Mechanism of Flecainide’s Antiarrhythmic Action in Experimental Atrial Fibrillation

Zhiguo Wang, Pierre Pagé, and Stanley Nattel

Class Ic antiarrhythmic drugs are effective in the treatment of atrial fibrillation, but their mechanism of action is unknown. In previous work, we have found that flecainide causes tachycardia-dependent increases in atrial action potential duration (APD) and effective refractory period (ERP) by reducing APD accommodation to heart rate. The present study was designed to evaluate the efficacy and mechanisms of action of flecainide in an experimental model of sustained atrial fibrillation (AF). AF was produced by a brief burst of atrial pacing in the presence of vagal stimulation and persisted spontaneously until vagal stimulation was stopped. The actions of flecainide at two dose levels were compared with those of isotonic glucose placebo in each dog, with a randomized order of blinded drug administration. Flecainide terminated AF in all 16 dogs, while glucose was effective in none ($p<0.0001$). Flecainide increased atrial ERP and reduced conduction velocity in a tachycardia-dependent manner. Doses of flecainide that converted AF resulted in larger changes in ERP than in conduction velocity, increasing the minimum pathlength capable of supporting reentry (wavelength). In addition, flecainide reduced regional heterogeneity in ERP and wavelength, an action opposite that of vagal stimulation. Atrial epicardial mapping with a 112-electrode atrial array was used to study the mechanism of flecainide action on AF. Under control conditions, multiple small zones of reentry coexisted. Flecainide progressively increased the size of reentry circuits, decreased their number, and slowed the frequency of atrial activation until the arrhythmia finally terminated; all changes were compatible with an increase in wavelength. We conclude that flecainide terminates atrial fibrillation in this experimental model by causing tachycardia-dependent increases in atrial ERP, which increase the wavelength at the rapid rates characteristic of AF to the point that the arrhythmia can no longer sustain itself. (Circulation Research 1992;71:271–287)

KEY WORDS • arrhythmia mechanisms • electrocardiography • antiarrhythmic drugs • action potential duration • refractory period • heart rate • flecainide • atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice.1 Recent studies have shown that the class Ic antiarrhythmic agents propafenone2–4 and flecainide5–14 are effective in terminating atrial fibrillation and preventing its recurrence. The availability of class Ic agents has been hailed as a useful addition to the pharmaceutical armamentarium in treating this arrhythmia.15 On the other hand, the effectiveness of class Ic agents in terminating AF raises questions about the factors determining AF and mechanisms of antiarrhythmic drug action. Class Ic agents are considered to slow cardiac conduction strongly, with little effect on refractoriness.16,17 Given the classically understood determinants of reentry,18,19 slowed conduction with no change in refractory period should increase the likelihood of a reentrant arrhythmia like AF.20–23

We have shown that flecainide causes tachycardia-dependent increases in atrial action potential duration (APD), apparently by attenuating APD accommodation to heart rate.24 These effects are paralleled by frequency-dependent increases in atrial refractoriness, which could account for the beneficial effects of flecainide in atrial fibrillation.24 The latter hypothesis has not, however, been tested.

The purpose of the present work was to evaluate the mechanisms of flecainide’s efficacy in an experimental model of atrial fibrillation. Specific goals included 1) the development of an animal model of sustained atrial fibrillation that is reliable and reproducible, 2) the assessment of flecainide’s concentration-dependent efficacy in this model using a blinded experimental design to exclude the possibility of investigator bias, 3) an evaluation of the electrophysiological effects of flecainide associated with termination of atrial fibrillation, and 4) an analysis of the mechanism of arrhythmia termination using a computer-based mapping system and epicardial electrode array capable of analyzing data from up to 112 simultaneously recorded electrograms. A

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preliminary communication of these results has appeared in abstract form.25

Materials and Methods

General Methods

Sixteen mongrel dogs of either sex weighing 18–27 kg were anesthetized with morphine (2 mg/kg i.m.) and \( \alpha \)-chloralose (100 mg/kg i.v.) and ventilated by a respirator (NSH 34RH, Harvard Apparatus, South Natick, Mass.) via an endotracheal tube at a rate of 20–25 breaths per minute with a tidal volume obtained from a nomogram. Arterial blood gases were measured to ensure adequate oxygenation (\( \text{SaO}_2 > 90\% \)) and physiological pH (7.38–7.45). Catheters were inserted into the left femoral artery and both femoral veins and kept patent with heparinized saline solution (0.9%). A median sternotomy was performed, an incision was made into the pericardium extending from the cranial reflection to the ventricular apex, and a pericardial cradle was created.

A pair of Teflon-coated stainless steel bipolar hook electrodes, one for stimulation and the other for recording atrial electrograms, were inserted intramurally into the tip of the right atrial appendage. The position of the stimulating electrode is indicated by the number “1” in Figure 1. A programmable stimulator and a stimulus isolator (Bloom Assoc., Flying Hills, Pa.) were used to deliver 4-msec square-wave pulses. Another pair of electrodes were fixed in the high right ventricle for stimulating and recording purposes. A demand pacemaker (GBM 5880 Demand Pacemaker, Medtronic, Inc., Minneapolis, Minn.) was used to pace the ventricles when the spontaneous ventricular rate was ≤90/ min. Operational amplifiers (Bloom Assoc.) and a Mingograf T-16, 16-channel recorder (Siemens-Elema Ltd., Toronto, Canada) were used to record the six standard surface electrocardiogram leads, arterial pressure, and stimulus artifacts. Electrocardiographic recordings were obtained at a paper speed of 200 mm/sec. To block complicating sympathetic reflex effects, particularly in the presence of varying vagal tone, we administered 0.5 mg/kg i.v. nadolol followed by 0.25 mg/kg every 2 hours. We have previously shown that this regimen produces sustained and stable \( \beta \)-blockade.26

Atrial Fibrillation Model

Vagally induced atrial fibrillation was used as a model in this study. Both cervical vagal trunks were isolated and decentralized, and bipolar hook electrodes were inserted via a 21-gauge needle into the middle of each nerve, with the electrode running within and parallel to vagal fibers for several centimeters. Bilateral vagal nerve stimulation (VNS) was delivered by an SD-9F stimulator (Grass Instruments, Inc., Quincy, Mass.), with a pulse width of 0.1 msec and a frequency of 10 Hz. The amplitude of stimulation was between 3 and 10 V, adjusted in each dog to two thirds of the threshold for the production of asystole under control conditions. Five seconds after the initiation of vagal stimulation, a short burst (1–3 seconds) of atrial pacing at a cycle length of 100 msec and with a current amplitude of four times the diastolic threshold for atrial capture was used to induce AF. AF induced in this way persisted spontaneously for over 30 minutes and converted within seconds of the termination of VNS. The presence of AF was determined by the occurrence of a rapid (>500/min under control conditions), irregular spontaneous atrial rhythm with varying atrial electrogram morphology and activation time.

Activation Mapping

An array of 112 bipolar electrodes with 1-mm interpolar and 6-mm interelectrode distance, evenly spaced in five thin plastic sheets, was used (Figure 1). In addition to the recording sites, the sheets also contained six pairs of bipolar electrodes (numbered 2–7 in the figure) for regional stimulation. The sheets covered the entire epicardial surface of both atria and were carefully fixed in position by sewing the edge of the plaques to the atria to assure good electrode contact with the epicar-
Flecainide in Atrial Fibrillation

Experimental Protocols

Protocol 1: Evaluation of the concentration-dependent efficacy of flecainide in terminating AF. AF was induced under control conditions as described above and its sustained nature over 30 minutes in the presence of vagal stimulation verified. A table of random numbers was used by a third party to determine the order of administration of either flecainide or an isotonic glucose placebo. This third party then prepared syringes containing the appropriate doses of flecainide and identical volumes of isotonic glucose and labeled them “A” and “B” to indicate their order of administration. The experimenters were blinded as to the agent administered until all experiments had been completed. Each agent was given as a loading dose (1 mg/kg flecainide or an equal volume of glucose solution) over 15 minutes, followed by a maintenance dose (1.33 mg/kg per hour flecainide or placebo). If fibrillation terminated during the infusion of drug A, termination of AF was attempted. If reinitiation was successful, VNS was continued for 30 minutes to determine whether AF would convert spontaneously. If reinitiation was prevented, the effects of drug A on vagal bradycardic actions and on atrial conduction and refractoriness were evaluated (according to protocols 2 and 3, below). The maintenance dose was then discontinued, and the reinduction of AF was attempted every 10 minutes thereafter. Sixty minutes after the discontinuation of drug infusion, a time that was always sufficient for the effects of drug A to dissipate, drug B was given. The same procedures were followed as described for drug A above.

If atrial fibrillation persisted for 30 minutes after the onset of drug infusion, the infusion was considered to have failed to terminate AF. Vagal stimulation was then discontinued and AF allowed to terminate spontaneously (which it inevitably did shortly after VNS was stopped). Rate-dependent changes in atrial conduction and refractoriness were then assessed, and a blood sample was obtained for subsequent assay of flecainide plasma concentration by high-performance liquid chromatography.

Protocol 2: Flecainide effects on the heart rate response to graded vagal nerve stimulation. These experiments were designed to determine whether flecainide in the doses used altered the electrophysiological effects of VNS. Sinus rate was used as index of vagal action. Vagal frequency–response curves (in nine dogs) and intensity–response curves (in three dogs) were first measured under control conditions. Atrial electrograms were recorded at 100 mm/sec for 10 seconds and the total number of complexes counted to determine spontaneous rate. For frequency–response curves, the vagal nerves were stimulated at a fixed amplitude of 10 V with increasing frequency from 2 Hz with 1 Hz increments until a maximum effect was observed. Each frequency was maintained for 30 seconds, with the sinus rate
evaluated over the last 10 seconds of stimulation at a given frequency. Intensity–response curves were obtained in a similar fashion, except that VNS frequency was fixed at 10 Hz, the initial stimulation voltage was 2 V, and stimulation intensity was augmented by 0.5-V steps. After each 30-second stimulation period at a given voltage or frequency, VNS was stopped, and the preparation was observed until sinus rate returned to control values.

Protocol 3: Drug effects on atrial refractoriness and conduction. Atrial effective refractory period (ERP) was assessed by the extrastimulus technique, and atrial activation times were determined by isochronal mapping. The direction of rapid propagation was determined from the isochrone maps, and a pair of adjacent bipolar electrode sites in the line of rapid propagation were selected. Conduction velocity was calculated as the distance between the sites divided by the interelectrode conduction time. The activation pattern was assessed for all activations to ensure that changes in conduction time were not caused by rate- or drug-dependent regional block or changes in the direction of impulse propagation.

Results were obtained at basic cycle lengths (BCLs) of 400, 300, 250, 200, and 150 msec. Two minutes were allowed at each BCL before atrial ERP and conduction velocity were measured. For ERP determination, a premature stimulus (S2) was inserted after every 10 basic (S1) stimuli while S2S2 decreased by 10-msec decrements until failure to capture occurred. The longest S2S2 interval that consistently failed to produce a propagated response was defined as the ERP. Measurements of ERP were made in both the presence and absence of VNS. ERP and conduction time were first determined under control conditions after termination of AF and then immediately after drug-induced conversion of AF or during the maintenance dose if the drug failed to convert AF within 30 minutes.

Regional Drug Effects on Wavelength

Vagal stimulation produces nonuniform regional changes in atrial ERP,30 resulting in nonuniform changes in local wavelength.31 To determine whether flecainide’s effects on wavelength were exerted in a spatially uniform fashion, we studied five additional dogs. Conduction velocity, atrial refractory period, and wavelength were determined during stimulation at a cycle length of 250 msec at each of the seven stimulation sites shown in Figure 1. For the conduction velocity measurement during stimulation at each site, conduction time between two adjacent bipolar electrodes in the direction of rapid impulse propagation was determined, with the proximal bipolar in the immediate vicinity of the stimulating electrode. The proximal bipolar was used to indicate when regional propagation failed during ERP measurement. Wavelength was calculated from the local conduction velocity and ERP measurement obtained during stimulation at each site under control conditions in both the absence and presence of VNS and then after flecainide administration with and without VNS. To assure that the results of these experiments were relevant to the blinded study described above, an identical protocol was used (in terms of AF induction, drug dose, and assessment of drug efficacy), but flecainide was administered in a nonblinded fashion. ERP and conduction measurements were obtained during drug administration as described above.

Data Analysis

The ability of flecainide to terminate AF was compared with that of an equal volume of glucose by Fisher’s exact test.32 Group data are presented as mean±SEM. Comparison between group means was made by two-way analysis of variance (ANOVA) with Scheffe’s test. Student’s paired t test was used when only two groups of results were compared. A two-tailed probability of less than 5% defined statistical significance.

Rate-dependent and regional effects of flecainide on atrial ERP, conduction velocity, and wavelength were evaluated by ANOVA with an F test for interaction. Wavelength changes were calculated based on the mathematical formulation of Wiener and Rosenblueth33 using the relation

$$\lambda = \text{ERP} \times CV = \text{ERP} \times L/CT$$

where λ is wavelength, CV is conduction velocity, L is length of the conducting pathway (i.e., interelectrode distance), and CT is conduction time.

Results

General Efficacy of Flecainide in AF

A total of 16 dogs were studied using the blinded protocol to determine the efficacy of flecainide in AF, and mapping data were obtained in 14 of these. The mean amplitude of vagal stimulation was 6 V (range, 3–10 V), and sustained AF was readily produced under control conditions in all dogs. Isotonic glucose did not convert AF to sinus rhythm in any dogs (0 of 16, 0% efficacy). In contrast, flecainide converted AF in nine of 16 dogs at the first dose and seven of 16 at the second dose for an overall efficacy of the drug of 100% (p<0.0001). The mean time of conversion of AF by flecainide was 13.8 minutes (range, 7–20 minutes). In five dogs used to study regional effects of flecainide, the first dose successfully terminated AF.

The mean concentrations of flecainide associated with arrhythmia termination and various degrees of suppression of arrhythmia induction are shown in Fig-
### Table 1. Effects of Flecainide on Atrial Effective Refractory Period, Conduction Velocity, and Wavelength

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<th>BCL (msec)</th>
<th>Effective refractory period (msec)</th>
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<td>(23.7±5.4%)</td>
<td>(31.0±10.1%)</td>
<td>(28.5±6.4%)</td>
<td>(28.3±8.9%)</td>
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</table>

BCL, basic cycle length; VNS, vagal nerve stimulation; flec, flecainide.

*p<0.05, †p<0.01, ‡p<0.001 compared with control in the absence of flecainide at the same cycle length. Results in parentheses are percent change produced by flecainide relative to corresponding control value. §p<0.001, ‖p<0.01 for rate dependence of drug effects by analysis of variance with F test for interaction. Values of percent change are determined relative to corresponding paired control data. All values are mean±SEM in milliseconds.
Figure 2. The mean concentration causing arrhythmia termination was 1.7±0.4 mg/l. Atrial fibrillation was not inducible until a mean concentration of 0.8±0.4 mg/l was attained after the drug was stopped, at which point the induced AF terminated spontaneously. When a mean concentration of 0.5±0.1 mg/l was achieved, sustained AF could once more be induced.

**Flecainide's Effects on the Response to Vagal Stimulation**

Flecainide produced no significant changes in the sinus node response to vagal stimulation. Figure 3 shows mean data from all dogs studied for the vagal frequency–response curves (left) and intensity–response curves (right). In both instances, results in the presence of flecainide were superimposable on results during isotonic glucose administration. These data indicate that flecainide did not exert its actions by generally attenuating the response to vagal stimulation.

**Effects of Flecainide on the Electrophysiological Determinants of Reentry**

The rate-dependent effects of flecainide on atrial ERP, conduction velocity, and the minimum wavelength for reentry are listed in Table 1 and shown in Figure 4. Minimal differences were seen between values of these variables under control conditions and measurements obtained in the presence of isotonic glucose placebo. Results obtained with dose 1 in the seven dogs whose AF was not converted by this dose are shown by the filled triangles in Figure 4, and results of the dose of flecainide that converted AF in each dog are shown by the open circles. Ineffective doses of flecainide had almost two thirds of the conduction slowing effect of effective doses but produced limited changes in atrial refractoriness and did not alter the wavelength. Effective doses of flecainide, on the other hand, produced substantial rate-related increases in atrial ERP and significantly increased the wavelength.

Vagal stimulation produced substantial decreases in atrial ERP but did not alter atrial conduction velocity (Table 1). Flecainide’s effect on atrial ERP in the presence of vagal stimulation (comparing results during VNS in the presence of the drug with those during VNS in its absence) was qualitatively similar to, but quantitatively greater than, its effect without VNS (Figure 4, upper left). The drug’s ERP-prolonging action was increased about 2.5-fold in both the presence and absence of VNS over the range of BCLs from 400 to 150 msec. In contrast to its effect on ERP, flecainide’s action on conduction velocity was not altered by VNS (Figure 4, lower left). As a consequence, the drug’s ability to increase the minimum wavelength for reentry was increased in the presence of VNS.

The changes in atrial conduction produced by flecainide are illustrated in Figure 5. When the right atrial appendix was paced, the site of earliest activation was at the tip of the appendix and latest activation was in the posteroinferior left atrium, as shown in all panels of the figure. When BCL was decreased from 400 msec (top left) to 150 msec (top right) under control conditions, a slight increase in overall atrial conduction time, from 75 msec to 83 msec, occurred. In the presence of flecainide at a BCL of 400 msec (bottom left), the pattern of conduction did not change but the conduction time increased to 88 msec. When the pacing cycle length was decreased to 150 msec in the presence of the drug, conduction slowed uniformly and the conduction time increased to 105 msec.

**Effects of Flecainide on Activation During Atrial Fibrillation**

During sinus rhythm, earliest activation was consistently found in the right atrium near the superior vena cava (site B in Figure 6). Excitation conducted rapidly throughout the right atrium and then appeared to slow during transseptal propagation. The anterior aspect and appendage were the first regions of the left atrium to be activated, perhaps via specialized conducting pathways,34
and the last region to be excited was the posterior left atrium adjacent to the atrioventricular ring.

During atrial fibrillation in the absence of flecainide, rapid atrial activity was observed. Figure 7 (panels A and B) shows electrograms recorded in two sets of eight electrodes from the anterior right atrium (electrodes A1–A8, panel A) and left atrium (I1–I8, panel B). The left atrial activity was more regular and discrete, so we chose to map atrial activation during one cycle of left atrial activity as shown by the vertical lines in panel B. Because many sites elsewhere were activated twice during this cycle, we created two maps to represent atrial activation during the cycle, the first showing initial activation at each site (panel C), and the second (panel D) incorporating the second time of activation for sites showing two discrete activations during the cycle (as seen in most electrograms in panel A). As shown in panel C, there were three zones of early activation: the superolateral right atrium adjacent to the right atrial appendage (sites A1, A5, A8, and B8), the mid–left atrium (site K), and the posterior aspects of both atria adjacent to the atrioventricular ring (sites E1, H5, and H6). Six islands of late activation are present. In several regions, zones of early and late activation lie close to one another and are separated by narrow isochrones indicating block or very slow conduction. Since conduction during sinus rhythm is rapid and relatively uniform (Figure 6), these zones of slow conduction (represented by the dotted lines in panel C) must represent refractory tissue. Electrical propagation around the zones of refractoriness results in delayed activation at sites close to the first areas to be activated. Subsequent propagation to these sites of early activation (shown by the white arrows in panel D) results in their reexcitation, as shown by the delayed activation in panel D of sites F1, F5, and K5; H5–H6 and H7–H8; and A8. Sites K1, J7, H5, and H6 were activated early and only once in the cycle shown. Propagation from the late-activated sites K2, H5, and H6 (shown by the white arrowheads in panel D) initiated the next cycle in these regions.
Consider the activation of sites A1–A8, whose electrograms are shown in panel A. Sites A1, A2, A3, and A8 are activated at the beginning of the cycle. These correspond to a zone of very early activation in panel C. Site A1 is activated slightly later and is followed by the activation of sites A2, A3, and A8. Site A1 was activated immediately before the other sites in the cycle, and the propagating wave front returned to activate A1 just over halfway into the cycle. The impulse then activates A1, A2, A3, and A8, the first sites activated and therefore the first to recover excitability. This is followed by activation of sites A2, A3, and A8, activated somewhat later in the primary cycle and therefore also reactivated later.

Some zones were activated only once during the cycle, such as electrodes I1–I3 shown in panel B. When such zones were activated early in the cycle and were adjacent to regions reactivated late in the cycle, propagation from the latter areas was able to initiate another cycle. For example, electrodes J1, K1, H2, and H3 were activated early in the cycle (panel C). Slow conduction resulted in delayed reexcitation of electrodes H4–H6; and K2 (panel D) approximately 70 msec after the initial excitation at electrodes J1, K1, H2, and H3. Propagation to the latter sites (as shown by the white arrowheads in panel D) initiated the next cycle in these regions.

The cycle illustrated in Figures 7C and 7D suggests several coexistent reentry circuits of relatively small diameter. We observed an average of five such apparent reentry circuits in each cycle of atrial fibrillation mapped under control conditions.

The effect of flecainide on atrial activation during AF is illustrated in Figure 8. The results shown are from the same dog as those in Figure 7. After 5 minutes of flecainide infusion (panel A), atrial activity is more homogeneous and two large macro-reentrant pathways are present. After 12 minutes, flecainide terminated AF. The last two cycles before termination (designated B and C in panels E and F) are shown in panels B and C. In the penultimate cycle (panel B), a single large macro-reentry circuit is present. The next cycle (panel C) begins at a zone similar to the sites of first activation in the penultimate cycle. When the reentering impulse reaches the dark blue zone, block occurs, as shown by failure of activation during cycle C at electrode sites E1–E2, and spontaneous atrial activity ceases. This is followed by an atrial activation originating near the sinus node (panel D), whose pattern of activation resembles sinus beats under control conditions (Figure 6).

Note that the low-amplitude potentials recorded at sites E1–E2 during cycle C are reflections of ventricular activation (corresponding in time to the surface QRS) and are also recorded before and immediately after sinus cycle D. The results of all experiments were similar in the sense that flecainide gradually increased the size and reduced the number of simultaneous reentry circuits, until one or two large circuits remained. No changes in atrial activation were noted after the administration of isotonic glucose.

Activation data adequate for map construction was available at the time of AF termination by flecainide in a total of 15 dogs (12 from the blinded series and three from studies of regional effects). In nine of these, the activation maps before AF termination resembled those shown in Figure 8, with a single macro-reentry circuit encountering refractory tissue. In the remaining six dogs, there were either two separate macro-reentry circuits that terminated independently (three dogs) or a dividing wave front resembling "figure of eight" reentry as previously described in chronically infarcted ventricular preparations.35,36 Figure 9 shows an example of the form of reentry at the time of AF termination by flecainide. Panels A and B show electrograms from two sets of electrodes at the time of arrhythmia termination, and panels C–F show activation maps of the last three cycles of activation at sites H3, H4, and H5. The first activation at each electrode site during the first cycle analyzed is shown in panel C. There is a large region of early activation in the posterior left atrium, and the impulse conducts toward the right atrium as shown. Functional arcs of block, possibly related to anatomic obstacles (the pulmonary veins to the left of electrodes N1–N4 and the inferior vena cava to the right of electrodes H4 and I1), cause the impulse to travel through an isthmus of excitable tissue and then divide into two wave fronts propagating back toward the posterior left atrium. The time lag is sufficient for the posterior left atrium to be reexcited during the second half of the same cycle, as shown by the dark blue isochrones in panel D. Propagation back through the functional isthmus shown by the arrowhead in panel D produces another cycle with a figure of eight pattern as shown in panel E. While the pattern of activation in panel E resembles that in panel C, conduction is more rapid and no subsequent reentrant activity is apparent. Over the last 100 msec of the cycle designated by E, no atrial activation was recorded. The final cycle before restoration of sinus rhythm is shown in panel F. This cycle originates from the region where activity was last noted in panel E but after an interval of over 100 msec. In keeping with the substantial recovery time at all electrode sites, activation propagates rapidly and rather uniformly during cycle F. It is impossible to determine whether the cycle shown in panel F originated from reentry through a zone of very slow conduction that was not detected or as a result of a site of ectopic activity. While the precise mechanism of arrhythmia termination

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**Figure 6.** Activation map during sinus rhythm. Earliest activation (light yellow) was in the right atrium adjacent to the superior vena cava. Latest activation (dark green) was in the posterior left atrium.
in Figure 9 is unclear, the number of reentry circuits is clearly reduced compared with predrug conditions, making arrhythmia termination more likely.

To quantify the effects of flecainide on atrial activation during AF, we sought an operational definition of a reentry circuit. Since a complete circuit of reexcitation was not always identifiable in an apparent zone of reentry, we defined a reentry region as a zone in which there was a difference of >50 msec in the activation time at adjacent electrode sites, with the earlier site of activation reactivating within 20 msec after the adjacent site of late activation. In the presence of flecainide, cycles of atrial activation were readily identifiable, and 10 consecutive cycles were mapped during each drug infusion after 5 minutes of drug infusion and immediately before arrhythmia termination (when the latter occurred). Under control conditions, as shown in Figure 7, the duration of activation cycles varied among electrode sites. Therefore, we mapped 10 consecutive windows of 80-msec duration. Under control conditions, there was an average of 5.0±0.7 cycles per 80-msec window. The number of circuits was significantly decreased after 5 minutes of flecainide infusion and further decreased immediately before AF termination (Figure 10).

We also determined the mean cycle length of AF under various conditions. The mean cycle length was determined for each study period by determining the number of cycles of activation recorded at each electrode site in a 1-second interval. The results obtained at all sites were averaged to obtain a representative mean cycle length for that study period. Flecainide significantly increased the mean cycle length of AF (Figure 10). Both mean cycle length and number of circuits were calculated for all dogs in which mapping studies were performed during the blinded study. Isotonic glucose did not alter the number of apparent reentrant circuits or the mean cycle length of AF.

Regional Effects of Flecainide and Vagal Nerve Stimulation

During the blinded studies, atrial stimulation was always performed at the single site designated by the number 1 in Figure 1. To evaluate regional changes in refractoriness, conduction, and wavelength, stimulation (BCL, 250 msec) was performed at seven separate sites in five additional dogs. Under control conditions there were small regional differences in refractory period and conduction velocity (Figure 11). Vagal stimulation did not alter conduction but significantly decreased atrial ERP at all sites. The magnitude of vagal action varied at different sites, with average decreases ranging from 10 msec at site 5 to 62 msec at site 2. Flecainide significantly reduced conduction velocity and increased ERP at all sites, in both the presence and absence of vagal stimulation. In the absence of vagal stimulation, flecainide's effect on ERP was relatively uniform throughout the atria. In the presence of vagal stimulation, flecainide's effect was somewhat greater at sites showing the greatest degree of vagally induced ERP abbreviation. Flecainide thus tended to make atrial ERP more uniform in the presence of VNS. Under control conditions, the wavelength (Figure 11, bottom) varied from 13 to 16 cm at the seven sites tested. Vagal stimulation significantly reduced wavelength to between 7.5 and 12 cm at all sites. Flecainide significantly increased wavelength in the presence and absence of VNS, with mean values in the presence of VNS ranging from 12 to 14 cm after flecainide administration.

The effects of flecainide on regional variability in atrial refractoriness are summarized in Figure 12. To quantify the variability in ERP, we calculated the standard deviation of ERP at all seven sites under each experimental condition. Flecainide significantly decreased atrial ERP variability in both the absence and presence of VNS, whereas VNS substantially increased ERP heterogeneity. In the presence of VNS, flecainide returned the standard deviation of atrial ERP toward values measured under control conditions without VNS in the absence of the drug.

Discussion

We have shown that flecainide predictably terminates AF in an experimental dog model and prevents the reinitiation of AF in a concentration-dependent fashion. These actions appear to be caused by tachycardia-related increases in atrial refractoriness produced by the drug, which result in significant increases in the wavelength for atrial reentry.

Relation to Previous Studies of Class I Drug Action in Atrial Fibrillation

Studies of the mechanisms of antiarrhythmic drug action in atrial fibrillation have been quite limited. Renema et al. showed that the wavelength was an accurate predictor of the inducibility of atrial arrhythmias in conscious dogs. Quinidine and d-sotalol increased the wavelength and prevented the induction of atrial fibrillation, while the class Ic drug propafenone had little effect on wavelength and apparently did not alter the ability to induce AF. In a subsequent study from the same laboratory, the experimental class Ic compound ORG 7797 was found to reduce the inducibility of AF. This action was associated with a tachycardia-dependent increase in atrial refractory period. The drug limited the minimum wavelength that could be produced by rapid pacing, thus presumably decreasing the number of simultaneous atrial reentry circuits possible and the likelihood of AF.

Our work differs from the above studies in that we have used a model of sustained AF, a blinded design to assess drug action, and epicardial mapping to address antiarrhythmic mechanisms. The results support the mechanisms hypothesized by Kirchhoff et al. in that the increase in wavelength produced by flecainide resulted in an increase in the size and a decrease in the number of reentry circuits, until AF was finally terminated. Kirchhoff et al found that ORG 7797 attenuated the decreases in atrial refractoriness resulting from increased heart rate, and we noted a similar effect of flecainide. These results parallel our previous direct observations of the effects of flecainide on atrial ADP in vitro, as well as recent studies of the drug's actions on atrial monophasic action potentials in vivo. It is possible that some of the rate-dependent increases in atrial ERP produced by flecainide were due to sodium-channel blockade, but in our previous in vitro and in vivo studies most of the drug's ERP-prolonging action was accounted for by increases in ADP.
In contrast to the limited information available about mechanisms of drug action in atrial fibrillation, much more work has been done to evaluate drug effects in animal models of atrial flutter.\textsuperscript{39-43} Agents that terminate atrial flutter share an ability to increase atrial refractoriness.\textsuperscript{39,40,42} On the other hand, the termination of atrial flutter by class I agents appears to be associated with conduction slowing and not with an increased wavelength or decreased excitable gap.\textsuperscript{41,43} The mechanism of experimental atrial flutter following atrial inci-
sion involves reentry around a fixed anatomic barrier and is therefore quite different from the functional “multiple wavelet” reentry occurring during atrial fibrillation.

Possible Mechanisms Underlying Flecainide’s Actions

Flecainide slowed atrial conduction and increased the refractory period. Whereas both actions were rate dependent, effects on refractoriness predominated, as indicated by drug-induced increases in the wavelength. Conceptually, the wavelength indicates the minimum path length that can support reentry. The relation between wavelength and the occurrence of reentry was first described by Mines. The concept was further developed by Lewis and formulated mathematically by Wiener and Rosenblueth. While Lewis’ analysis of the wavelength was based on an anatomically fixed reentry circuit, the wavelength concept was linked to a functionally determined form of reentry by the “leading circle” model of Allessie et al. The latter concept is more directly pertinent to the type of system described in the present study, in which zones of regional refractoriness, rather than anatomic barriers, determine propagation patterns during arrhythmia. In fact, the likelihood of atrial flutter and atrial fibrillation have recently been shown to relate closely to the wavelength in atrial tissue. Decreases in atrial wavelength reduce the size of atrial reentry circuits, reduce the revolution time, and facilitate the induction of atrial flutter and fibrillation. Increases in wavelength have the opposite effect. In the presence of vagal stimulation, wavelength at a short BCL (150 msec) averaged less than 7 cm (Figure 4), a value below the threshold wavelength for AF of 7.8 cm noted by Rensma et al. As a result of tachycardia-dependent ERP prolongation, flecainide increased the wavelength under the same conditions to about 9 cm, a value similar to control in the absence of vagal stimulation and a value at which AF cannot be sustained. The effects of flecainide that we observed on the size, number, and cycle lengths of atrial reentry circuits are all consistent with the predicted consequences of the increases in wavelength that were produced by the drug. In addition to increasing atrial wavelength, flecainide reduced regional disparities in atrial ERP and wavelength in both the presence and absence of vagal stimulation (Figures 10 and 11). This property could contribute to flecainide’s ability to prevent the occurrence of AF by reducing the heterogeneity of atrial refractory properties, particularly in the presence of increased vagal tone.

The probable central mechanism in flecainide’s actions on atrial wavelength is its ability to cause tachycardia-dependent increases in atrial APD, resulting in parallel changes in refractoriness. The underlying ionic mechanisms remain to be determined. Flecainide blocks the delayed rectifier current (iK) in cat ventricular myocytes. While iK is a major repolarizing current in many cardiac tissues, it appears to be of little importance in canine atrial tissue and has been reported to be negligible in humans. The transient outward current (iNa) is of greater importance in dog and human atrial cells, but flecainide is a relatively weak blocker of this current. Since decreases in atrial APD accommodation to heart rate appear to underlie flecainide’s rate-dependent effects on repolarization, studies of the ionic mechanism underlying APD accommodation may provide deeper insights into the drug’s ionic properties. We have provided preliminary evidence that at least in canine atrium, flecainide’s effect on APD accommodation may be due to reduced sodium entry resulting in a diminution of electrogenic Na+,K+-ATPase activity.

Clinical Relevance

While atrial fibrillation remains a common clinical arrhythmia, it is often resistant to drug therapy. The effectiveness of class Ic drugs opens up a new, potentially useful therapeutic option, but one whose mechanism has been uncertain. In the present work, we have shown that tachycardia-dependent atrial ERP prolongation accounts for the efficacy of flecainide in a dog model of AF. Since the rate dependence of flecainide’s effects on APD and atrial ERP of isolated human tissue is even greater than its rate dependence on dog atrium, it is likely that similar mechanisms account for the drug’s ability to terminate AF in humans. Boahene et al. have noted a marked increase in the AA interval produced by propafenone before AF termination. This finding is analogous to the effect of flecainide on AF cycle length that we observed before termination (Figure 10) and suggests an increase in the wavelength after propafenone administration in humans.

The ability of class Ic agents to terminate AF decreases with increasing duration of the arrhythmia. When AF is treated within 48 hours of its onset, class Ic agents terminate the arrhythmia in 70–86% of cases. In our dog model of acute AF, flecainide was uniformly effective if enough of the drug was given. In fact, efficacy in most dogs occurred at a dose (1 mg/kg) equal to the effective dose reported for humans. A recent clinical study suggests that the persistence of AF may result in structural (and presumably functional) abnormalities of atrial tissue. The reduced efficacy of class Ic agents in chronic AF may be caused by the marked abnormalities in cellular electrophysiology often associated. The membrane
FIGURE 8. Activation maps after flecainide administration to the same dog whose results under control conditions are shown in Figure 7. Panel A: Five minutes after flecainide administration, activation is more homogeneous and there are two large clockwise reentry circuits. Panel B: Penultimate cycle of atrial fibrillation (AF) after flecainide administration. A single large counterclockwise reentry pattern is present. Panel C: The last cycle of AF in the presence of flecainide. Failure of propagation into the dark blue zone (electrodes E1–E8, shown in panel F) results in arrhythmia termination. Panel D: The first atrial activation after termination of AF. The activation pattern is very similar to activation during sinus rhythm under control conditions (Figure 6), although propagation is slowed, reflecting the conduction slowing action of flecainide. Panels E and F: Electrograms recorded at the time of AF termination by flecainide. The cycles designated B, C, and D are delimited by pairs of vertical lines, and their activation maps are shown in corresponding panels B, C, and D. Similar patterns of activation leading to AF termination after flecainide were seen in eight other dogs. Note that the low-amplitude potentials in electrodes E1–E2, in cycle C and after cycle D are reflections of ventricular activation and correspond in time to the QRS on the surface ECG.
Figure 9. Example of termination of atrial fibrillation (AF) by a mechanism different from that shown in Figure 8. Panels A and B: Electrograms from 16 sites recorded at the time of termination of AF. The vertical lines designate the last three cycles recorded in electrodes H1, H2, and H3 before the resumption of sinus rhythm. V, electrograms corresponding to ventricular activation. Panel C: Isochrone activation map of third to last cycle, using first time of activation at each site. Panel D: Activation map of same cycle as shown in panel C but with second activation used to time activation at sites activated twice during the cycle. Panels E and F: Activation maps of cycles designated by E and F in panels A and B. (For detailed discussion, see text.)

depolarization, sodium channel inactivation, and severe conduction slowing that occur with chronic atrial disease would decrease the wavelength, making the arrhythmia intrinsically more resistant. Furthermore, they might sensitize the tissue to the sodium-channel blocking and conduction slowing actions of flecainide,
offsetting the increases in refactororiness caused by the drug.

We found that flecainide always regularized AF before terminating the arrhythmia. The regularization resulted from a reduction in the number of simultaneous reentry circuits, an effect consistent with the increase in atrial wavelength caused by the drug. One clinical complication that has been noted with class Ic agents has been the conversion of atrial fibrillation to slow atrial flutter, sometimes causing 1:1 conduction and a rapid ventricular response. This observation is compatible with our finding that flecainide decreased the number and increased the size of reentry circuits, often leading to a single macro-reentrant loop, before arrhythmia termination and supports the concept of a class Ic drug-induced increase in atrial wavelength as a mechanism of its clinical action on AF.

An ability to prolong refactororiness without altering conduction would be the ideal property of a drug to treat reentrant arrhythmias. Unfortunately, currently available class 3 drugs increase APD in a bradycardia-dependent way, favoring the occurrence of early afterdepolarizations and torsades de pointes ventricular arrhythmias at slow heart rates. If an agent could be found that selectively increases APD at the rapid rates associated with reentrant arrhythmia, the risk of drug-induced long QT syndromes would be minimized without necessarily limiting drug efficacy. Flecainide’s actions on atrial APD and refactororiness appear to possess this desirable tachycardia dependence. Unfortunately, the indications for using flecainide in the treatment of AF remain to be clarified, in view of the Cardiac Arrhythmia Suppression Trial (CAST) results indicating that the drug increases the risk of sudden death among patients with frequent ventricular ectopy after a myocardial infarction. The mechanism of this adverse effect is unclear, but evidence points toward an arrhythmogenic effect of strong sodium-channel blockade in the presence of acute myocardial ischemia. If the ionic mechanism of flecainide’s rate-dependent APD-prolonging properties were identified and could be dissociated from sodium-channel blockade, molecular modification could result in a compound with improved efficacy against AF with limited adverse effects. The relative safety of class Ic compounds compared with alternative therapies for AF remains uncertain. For example, a recent meta-analysis suggests that quinidine therapy may result in a much higher mortality among patients treated for ventricular ectopy than several other drugs, including flecainide.

Limitations of the Present Work

The major potential limitation of the present work is the specific nature of the animal model. It is likely that the properties of atrial fibrillation in the vagotonic dog model are different from arrhythmias in the diseased, dilated atria associated with chronic AF in humans. On the other hand, the dog model may more closely resemble paroxysmal AF, particularly in patients with relatively normal atria. Moreover, the occurrence of AF in some cases of paroxysmal arrhythmia in humans appears to depend on increases in vagal tone. Flecainide therapy was highly effective in a group of 40 patients with drug-resistant AF, 31 of whom had a vagally dependent form of arrhythmia. The wavelength is rate dependent and likely shorter during the rapid activation characteristic of AF than during sinus rhythm. Conduction velocity and refractory period cannot be measured directly during AF, and the
wavelength cannot be directly calculated. We are therefore forced to draw inferences about flecainide’s actions on wavelength from its effects during rapid 1:1 atrial pacing. However, given the slope of the relation between drug effects on atrial ERP and the BCL (Figure 4), it is likely that flecainide’s effect on wavelength during AF is larger, if anything, than its effect during rapid atrial pacing.

Activation mapping of reentry is most easily interpreted when applied to single, discrete macro-reentry circuits. There are major limitations, particularly in terms of resolution, when studying nonfixed, multiple wavelet reentry, particularly of the type seen under control conditions in the presence of vagal stimulation. Our goal was not, however, to study in detail the physiological mechanism of AF, which has been well described previously, with our results being in qualitative agreement. Our goal was rather to evaluate the effects of flecainide on epicardial activation during vagally induced AF and to observe (if possible) the activation changes leading to arrhythmia termination. We found that flecainide qualitatively altered epicardial activation in this model of AF and led to arrhythmia termination in a fashion entirely compatible with its observed effects on wavelength. While procainamide has been shown to stabilize AF by reducing the number of apparent reentry circuits, we are unaware of studies in the literature on the changes in epicardial activation on drug termination of AF.

The basic train used to evaluate ERP consisted of 10 basic (S1) stimuli, which is much less than the mean onset time constant of about 30 beats for flecainide block of maximal phase 0 upstroke velocity in vitro but conduction slowing in vivo. However, because of the drug’s very slow recovery kinetics, the 10-msec decrements in coupling interval of the S1 extrastimulus should not have had any detectable effect on the level of sodium channel block. Furthermore, since the extrastimulus was consistently inserted after every 10 S1 stimuli and caused capture until the refractory period had been attained, the activation rate and level of block should have been quite constant until the atrial ERP had been measured. All conduction time measurements were obtained before ERP determination during pacing at the BCL, which had been continued for at least 2 minutes without the introduction of any extrastimuli.

Conclusions
Flecainide causes rate-related increases in atrial ERP and the wavelength for atrial reentry in the dog. It predictably terminates AF (which is otherwise sustained) in the presence of vagal stimulation, with effects on atrial activation during AF consistent with its rate-dependent effects on refractoriness and wavelength. These properties may underlie the beneficial actions of flecainide on atrial fibrillation in humans.

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