Effects of Procainamide on Wave-Front Dynamics During Ventricular Fibrillation in Open-Chest Dogs

Yvonne Y. Kwan, MD; Wei Fan, MD; Dustan Hough, BS; John J. Lee, MD; Michael C. Fishbein, MD; Hrayr S. Karagueuzian, PhD; Peng-Sheng Chen, MD

Background—There is increasing evidence that both functional reentrant wave fronts and multiple wavelets are present during ventricular fibrillation (VF). However, the effects of procainamide on the characteristics of activation waves during VF are poorly understood.

Methods and Results—Seven dogs were studied; six underwent subendocardial chemical ablation procedures. A plaque with 317 to 480 bipolar electrodes was sutured to the right ventricular free wall, and the patterns of activation were registered with a computerized mapping system. VF was electrically induced, and the patterns of activation were registered at baseline and during procainamide infusion (serum concentration, 9.3 ± 1.9 μg/mL). Among the six dogs that had their subendocardium ablated, reentrant wave fronts were present in 6 of the 108 runs of VF at baseline and in 6 of the 100 runs of VF during procainamide infusion. By analyzing the wave fronts, we found that the cycle length, refractory period, conduction velocity, and wavelength at baseline were 101 ± 9 ms, 54 ± 5 ms, 0.93 ± 0.21 mm/ms, and 51 ± 16 mm, respectively, and during procainamide infusion, values became 125 ± 11 ms (P < .001), 119 ± 7 ms (P < .001), 0.42 ± 0.02 mm/ms (P < .001), and 50 ± 4 mm (P = .8), respectively. The vast majority of the activation waves do not form organized reentry. These activation waves broke up more frequently at baseline than during procainamide administration. The number of activation waves was 7.25 ± 1.39 s⁻¹ · cm⁻² at baseline and 4.45 ± 1.80 s⁻¹ · cm⁻² during procainamide administration (P < .001). The dog without subendocardial ablation had similar results.

Conclusions—Procainamide decreases the number of wavelets during VF by preventing spontaneous wave breaks. This represents a novel mechanism of antiarrhythmic drug action. (Circulation. 1998;97:1828-1836.)

Key Words: procainamide • fibrillation • waves • conduction

Antiarrhythmic drugs have been used extensively in the treatment of patients with life-threatening ventricular arrhythmias. However, the effects of antiarrhythmic drugs on the wave-front dynamics during ventricular fibrillation (VF) are poorly understood. According to the multiple wavelet hypothesis,1 cardiac fibrillation is maintained by spontaneous wave breaks that constantly regenerate daughter wandering wavelets. However, it is unclear whether spontaneous wave breaks occur during VF and whether antiarrhythmic drugs prevent the spontaneous wave breaks. One factor that contributes to these gaps of knowledge is that the patterns of activation during VF are complex and change from time to time. It is difficult to study these complicated patterns of activation with conventional recording techniques. We recently developed methods to map VF by displaying the patterns of activation dynamically, allowing better study of the dynamics of activation waves.2 The same methods can be applied to study the effects of antiarrhythmic drugs on the patterns of activation during VF; the study also showed that the patterns of activation during VF are affected by the chemical subendocardial ablation, which increases the incidences of organized reentry and reduces the breakthrough patterns on the epicardium. In the present study, we performed computerized mapping studies in dogs with and without subendocardial ablation, before and during procainamide administration. The purpose of the study is to test the hypothesis that spontaneous wave breaks occur during VF, and procainamide prevents the spontaneous wave break, resulting in more organized activation patterns.

Methods

The research protocol was approved by the Institutional Animal Care and Use Committee of the Cedars-Sinai Medical Center and follows the guidelines of the American Heart Association.

Recording Electrodes

Fig 1 shows the electrode location on the recording electrode array. Electrodes 1 to 317 were used in protocol 1 and all 480 electrodes were used for protocol 2. The electrodes were constructed with 0.4-mm-diameter stainless steel wires. The wires were fully insulated except at the tips, which served as tissue contact points. The bipolar electrodes, with an interpolar distance of 0.5 mm, were spaced at...
Protocol 1: Effects of Procainamide on Activations During VF in Dogs With Subendocardial Ablation

Six adult mongrel dogs (mean weight, 23.6 ± 4.8 kg) were studied. These dogs were also used to study VF activations at baseline (before procainamide administration). However, the data analyses of this study were done on an de novo basis. Each dog was anesthetized with pentobarbital. Rectal temperature was monitored and maintained at 36° to 37°C by heating the table with warm circulating water. The chest was opened through a median sternotomy, and the heart was suspended in a pericardial cradle. The right ventricular subendocardial tissue and Purkinje fiber network for two reasons: (1) to increase the incidence of reentry observed on the epicardium, and (2) to decrease the epicardial breakthrough of VF wave fronts. The method of subendocardial ablation has been reported previously.1

Study Protocol

Eight pacing wires, 3 mm apart, were sutured to the left edge of the recording plaque. Baseline (S1) unipolar cathodal pacing using 10-mA, 5-ms stimuli was delivered simultaneously from these pacing electrodes. The chest wall was used as the anode to create planar activation wave fronts.6,7 To deliver the strong premature stimulus (S2), a patch electrode measuring 3.16 × 0.85 cm was sutured to the upper edge of the plaque (Fig 1). After eight S1 stimuli at a cycle length of 300 ms, a second channel of the programmable high-voltage stimulator (HVS-02; Ventritex) was used to deliver a premature stimulus (S2). The S2 delivers a 0.85-cm shock to the patch electrode on the edge of the plaque electrode array, thus inducing VF.8,9 The patterns of activation were recorded by our computerized mapping system for later analysis. The dog then was rescued by defibrillation shocks. There always was at least a 5-minute interval between fibrillation-defibrillation episodes. A total of 18 episodes were recorded for each dog at baseline.

Procainamide was then administered to the dog. The dosage was 20 mg/kg loading over 30 minutes, followed by 2 mg·kg⁻¹·min⁻¹ maintenance infusion. The first episode of VF was induced after 10 minutes of stable maintenance infusion. A total of 18 episodes of VF were induced, and the data were recorded for later analysis. The dog was immediately defibrillated at the end of data recording. There was a 5-minute interval between fibrillation-defibrillation episodes. At the end of the study, blood samples were taken for procainamide serum level determination, and the dog was killed through induction of VF without defibrillation. The mapped tissue was excised for histopathological examinations.

Protocol 2: Effects of Procainamide on Activations During VF in Dogs Without Subendocardial Ablation

One dog was included in protocol 2 to determine whether the effects of procainamide observed in protocol 1 were due to subendocardial ablation or to the prolonged duration needed to complete the study protocol. The surgical preparation was the same as that in protocol 1 except that no subendocardial ablation was performed in this dog and the electrode array was expanded to 480 electrodes. VF was induced with rapid ventricular pacing from bipolar pacing electrodes on the ventricular apex. To minimize the duration of the study, only three episodes of VF were induced at baseline. The dog was defibrillated immediately after the data acquisition, and a 5-minute interval was used between VF episodes. The entire data acquisition at baseline took <15 minutes. We then started an intravenous infusion of procainamide with the same loading dose as that used in protocol 1. The first episode of VF was induced 10 minutes after the completion of the loading dose of procainamide. The patterns of activation were acquired with the computer, and the dog was immediately defibrillated. Two additional episodes of VF were induced, with 5-minute intervals between episodes. The total duration of data acquisition was <15 minutes. Due to the short duration of the experiment, no maintenance dose was used. Blood was drawn at the end of the study to determine procainamide concentration.

Data Analysis

To study reentrant wave fronts during Wiggers’ stage II VF, we selected for analyses from each dog three episodes of VF before and during procainamide administration. These episodes were selected because they have the highest percentage of electrodes with good tissue contact giving rise to clear recordings of VF. We studied 3 to 5 seconds of data beginning 2.5 seconds after the time of the shock that induced VF. We began data analysis 2.5 seconds after S2 to avoid the reentrant wave fronts that were initiated directly by the S2 stimulus; thus, all observed reentry would have been generated spontaneously during VF.8,9 We screened all episodes of VF to identify reentrant excitations. We then selected for analysis only the
A reentrant wave front is defined as a wave front that completes a circular pathway and reenters at least three rotations in the mapped area. Once reentrant wave fronts are detected, the data that contain the reentrant wave fronts are edited manually. The data are displayed again dynamically on the screen, and the events leading to the initiation of reentry are analyzed. These manually edited data form the basis of this report; most of the data are presented in the form of snapshots of the dynamic display.

Determination of refractory period, conduction velocity, wavelength, and core size during VF

Lee et al recently demonstrated the spontaneous initiation of reentrant wave fronts in VF is due to a critical interaction between two wave fronts. After the first wave front passes the mapped tissue, it results in a dispersion of refractoriness. The leading edge of the wave front is less repolarized, whereas the trailing edge is more repolarized. When the second wave front propagates roughly perpendicularly into the same area, part of the wave front encounters refractory tissue and stops propagating. The remaining portion of the wave front encounters nonrefractory tissue and continues to propagate, resulting in a wave break. In this study, the temporal difference between the leading edge of the first wave front and the point of wave break was used to estimate the refractory period of the first wave front. This timing, which is associated with generation of the wave break, is also known as the “critical intersection interval” or “vulnerable period.”

The conduction velocity in each episode was determined by analyzing the first of the two interacting wave fronts that were involved in the initiation of functional reentry. The conduction velocity was calculated by the following method, which is demonstrated in Fig 2. The propagating wave front is first visualized through dynamic display. Starting from the time the wave front first invades the mapped region, the leading edge is identified. The leading edge then is followed every 5 ms until it exits the mapped region. The number of interelectrode spaces traveled by the wave is multiplied by 1.6 mm (interelectrode distance) to obtain the total distance the wave propagates. The ratio of the distance the wave travels over the time interval it takes to propagate from point a to point c is the conduction velocity.

The wavelength of that episode is the product of the refractory period and conduction velocity. The wavelength obtained with this method represents the wavelength of the first wave front that interacted in the formation of the reentrant circuit. It does not represent the wavelength of the circuit itself, which may vary along episodes that had at least three complete reentrant rotations. Because activation waves may travel in one circular path, creating an “illusive reentry” rather than a true reentrant circuit, episodes with fewer than three rotations were excluded from the study to avoid illusive reentrant rotation. The method for selecting the time of activation has been reported in detail elsewhere.

A through C, Leading edge of the propagating wave traveling from the bottom to the top of the mapped tissue as indicated (arrow). The tail end of the leading edge is indicated by the solid line separating the red dots from the yellow dots. The numbers on top of each panel indicate the times of activation (in ms), with the beginning of data acquisition as time 0. In the time interval between 6080 and 6106 ms (25 ms), the wave traveled seven interelectrode spaces, or an interelectrode distance of 7 × 1.6 mm, or 11.2 mm. The conduction velocity of this wave was 11.2 mm/25 ms, or 0.44 mm/ms.

Figure 2. Method for determining conduction velocity of a propagating wave. A through C, Leading edge of the propagating wave traveling from the bottom to the top of the mapped tissue as indicated (arrow). The tail end of the leading edge is indicated by the solid line separating the red dots from the yellow dots. The numbers on top of each panel indicate the times of activation (in ms), with the beginning of data acquisition as time 0. In the time interval between 6080 and 6106 ms (25 ms), the wave traveled seven interelectrode spaces, or an interelectrode distance of 7 × 1.6 mm, or 11.2 mm. The conduction velocity of this wave was 11.2 mm/25 ms, or 0.44 mm/ms.

Figure 3. Activation patterns during baseline pacing. A, Patterns of activation at baseline. B, Activation recurring during procainamide administration. The time of activation is color coded according to the color bar at the top of each panel, with time 0 being the onset of S1. The conduction velocity of A is calculated by dividing 32 mm by 40.8 ms (the difference between the right and left column time average, 50.8 ± 9.8 ms) or 0.78 mm/ms. The conduction velocity in B is 0.73 mm/ms.
the reentrant path. The core size of the reentrant wave front also was determined according to methods reported elsewhere.

Determining the Number of Activation Waves During VF

The activation waves are “those continuous units which, at a given instant, are being excited by neighboring elements.” During the course of VF, one wave may be broken up into several different daughter wavelets separated by recovering tissues. For the purpose of the present study, we consider each daughter wavelet to be a new activation wave. To determine the number of such activation waves, we advance the time of dynamic display of VF activation in 5-ms steps. The leading edge of an activation wave is denoted by red illuminations; the changing color of the activation wave aids in identifying the direction of wave-front propagation. All the activation wave fronts that are mapped within the electrode plaque area are identified and summed as the dynamic display is advanced. A total of 3 seconds of data (each second of data is from a different VF episode) is obtained from each animal (total of six dogs) under each experimental arm (control versus procainamide treatment).

Histopathological Examination

At the conclusion of the experiments, the dogs were killed with an overdose of pentobarbital. The electrode array was removed, and the underlying tissue was excised from the remainder of the heart and fixed in 10% neutral buffered formalin. A section was obtained 1 mm from and parallel to the epicardium to determine the fiber orientation and presence, if any, of anatomic barriers. Transmural

<table>
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<th>Characteristics of Activation Waves During Ventricular Fibrillation With and Without Procainamide</th>
<th>Control</th>
<th>Procainamide</th>
<th>P</th>
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<td>119±7</td>
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<td>Wavelength, mm</td>
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<td>4.0±0.9</td>
<td>.56</td>
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<tr>
<td>No. of activation waves, s⁻¹·cm²</td>
<td>7.25±1.39</td>
<td>4.45±1.80</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Figure 4. Wave break and generation of reentry at baseline. A and B, Wave 1 propagating from right to left. The numbers on top of each panel represent the time (in ms) at which the recording was obtained, with the beginning of data acquisition as time 0. The VF was induced at 2034 ms. Each dot represents one electrode. When an electrode is activated, it lights up in red initially and then turns yellow, followed by green, light blue, and finally dark blue. The leading edge of the wave is registered in red, and the tail of the wave in dark blue. The dark blue region becomes the least refractory part of the propagating wave. C. Second wave traveling into the mapped region propagating roughly perpendicular to wave 1. D. Wave break point (marked by two parallel line segments). Part of wave 2 fails to propagate due to residual refractoriness remaining from the first wave front; the part that propagate turns around, initiating reentry as demonstrated in E through J. Double-headed arrow at the bottom right corner shows the direction of myofiber orientation, which is 10° clockwise, with east as 0°.
The concentration of procainamide was 9.3 ± 1.9 μg/mL. Fig 3 shows the patterns of activation at baseline (Fig 3A) and during procainamide administration (Fig 3B); planar waves can be seen in both. There was no evidence of anatomic conduction block in the mapped region either at baseline or during procainamide administration.

Characteristics of Activation Waves in Wiggers’ Stage II

All VF episodes were sustained both at baseline and during procainamide infusion. No episodes terminated spontaneously. The characteristics of activation waves during VF before and during procainamide administration are summarized in the Table. Before procainamide infusion, a total of 108 episodes of VF were analyzed, and 6 episodes of reentry were identified. The mean number of rotations was 3.7 ± 1.0. In each episode, reentry was induced by the interaction of two wave fronts (Fig 4). The cycle length, refractory period (critical intersection interval), conduction velocity, and wavelength were calculated to be 101 ± 9 ms, 54 ± 5 ms, 0.93 ± 0.21 mm/ms, and 51 ± 16 mm, respectively. Fig 5 shows the actual electrograms recorded from the same reentry as demonstrated in Fig 4. The electrodes 121, 182, 200, 239, and 259 registered the first wave front. The second wave front (electrodes 12, 34, 55, 120, and 121) interacted with the first wave front in electrode 121, which resulted in wave break and reentry. Subsequent beats showed that the sequence of activation reversed after the wave break because during reentry, the wave front traveled in the direction opposite to the original direction of the second wave front.

The total duration needed to acquire the data during procainamide infusion was ≈ 90 minutes. During procainamide administration, 100 episodes of VF were analyzed, and 6 episodes of reentry were identified. The mean number of rotations was 4.0 ± 0.9 (P = .56). In each episode, reentry was also induced by an interaction of two wave fronts. Fig 6 shows an example. Fig 6A to 6C shows the first wave front propagating from the right to left. When the second wave front arrives from the upper part of the plaque (Fig 6D), it is broken (shown by the double horizontal line segments). The wave front then circles around but is blocked near the core (Fig 6F). An outside wave front then moves around and completes the reentrant circuit (Fig 6G to 6L). Fig 7 shows the bipolar electrogram recorded at the site of wave break. Channels 137, 197, and 258 registered the first wave front, and channels 14 and 36 registered the second wave front. The sequence of the activation was reversed after the wave break. The cycle length, refractory period, conduction velocity, and wavelength were calculated to be 125 ± 11 ms (P < .001), 119 ± 7 ms (P < .001), 0.42 ± 0.02 mm/ms (P < .001), and 50 ± 4 mm (P = .8), respectively (compared with baseline).

Core Size

A major difference between the reentry at baseline and the reentry after procainamide administration is the morphology and size of the core. At baseline (Fig 4), reentry generally occurred along a circular or an elliptical pathway.² The core size averaged 13.3 ± 2.1 mm². However, during procainamide infusion (Fig 6), the core became irregular in shape. Certain wavelets may have been terminated near the core (Fig 6F) before completing reentry. Other parts of the wave front then propagate around it and form a near-circular path (Fig 6G to 6L). The average core size during procainamide administration was 38.7 ± 6.1 mm² (P < .001).

With the assumption that the core of reentry is circular and reentry is reasonably stationary, we can calculate the velocity or reentrant excitation with the following method. First, we determine the radius from the area. We then determine the perimeter on the basis of the radius. The conduction velocity is the ratio between the perimeter and the reentrant cycle length. With this method, the velocity of reentrant rotations around the core at baseline and during procainamide administration was 0.19 ± 0.02 and 0.22 ± 0.05 m/s, respectively (P = NS).
Effects of Procainamide on Spontaneous Wave Break During VF

A major finding of this study is that the procainamide significantly decreased the number of activation waves during VF by preventing spontaneous wave break. From each episode of VF, we randomly selected 1 second of data to analyze the number of activation waves. The number of activation waves during a total of 18 seconds of VF at baseline and during a total of 18 seconds of VF during procainamide infusion were 7.25 ± 1.39 and 4.45 ± 1.80 s⁻¹ cm⁻², respectively (P < .001).

Fig 8 shows the effect of procainamide on the number of activation waves. Fig 8A shows representative patterns of activation during VF at baseline in protocol 1. There are a total of five wavelets recorded within the mapped region before procainamide infusion. At 5275 ms, there are three clearly defined wave fronts. Wave 3 broke up, forming a fourth wavelet at 5285 ms. Part of the fourth wavelet changed direction again, propagating in a clockwise direction and forming a fifth wavelet at 5305 ms. Fig 8B shows a representative example of the effect of procainamide on the activation waves during VF in the same dog. Note that both panels show a time lapse of 30 ms. Under the effects of procainamide (Fig 8B), the number of activation waves dramatically decreases. There is only one activation wave spreading through the electrode plaque (768 mm²) during this 30-ms interval.

Procainamide does not unanimously result in a single propagating wave front. However, a single propagating wave front is observed much more frequently during procainamide administration than at baseline. The ability of procainamide to prevent wave break resulted in more regular and uniform bipolar electrogram morphologies than that at baseline, although the surface ECG still showed patterns compatible with VF (Fig 8B).

Protocol 2

All three episodes of VF at baseline and during procainamide administration were analyzed. At baseline, spontaneous wave breaks occurred frequently. Fig 8C shows a typical example. At 4250 ms, there were three wave fronts propagating in the direction indicated (arrows). Wave front 2 broke off, forming
Another wavelet identified as wave front 4 at 4265 ms. Two other wavelets identified as wave fronts 6 and 7 entered the mapped region as designated at 4280 and 4285 ms, respectively. Thus, a total of seven wavelets were recorded within the mapped area during this 35-ms interval.

The serum concentration of procainamide in this dog was 14.6 μg/mL. Fig 8D shows data obtained from the same dog during procainamide infusion. There was only one activation wave front captured during this 35-ms interval. The activations were more regular, with a longer cycle length in the procainamide-treated group than in the control group. One second of activation was randomly selected to determine the number of activation waves. The number of activation wave fronts was 3.7 to 5.2 s⁻¹ · cm⁻² at baseline. The number decreased to 1.5 to 2.3 s⁻¹ · cm⁻² during procainamide infusion.

As reported by Lee et al., the patterns of activation during VF in dogs without subendocardial ablation showed more epicardial breakthrough patterns and fewer organized reentry than those in dogs with subendocardial ablation. Furthermore, the conduction velocity calculation may be influenced by the subendocardial spread of activation via the Purkinje fiber network; therefore, we were not able to calculate the core size, refractory period, or conduction velocity in this dog.

Histopathological Findings

No anatomic barriers were present in any of the tissue specimens. Transmural sections showed that the Purkinje fibers and adjacent subendocardial contractile myofibers were necrotic. The layer of necrotic subendocardial myocardial cells approximated a zone of up to six or seven myocardial cells, or a depth of ≈0.5 mm. These histological findings have been previously reported.

Discussion

Effects of Procainamide on Spontaneous Wave Break

A major finding of this study is that procainamide prevents the spontaneous wave break during VF. This represents a novel mechanism of antiarrhythmic drug action that has not been previously reported. According to the multiple wavelet hypothesis of fibrillation, the ability of a propagating wave to break up into daughter wavelets is important in sustaining fibrillation. During in vivo VF, two kinds of wave breaks have been observed. The first was the wave break through the interaction of two propagating wavelets. The first wavelet resulted in a residual refractoriness. When the second wavelet arrived, part of it was able to propagate and the remaining portion was blocked by the refractoriness, resulting in wave break. The other kind of wave break was the spontaneous wave break (ie, wave breaks without apparent wave collisions). Computer simulation studies have demonstrated that spontaneous break up of reentrant wave front can occur during the course of fibrillation. The mechanisms of wave break is unclear but may be related to the action potential restitution properties of the myocardial cells.

In this study, we found that procainamide clearly did not prevent the formation of reentry through the first mechanism of wave break; however, it significantly decreased the number of activation wave fronts by decreasing the incidence of spontaneous wave break due to the second mechanism. Because fewer daughter wavelets were generated, the VF activation during procainamide infusion was more regular and coherent than the VF activation at baseline. These findings have their clinical correlates. Buxton et al. studied 79 patients with only polymorphic ventricular tachycardia or VF inducible by programmed stimulation. After procainamide administration, 24 of these 79 patients had monomorphic ventricular tachycardia induced. The conversion from polymorphic ventricular tachycardia or VF to monomorphic ventricular tachycardia in these patients could be explained by the prevention of spontaneous wave break with procainamide.

Proarrhythmic Potential of Procainamide

The procainamide, however, also has significant proarrhythmic potentials. Starmer et al. used computer simulation to study the effects of sodium channel blockade on ventricular vulnerability. They found that blocking these channels can result in a delay of the onset of the vulnerable window (“antiarrhythmic”) and a prolongation of the duration of the vulnerable window (“proarrhythmic”). The increased refractoriness with sodium channel blockade is the mechanism by which the vulnerable window is delayed. However, sodium channel blockade also reduced the conduction velocity, resulting in prolonged duration of the vulnerable window. The authors concluded that because both antiarrhythmic and proarrhythmic properties are coupled with the sodium channel availability, it is not possible to separate the antiarrhyth-
mic potential from the proarrhythmic potential in class I antiarrhythmic agents.

In a previous study, we demonstrated that the ventricular vulnerable periods during VF were $58 \pm 14$ ms at baseline and $101 \pm 18$ ms during lidocaine infusion. In the present study, we found that the critical intersection intervals (vulnerable periods) associated with the induction of reentrant wave fronts were $54 \pm 5$ ms at baseline and $119 \pm 7$ ms during procainamide infusion. These data show that the onset of vulnerable period was delayed and the width of the vulnerable window (as demonstrated by the standard deviation) was prolonged during sodium channel blockade. These findings are compatible with the results of the simulation studies. The enlarged vulnerable window may explain the reason why the incidence of organized reentry was not decreased by procainamide administration despite the reduction of the total number of wandering wavelets.

**Wavelength and Antiarrhythmic Action**

Previous studies have shown that wavelength is an important parameter in determining antiarrhythmic efficacy. Theoretically, a drug that increases wavelength would decrease the number of reentrant waves. Because functional reentrant waves are thought to be the underlying mechanism for VF, a drug that decreases the number of reentrant waves would have antiarrhythmic effects. The results of the present study show that procainamide has no significant effect on wavelength. A possible explanation for this result is that procainamide is not an effective antiarrhythmic agent or that wavelength alone is not a useful parameter in predicting antiarrhythmic efficacy.

To explain the discrepancy between the results of the present study and those obtained from previous studies, we must consider the effects of cardiac rhythm on myocardial refractory period and conduction velocity. These electrophys-
iological properties were measured during actual VF in this study; they were measured during paced rhythm by programmed electrical stimulation in previous studies. Neither methods are ideal to measure the wavelength of activations during VF. Although the wavelength measured at baseline may not represent the wavelength during VF, our method of measuring wavelength is also limited to the wavelets that participated in reentry formation. The wavelengths of the vast majority of wavelets in VF were not measured. Recently, Girouard et al reported that multiple wavelengths could coexist in a single reentrant circuit. This latter finding revealed that a single measurement of wavelength may not be helpful in determining the vulnerability to fibrillation in intact ventricles. Whether the wavelength is important in determining antiarrhythmic efficacy remains unclear.

Study Limitations

One limitation of the study is that we studied only the right ventricle of normal healthy dogs. In clinical practice, most patients with life-threatening ventricular arrhythmias treated with procainamide have organic heart diseases, which may complicate the patterns of activation during VF. It is unclear whether the results of this study can be directly applicable to VF in patients with organic heart diseases. A second limitation is that we did not study the potential effects of procainamide in the initiation of VF. Although procainamide does not terminate VF or prevent the regeneration of reentry in this study, it may still be useful in clinical practice by preventing the spontaneous initiation of ventricular tachycardia or fibrillation.

In this study, we demonstrated that spontaneous wave breaks (wave breaks without apparent wave collisions) occur frequently during VF. Procainamide decreases the number of wavelets during VF by preventing the spontaneous wave breaks. This is a novel mechanism of antiarrhythmic drug action.

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