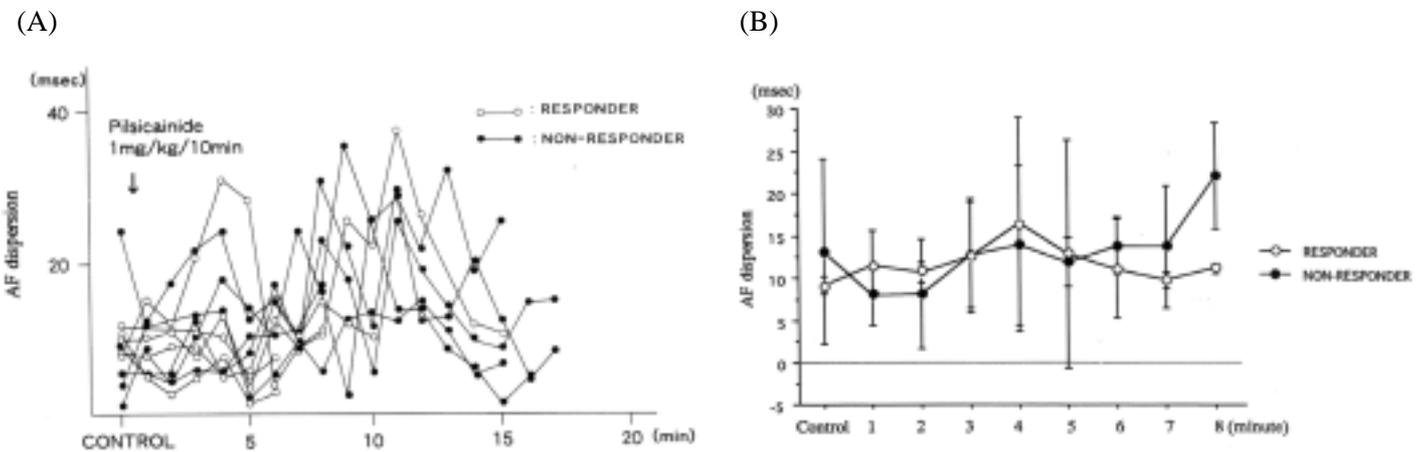
**Table 1. Study Population**

	responder	non-responder	P value
No. of pts.	6	5	NS
Age (yrs)	$64 \pm 22$	$65 \pm 8$	NS
Men/Women	5/1	2/3	NS
Disease (No. of pts.)			
SSS	2	2	NS
Paroxysmal AF	4	2	NS
WPW	0	0	NS
AVNRT	0	1	NS
Echocardiogram			
LA (mm)	$37 \pm 10$	$42 \pm 4$	NS
LVDd (mm)	$44 \pm 10$	$46 \pm 4$	NS
EF (%)	$80 \pm 8$	$88 \pm 1$	NS
LA thrombus	2	2	NS

pts: patients; AF: atrial fibrillation; AVNRT: atrioventricular nodal reentrant tachycardia; WPW: Wolf Parkinson White syndrome; LA: left atrium; LVDd: dimension of left ventricle (diastolic phase); EF: ejection fraction

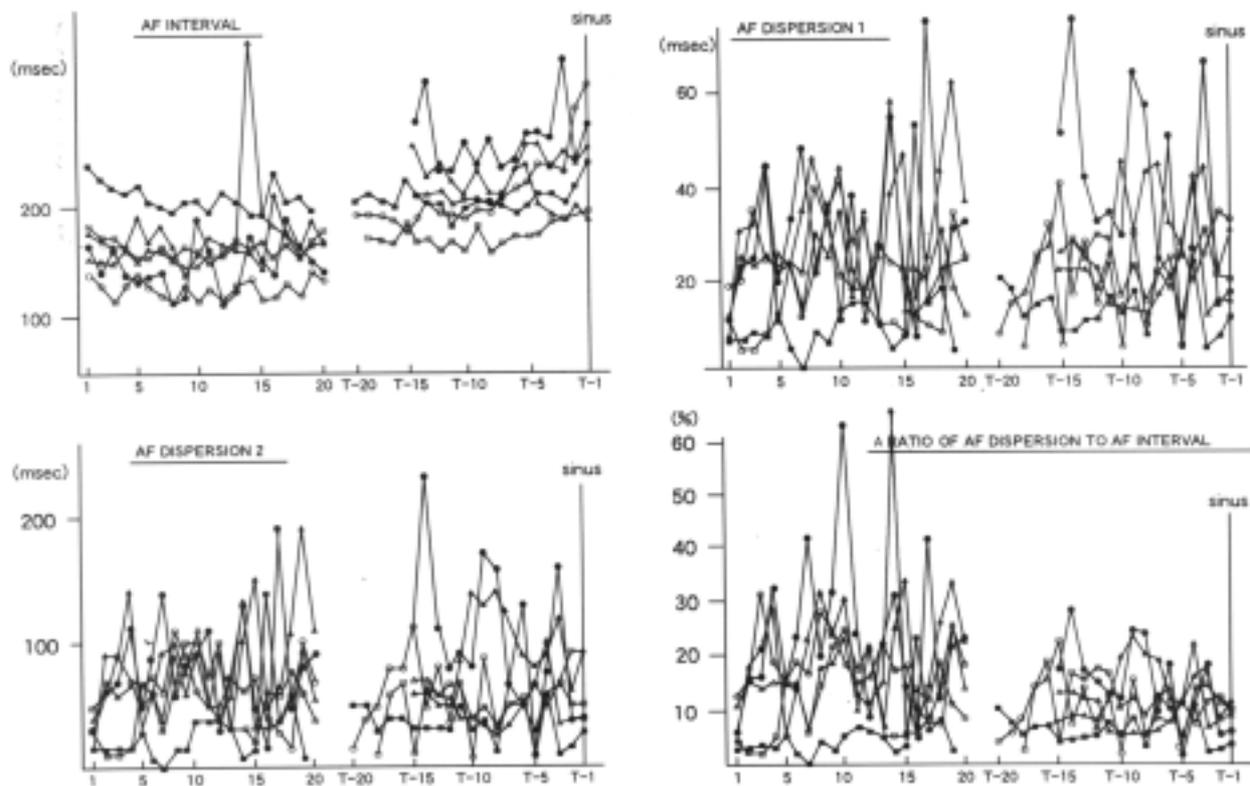


**Figure 1.** Beat-to-beat changes in the intra-atrial interval of atrial fibrillation during infusion of pilsicainide in the individual patients (A). AF interval during the last 6 cycles just before termination (0) of atrial fibrillation in responders and on the completion of the infusion of the total dosage of pilsicainide (0) in non-responders. The AF interval just prior to termination of atrial fibrillation was significantly greater than those of previous AF interval in both groups (B).

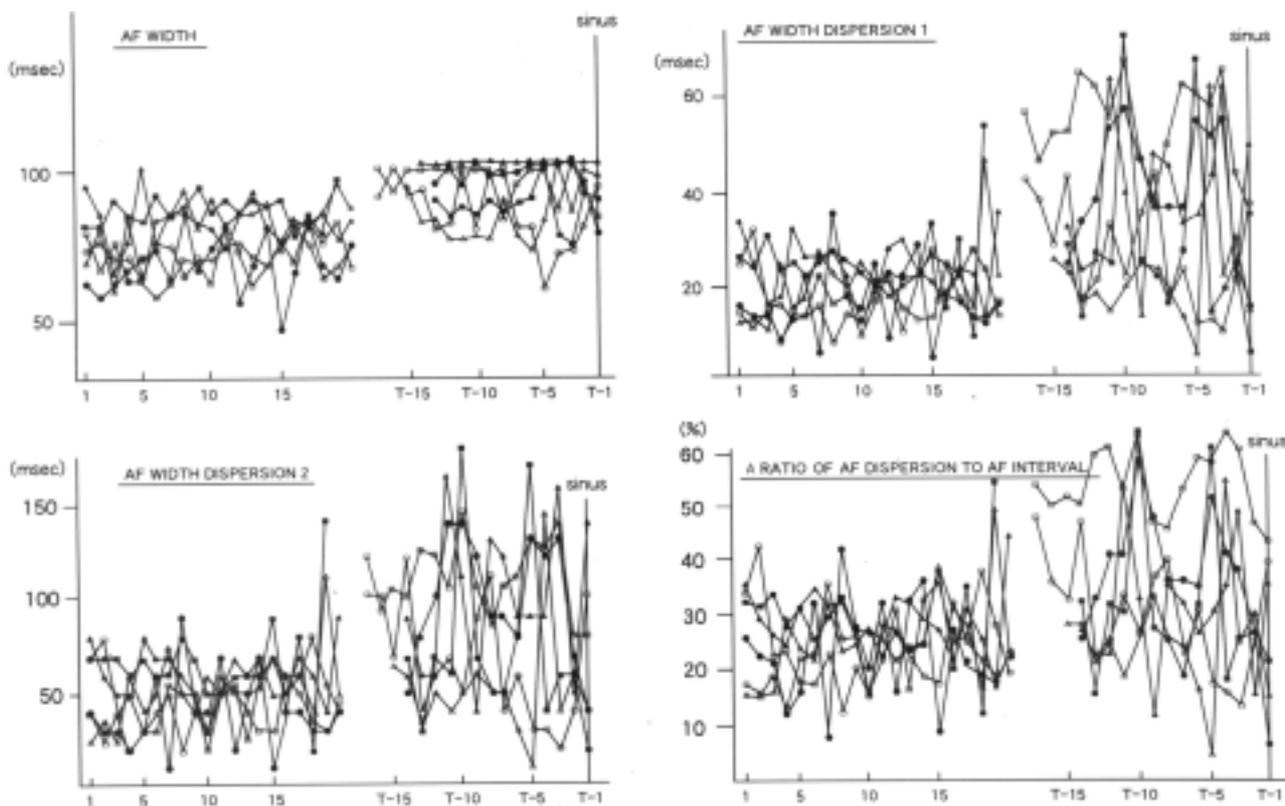


**Figure 2.** Beat-to-beat changes in the dispersion of the intra-atrial interval of atrial fibrillation during infusion of pilsicainide in the individual patients (A). AF dispersion during the last 6 cycles just before termination (0) of atrial fibrillation in responders and on the completion of the infusion of the total dose of pilsicainide (0) in non-responders. The AF dispersion decreased at all atrial potentials just prior to termination in responders, but not in non-responders (B).

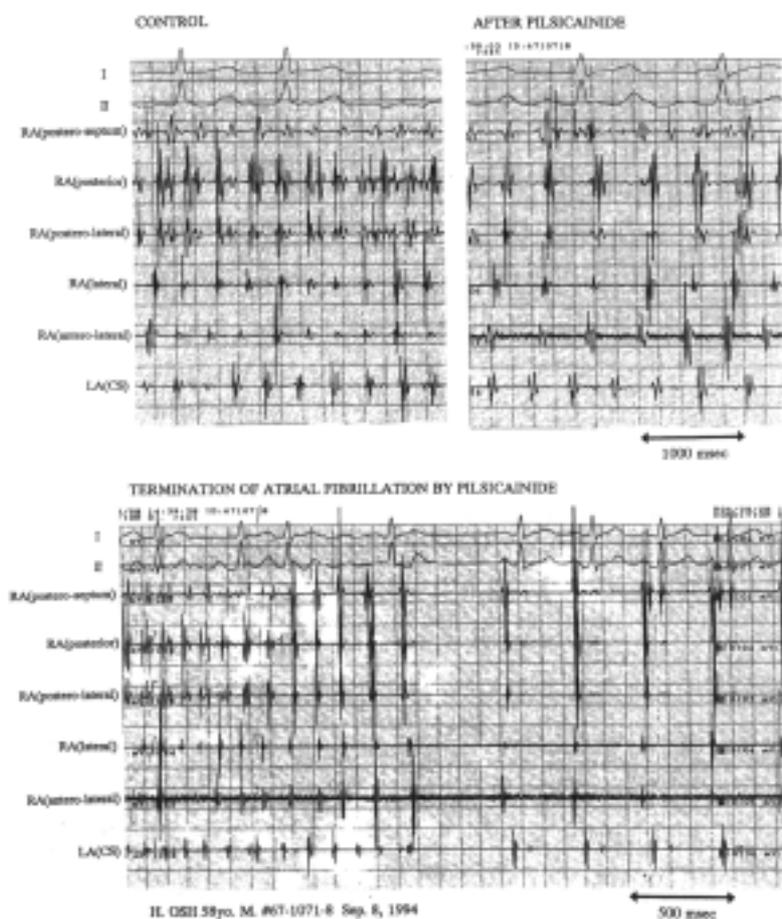
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**Figure 3.** The time course of beat-to-beat changes in the intra-atrial interval and dispersion during termination of atrial fibrillation by pilsicainide in responders.



**Figure 4.** The time course of beat-to-beat changes in the width of intra-atrial potentials and dispersion during termination of atrial fibrillation by pilsicainide in responders.



**Figure 5.** Intracardiac electrocardiogram recorded during termination of atrial fibrillation by infusion of pilsicainide in representative responders.

atrial electrograms from the quite chaotic pattern as type III atrial fibrillation advocated by Wells et al.<sup>6</sup> to discrete pattern separated by an isoelectric baseline as type I atrial fibrillation and the prolongation of AF interval just prior to termination of atrial fibrillation. Lower panel shows another example of the termination of atrial fibrillation. Increase of atrial potential at anterior to lateral right atrium is observed just before termination of atrial fibrillation.

## Discussion

One explanation of the mechanism of termination of atrial fibrillation is the circulating wavelet hypothesis,<sup>7</sup> which proposes that wavelets may fuse until only one wavelet is left to circulate or that there is a conduction block of all wavelets. Atrial fibrillation is not related to an anatomical obstacle, that is, the establishment of circus movement during atrial fibrillation does not require a fully excitable gap.<sup>8</sup> Wavefronts associated with atrial fibrillation are

believed to proceed along the pathway that restores the refractory period. The cycle length of the circus movement equals the interval of circuit divided by the conduction velocity. In the circuit without excitable gap, because the ratio of the interval of circuit to the conduction velocity is equivalent to the refractory period, the cycle length of the circus movement equals the refractory period.<sup>9</sup> Thus the refractory period result in the establishment of circus movement during atrial fibrillation. We measured the intervals of local intra-atrial potentials instead of the refractory period, because most studies investigating termination of atrial fibrillation in animals<sup>10-12</sup> and humans<sup>13-16</sup> have found that the atrial rate decreases before termination of atrial fibrillation. Allesie et al.<sup>12</sup> reported that the atrial waveform became "coarser" prior to termination, suggesting that fusion was responsible for termination of atrial fibrillation. Wang et al.<sup>16</sup> reported that atrial fibrillation could be terminated by increasing the wavelength to the point at which the atrial fibrillation could no longer sustain itself. They also suggested that termination of atrial fibrillation may occur via fusion

of wavelets. However, Sih et al.<sup>17</sup> reported that the atrial rate increased prior to termination in 3 of 15 episodes, all 3 episodes terminated spontaneously. Thus, two types of alterations in the atrial rate have been observed prior to the cessation of atrial fibrillation. We hypothesize that termination of atrial fibrillation associated with a decreasing atrial rate and termination associated with an increasing atrial rate before conversion to sinus rhythm involve different mechanisms. The circulating wavelet hypothesis of fibrillation suggests that fibrillation may terminate via one of two different mechanisms: the fusion of wavelets until only one wavelet is left to circulate or blockade of all wavelets.<sup>7</sup>

Pilsicainide is a developed antiarrhythmic drug in Japan which belongs to the class 1C antiarrhythmic drugs.<sup>18-19</sup> Hattori et al. proposed that pilsicainide belongs to the class 1C antiarrhythmic drugs characterized by slow kinetics with respect to blocking of the sodium channel.<sup>20</sup> Terazawa et al. presented that pilsicainide did not prolong the effective refractory periods of the atrium and ventricle, and stated that prolongation of conduction time without any alteration of refractoriness may suggest class 1C antiarrhythmic activity of this drug at therapeutic serum concentrations.<sup>21</sup> Hattori et al. have shown that pilsicainide has only minor effects on rabbit sinoatrial node activity and on Ca<sup>2+</sup>-mediated slow action potentials of guinea-pig papillary muscles.<sup>19</sup> They conclude that pilsicainide is a selective sodium channel blocker. In the present study, termination of atrial fibrillation may be induced by pilsicainide, a class 1C antiarrhythmic drug that slows conduction. Class 1C antiarrhythmic agents have been shown to be effective in the management of atrial fibrillation.<sup>22-25</sup> The mechanism of action of class 1C agents is an increase in atrial refractoriness.<sup>24</sup> The intervals of the atrial potentials increased after administration of pilsicainide, that is, the atrial rate was decreased in the present study. The atrial rate was significantly decreased in patients in whom atrial fibrillation was successfully terminated compared with those in whom atrial fibrillation was not terminated. The atrial rate showed a sudden decrease just before conversion to sinus rhythm in responders. We measured the dispersion of the intervals of atrial potentials (the standard deviation of the atrial interval and the difference between the maximal and minimal AF intervals) as an indicator of synchronization among atrial recording sites. The present results suggest that synchronizations of AF interval at all recording sites was involved in the drug-induced termination of atrial fibrillation. Type III atrial fibrillation has been changed type I atrial fibrillation may indicate that complex

circuits fuse with simple circuit. Pilsicainide induced significant changes in the atrial rate and the dispersion prior to termination suggesting fusion of wavelets was responsible for termination of atrial fibrillation. The spontaneous termination of atrial fibrillation observed by Sih et al.<sup>17</sup> may have been induced by the simultaneous blockade of all wavelets because of the absence of synchronization. Spontaneous termination of atrial fibrillation is sometimes associated with a decreasing atrial rate before termination.<sup>14</sup> We propose that these phenomena are related to different mechanisms and in this respect we differ with Sih et al.,<sup>16</sup> who suggested that the mechanism of antiarrhythmic drug-induced termination could be differed from that of spontaneous termination. They suggested that drug-induced termination may be due to the simultaneous blockade of all wavelets and that spontaneous termination may be due to the fusion mechanism. The duration of atrial fibrillation was less than 30 minutes in subjects with spontaneous termination in the study by Sih et al, which may not be long enough to establish a stable circuit for atrial fibrillation. Prolongation of the interval and changes in the dispersion of atrial fibrillation were also observed in non-responders in the present study. Although Boahene et al. have suggested that slowing of the atrial rate by antiarrhythmic drugs is an important factor in termination of atrial fibrillation,<sup>15</sup> a decrease in the atrial rate may not be sufficient to induce termination.<sup>16</sup> Sih et al. reported that the degree of synchrony of activity among intra-atrial recording sites also failed to predict termination of fibrillation.<sup>16</sup> The AF width of intracardiac potentials may be inversely correlated with the focal conduction velocity. A wide intracardiac potential causes the wavefront passing through the bipolar electrodes more slowly. Prolongation of the AF width before termination of AF may indicate the slowing of fibrillating activity in the focal atrium. Furthermore, alternating beat-to-beat changes in the AF width dispersion just before conversion suggested that the conduction velocity was unstable in both atria. Thus, successful termination of atrial fibrillation required a sudden prolongation in the refractory period without any change in the dispersion of refractory period in both atria and a decreased conduction velocity in association with the alternating changes in the each atria.

### Study Limitation

A limitation of the present study is that only twelve atrial electrocardiograms (11 for right atrium and one for left atrium) were used in this study.

Although we used the decapolar coronary sinus catheter recording for left atrium, in fact, only one atrial electrocardiogram from the decapolar coronary sinus catheter was used for the analysis in this study. If all five bipolar electro-cardiograms from the decapolar coronary sinus catheter and another 20 pole halo catheter along the crista terminalis would be used, further detailed results might be obtained. The atrial rate decreased and the dispersion of the cycle length of intra-atrial potentials showed alternating increases and decreases prior to termination even in the non-responders. Class 1C antiarrhythmic agents slow intracardiac conduction, prolong the refractory period,<sup>24,26</sup> and reduce regional heterogeneity in the refractory period and in wavelengths.<sup>17</sup> Thus, the slowing of the atrial rate and the change in the dispersion of the atrial cycle length may have been merely the effects of pilsicainide. The present results suggest that patients in whom pilsicainide fails to terminate atrial fibrillation may still achieve termination of fibrillation. Thus, the presence of prolongation of the atrial interval (slowing of the atrial rate) and decreasing the dispersion at suitable time were required for the termination of atrial fibrillation.

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