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EXPERIMENTAL STUDIES

Idiopathic Atrial Fibrillation in Dogs: Electrophysiologic Determinants and Mechanisms of Antiarrhythmic Action of Flecainide

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Objectives. **This study sought to determine the mechanisms of idiopathic atrial fibrillation and the atrial antifibrillatory action of flecainide in dogs.**

Background. **In a small subset of dogs, sustained atrial fibrillation can be readily induced in the absence of vagal tone. The electrophysiologic mechanisms underlying this ability to sustain atrial fibrillation, and of flecainide action on the arrhythmia, are unknown.**

Methods. **Six dogs with inducible sustained atrial fibrillation were studied before and after flecainide administration and compared with a control group of 10 dogs.**

Results. **Dogs with atrial fibrillation differed in displaying more shortening of the atrial refractory period with increased rate, resulting in a significantly shorter refractory period and wavelength for reentry at rapid rates, and in increased regional dispersion in refractoriness. Activation maps during sustained fibrillation showed a mean (±SE) of 6.3 ± 0.4 coexistent zones of reentry, compatible with short wavelengths, whereas in control dogs activation during self-limited atrial fibrillation was better organized, and the number of reentrant circuits was smaller. Quantitative analysis demonstrated significantly greater inhomogeneity of activation during atrial fibrillation in dogs with atrial fibrillation than in control animals. Flecainide terminated atrial fibrillation by increasing the duration and homogeneity of atrial refractoriness at rapid rates, thereby reducing the number of reentry circuits and the heterogeneity of activation.**

Conclusions. **The ability of atrial fibrillation to sustain itself resulted from enhanced rate-dependent shortening of atrial refractoriness and increased regional heterogeneity. Flecainide reversed these changes and restored sinus rhythm. These results suggest potential mechanisms of idiopathic atrial fibrillation and are pertinent to understanding the clinical actions of flecainide.**

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Although atrial fibrillation is one of the most common arrhythmias encountered in clinical practice, the mechanisms and determinants of atrial fibrillation remain incompletely understood. One of the factors limiting our understanding of atrial fibrillation is a lack of readily accessible and appropriate animal models. Investigators have studied repetitive atrial responses and brief episodes of atrial fibrillation induced by programmed electrical stimulation in normal animals (1,2), but the self-limited and potentially variable nature of these arrhythmias make them difficult to study and render the results of uncertain relevance to sustained arrhythmias. Cholinergic stimulation enhances susceptibility to atrial fibrillation (3–6), and we have previously used vagally mediated sustained atrial fibrillation extensively as a model to study the mechanisms of antiarrhythmic drug action (7–9). An important limitation of the cholinergic atrial fibrillation model is that interactions between cholinergic and drug effects may occur, making it difficult to determine the extent to which observations in this model can be applied to the clinical setting.

We have previously shown (7) that flecainide terminates atrial fibrillation in the vagotonic model by causing tachycardia-dependent increases in atrial refractoriness and wavelength at the rapid rates characteristic of atrial fibrillation. These observations are consistent with previous observations of flecainide's cellular effects on superfused atrial preparations from multiple species, including dogs and humans (10). The changes in refractoriness caused by flecainide were increased in the presence of vagal stimulation, raising questions about the relevance of flecainide's effects in the vagal model to effects on atrial fibrillation in the presence of normal autonomic tone.

Over a 3-year period, ~300 dogs have undergone atrial stimulation protocols that included refractory period determinations and pacing at various basic cycle lengths in our laboratory. In six of these dogs, all of whom had bilateral cervical vagotomies as part of the experimental preparation, sustained atrial fibrillation could readily be induced by critically timed atrial extrastimuli or rapid atrial pacing. The purpose of the present experiments was to evaluate the physiologic substrate of atrial fibrillation and its response to flecainide administration in these dogs. Specific objectives included the following: 1) to assess atrial electrophysiologic

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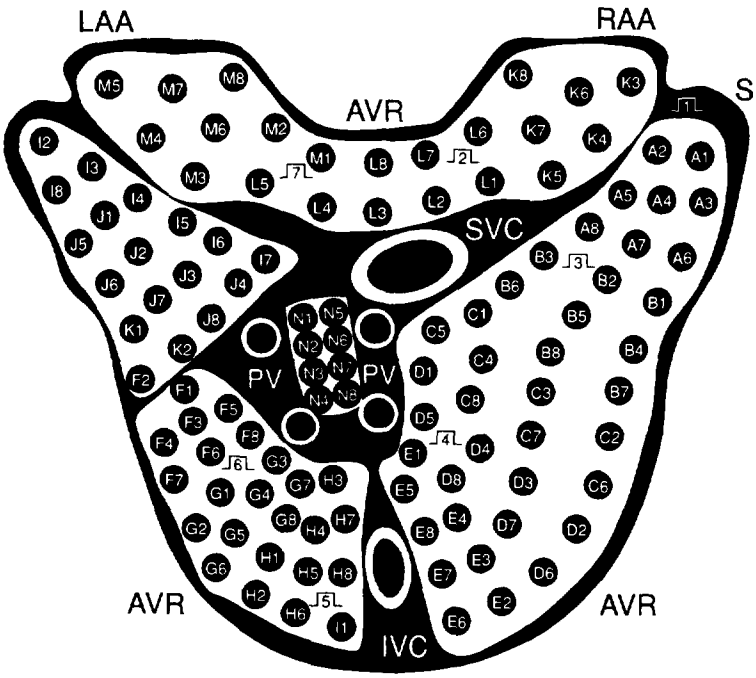

Figure 1. Diagram of the electrode arrays. The position of each recording electrode is shown by a code containing a **letter** (from A to N) and a **number** (from 1 to 8). **Numbers without letters** indicate the positions of stimulating electrodes. AVR = atrioventricular ring; IVC (SVC) = inferior (superior) vena cava; LAA (RAA) = left (right) atrial appendage; PV = pulmonary veins; S = site of stimulation used to determine the rate dependence of conduction and effective refractory period.

properties associated with the ability to sustain atrial fibrillation; 2) to relate these properties to the mechanisms underlying the ability to manifest sustained atrial fibrillation; and 3) to determine the effects of flecainide on atrial electrophysiology and the ability to sustain atrial fibrillation. A concurrent control group of 10 dogs was selected to compare results in dogs with nonvagal atrial fibrillation with more typical dogs in whom it is impossible to produce sustained atrial fibrillation in the absence of intense vagal nerve stimulation.

Methods

Adult mongrel dogs (weight 21 to 31 kg) were anesthetized with morphine (2 mg/kg body weight intramuscularly) and alpha-chloralose (100 mg/kg intravenously) and ventilated with room air supplemented with oxygen. Respiratory variables were adjusted to maintain physiologic arterial blood gases (arterial oxygen saturation >90%, pH 7.38 to 7.44). Catheters were inserted into the left femoral artery and both femoral veins and were kept patent with heparinized saline solution (0.9%). A median sternotomy was performed, and a pericardial cradle was created. Body temperature was kept constant with a homeothermic heating blanket. Two bipolar Teflon-coated stainless steel electrodes were inserted into the right atrial appendage for recording and stimulation. A programmable stimulator (Digital Cardiovascular Instruments) was used to deliver 4-ms pulses at twice-threshold current. A demand pacemaker (GBM 5880 Demand Pacemaker, Medtronic, Inc.) was used to pace the right ventricle when the ventricular rate was <90/min. A P23 1D pressure transducer (Statham Medical Instruments), electrophysiologic amplifiers (Bloom Ltd.) and a paper recorder (Astromed MT-95000) were used to record standard surface electrocardiographic leads, an atrial electrogram and stimulus artifacts. The vagus nerves were isolated in the neck, doubly ligated and divided. Nadolol was administered at an initial dose of 0.5 mg/kg intravenously, followed by 0.25 mg/kg every 2 h to produce sustained and stable beta-adrenergic blockade (11).

Atrial fibrillation model. The presence of atrial fibrillation was determined by the occurrence of a rapid (>400/min under control conditions), irregular atrial rhythm with varying electrogram configuration and cycle length. Atrial fibrillation induction was performed with a brief burst of rapid pacing at a cycle length of 100 ms and four times threshold current. The ability to maintain sustained atrial fibrillation was confirmed by the persistence of fibrillation for >30 min on at least two occasions. The six dogs that manifested sustained atrial fibrillation in the absence of vagal stimulation were assigned to the atrial fibrillation group. In the 10 control dogs, atrial fibrillation could be induced by atrial burst pacing but rarely lasted more than several seconds after induction, and it was never sustained >2 min.

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 sewn to both atria to cover the atrial epicardial surface (Fig. 1), as previously described (7,8). In addition to the recording sites, the sheets also contained six pairs of bipolar electrodes for regional stimulation.

Each signal was filtered (30 to 400 Hz), digitized with 12-bit resolution and a 1-kHz sampling rate and transmitted through duplex fiberoptic cables into a microcomputer (model 286, Compaq Computer). Software routines were used to amplify, display and analyze each electrogram as well as to generate

maps showing activation times at each electrode site (12). Interpolation techniques were used to produce isochrone maps of epicardial activation, but only measured activation times (not interpolated data) were used for quantitative analysis. Each electrogram was analyzed by the use of computer-determined peak-amplitude criteria (13,14) and was reviewed manually to exclude low amplitude signals with indiscrete electrograms. The accuracy of measured activation times was ±0.5 ms.

Experimental protocols. Activation data were acquired at the onset of atrial fibrillation, 5 min after the onset of drug administration and again at the time of atrial fibrillation termination. The acquisition system samples data continuously and stores them in a memory buffer, so that 8 s of data beginning up to 8 s before a manual trigger can be obtained. This allowed us to acquire activation data immediately before and at the time of atrial fibrillation termination.

Atrial refractoriness and conduction properties were assessed under control conditions and then after flecainide administration. Atrial effective refractory period 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 bipolar electrode sites (1.6 to 2.0 cm apart) in the line of rapid propagation was used to measure local conduction velocity by dividing the distance between the sites by the interelectrode conduction time. The activation pattern was assessed for all activations to ensure that changes in conduction time were not caused by changes in the direction of impulse propagation. The wavelength (minimal path length that can support reentry) was calculated as the product of conduction velocity and effective refractory period, as described by Wiener and Rosenblueth (15).

Results were obtained during stimulation at the right atrial appendage (Fig. 1, site 1) at basic cycle lengths of 400, 300, 250, 200 and 150 ms. Two minutes was allowed at each basic cycle length before atrial effective refractory period and conduction velocity were measured. For effective refractory period determination, a premature stimulus (S_2) was inserted after every 10 basic (S_1) stimuli, with the S_1S_2 interval decreased by 10-ms decrements until failure to capture occurred. The longest S_1S_2 interval that consistently failed to produce a propagated response was defined as the effective refractory period.

To evaluate the possible role of regional variation in refractoriness and to assess whether the effects of flecainide were exerted in a spatially uniform fashion, we determined conduction velocity, atrial refractory period, and wavelength during stimulation at a cycle length of 250 ms at each of the seven stimulation sites shown in Figure 1.

In dogs with sustained atrial fibrillation, control measurements were performed, and then atrial fibrillation was induced. After atrial fibrillation had persisted for 30 min, flecainide was infused as a loading dose of 1 mg/kg over 15 min, followed by a maintenance infusion of 1.33 mg/kg per h. Plasma drug concentrations were measured with previously described high performance liquid chromatography methods (16). After the termination of atrial fibrillation, arrhythmia induction was attempted every 10 min. For control dogs, atrial effective refractory period, conduction velocity and wavelength were determined at various basic cycle lengths and in various regions, as in dogs with atrial fibrillation. Bilateral vagal nerve stimulation was performed in control dogs with 0.1-s, 10-Hz stimuli at a voltage two-thirds the threshold for inducing 3 s of asystole to compare electrophysiologic properties of dogs with sustained atrial fibrillation with those of control dogs under conditions (vagal stimulation) permitting the induction of sustained atrial fibrillation in control dogs.

Data analysis. Group data are presented as mean value ± SE. Comparisons between group mean values were made by two-way analysis of variance with the Scheffé test (17) or Student *t* test when only two groups of results were compared. Rate-dependent and regionally determined effects of flecainide on atrial effective refractory period, conduction velocity and wavelength were evaluated by analysis of variance with an F test for interaction (17). A two-tailed probability <5% defined statistical significance.

The properties of atrial activation during atrial fibrillation were quantified in two ways. 1) The number of apparent atrial reentrant circuits was determined as previously described (7) on the basis of the number of discrete zones in which adjacent electrodes were activated at the beginning and end of a local cycle, with reactivation of the early activation zone initiating local activity in the next cycle. 2) An index of inhomogeneity of activation was calculated. We reasoned that homogeneous activation should result in orderly successive activation of adjacent electrodes in the line of propagation of the atrial impulse. When activation becomes disorganized, activation times of adjacent sites become less coupled to one another, and the differences between activation times at adjacent sites should increase. We therefore calculated the absolute value of the difference in activation times at adjacent electrode pairs and determined the average value for activation time differences at all adjacent electrode pairs. The mean activation time difference was then divided by the cycle length to determine the fraction of the overall atrial fibrillation cycle occupied by activation time differences at adjacent electrodes. The latter value was termed the index of inhomogeneity. An advantage of this index over an analysis of the number of reentrant circuits is that quantitative results are obtained without a need for an interpretation of patterns of reentry, which of necessity introduces a subjective element.

Results

Electrophysiologic properties associated with ability to manifest sustained atrial fibrillation. There were no gross configurational abnormalities in dogs with atrial fibrillation—they had no evidence of heart failure, atrial enlargement or other pathologic findings. There was no difference in size between dogs with atrial fibrillation (mean weight 22.2 ± 1.4 kg) and control dogs (mean weight 21.9 ± 0.9 kg). Table 1 compares the results obtained at a cycle length of 150 ms in

Table 1. Comparison of Electrophysiologic Variables in Dogs With Atrial Fibrillation Versus Control Dogs With and Without Vagal Stimulation (mean ± SE)

	CV* (cm/s)	ERP* (ms)	WL* (cm)	HR (beats/min)	Wenckebach CL (ms)
Dogs with AF	90 ± 4	80 ± 7	7.2 ± 0.6	123 ± 5	202 ± 6
Control dogs					
No VNS	92 ± 5	95 ± 3†	8.7 ± 0.7†	121 ± 2	198 ± 3
With VNS	108 ± 4	64 ± 5†	6.9 ± 0.5	74 ± 3‡	422 ± 12§

*Measured at basic cycle length of 150 ms. †$p < 0.05$, ‡$p < 0.01$, §$p < 0.001$ versus corresponding value in dogs with atrial fibrillation (AF). CL = cycle length; CV = conduction velocity; ERP = effective refractory period; HR = spontaneous sinus rate; VNS = vagal nerve stimulation; WL = wavelength.

dogs with atrial fibrillation to results in control dogs with and without vagal nerve stimulation. Atrial conduction velocity was not significantly different among the three groups of dogs. Atrial refractoriness and wavelength were significantly shorter in dogs with atrial fibrillation than in control dogs, and the wavelength in dogs with atrial fibrillation was not significantly different from that in control dogs subjected to vagal stimulation. Spontaneous sinus rate was substantially less and Wenckebach cycle length considerably greater in control dogs during vagal nerve stimulation than in dogs with atrial fibrillation or control dogs under basal conditions.

Figure 2 (A to C) shows the rate dependence of electrophysiologic properties in control dogs and dogs with atrial fibrillation. The overall pattern of rate dependence was similar in the two groups. However, atrial refractoriness decreased to a greater extent as pacing cycle length decreased in dogs with atrial fibrillation than in control dogs and was significantly less in these animals at the shortest cycle length (150 ms) than in control dogs (Fig. 2A). Correspondingly, the wavelength for reentry showed greater abbreviation with rate in dogs with atrial fibrillation and was significantly shorter than that in control dogs at a basic cycle length of 150 ms. In addition to showing greater rate-dependent abbreviation, the effective refractory period in dogs with atrial fibrillation showed much greater regional variability (Fig. 3). Although conduction velocity showed less regional variability than effective refractory period, conduction tended to be slower in regions of briefer refractoriness. As a result, there were large regional differences in the wavelength for reentry. The within-dog standard deviation of the effective refractory period was used as an index of regional variation in refractoriness. The standard deviation of refractoriness averaged 19 ± 3 ms in dogs with atrial fibrillation and 11 ± 2 ms in control dogs ($p < 0.01$). The standard deviation of wavelength averaged 4.3 ± 0.4 and 2.6 ± 0.3 cm in the same groups, respectively ($p < 0.05$).

The increase in regional dispersion of refractoriness in dogs with atrial fibrillation appeared to result from shorter left atrial refractory periods (Fig. 1, sites 5 to 7). Figure 4 shows regional values of atrial effective refractory period from individual dogs with atrial fibrillation and control dogs for which we had complete data from at least six of the seven stimulation sites. Dogs with atrial fibrillation (right) had consistently shorter

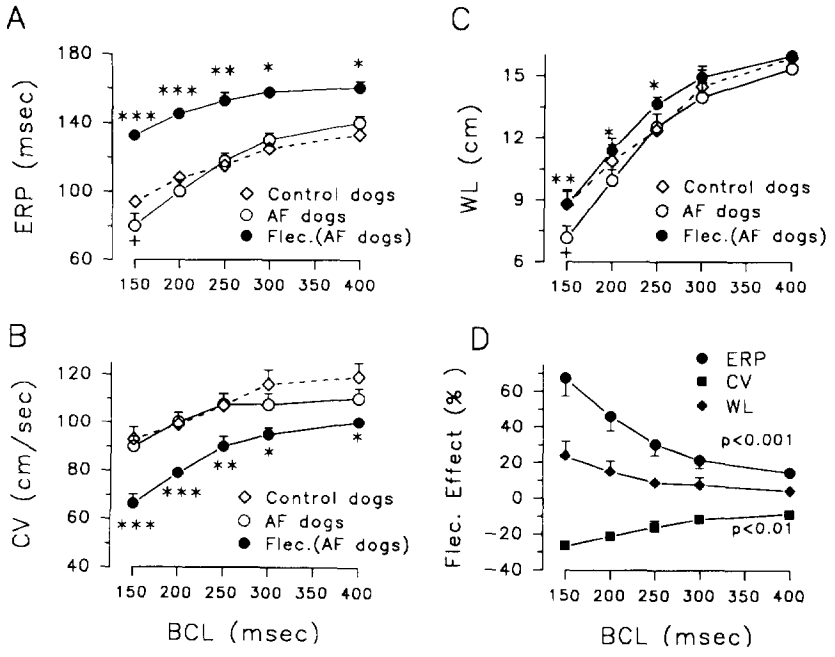

Figure 2. **A** to **C**, Rate dependence of electrophysiologic properties in dogs with atrial fibrillation (AF) and control dogs and effects of flecainide (Flec.) on dogs with atrial fibrillation. Dependence of **(A)** atrial effective refractory period (ERP), **(B)** conduction velocity (CV) and **(C)** wavelength (WL) on basic cycle length (BCL). **D**, Percent change in effective refractory period, conduction velocity and wavelength caused by flecainide in dogs with atrial fibrillation as a function of basic cycle length. Statistically significant cycle length–dependent effects were noted for effective refractory period ($p < 0.001$) and conduction velocity ($p < 0.01$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ for value before and after flecainide in dogs with atrial fibrillation at each basic cycle length. †$p < 0.05$ for dogs with atrial fibrillation versus control dogs. Results are mean ± SE.

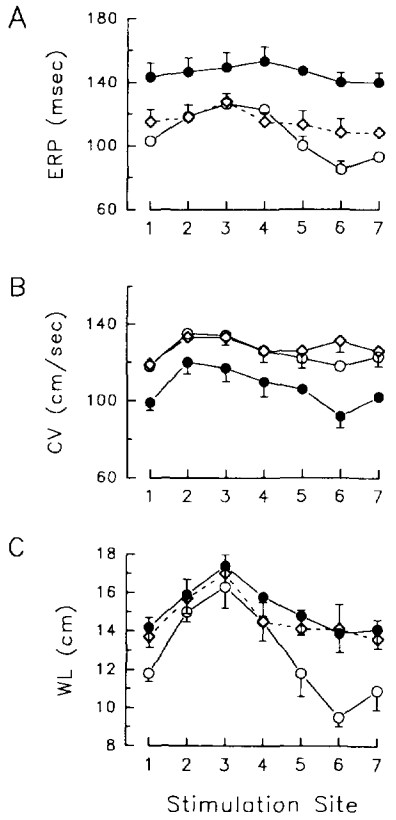

Figure 3. Regional distribution of electrophysiologic properties in control dogs **(diamonds)**, dogs with atrial fibrillation **(open circles)** and dogs with atrial fibrillation after flecainide (Flec.) **(solid circles).** Data were obtained during stimulation at a cycle length of 250 ms at each of the sites shown in Figure 1. Results are shown in **panel A** for effective refractory period (ERP), **panel B** for conduction velocity (CV) and **panel C** for wavelength (WL).

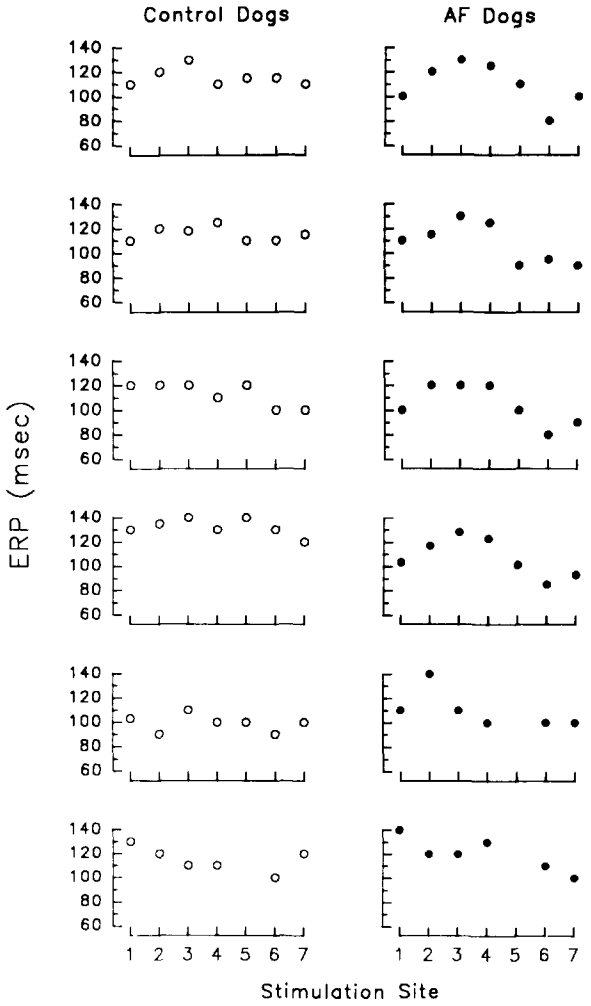

Figure 4. Examples of regional variation in effective refractory period (ERP) as measured during stimulation at a basic cycle length of 250 ms at each of the seven sites shown in Figure 1. **Left,** Results from six individual control dogs. **Right,** Results from six dogs with atrial fibrillation. Regional variation was significantly greater ($p < 0.05$, analysis of variance) among dogs with atrial fibrillation than among control dogs.

refractory periods at left atrial sites (particularly sites 6 and 7 [Fig. 1]) than the values in the rest of the atria. In contrast, effective refractory period values showed less regional variation in control dogs (left). Overall, mean regional variation in effective refractory period was significantly greater in dogs with atrial fibrillation than in control dogs ($p < 0.05$).

Activation during atrial fibrillation in control dogs and dogs with sustained atrial fibrillation. Bursts of rapid atrial pacing produced short runs of atrial fibrillation in control dogs. Atrial fibrillation induction was attempted 10 times in each control dog, and the mean duration for all control dogs was 12.1 ± 7.2 s. Activation mapping was used to relate the characteristics of atrial fibrillation to electrophysiologic properties and the ability of atrial fibrillation to sustain itself. Figure 5 (top) shows selected electrograms and activation data from a cycle of atrial fibrillation in a control dog and corresponding data from a dog with atrial fibrillation (bottom). In the control dog shown, atrial fibrillation lasted an average of 15 s (range 1 to 50). Panel B shows the activation map (with 10-ms isochronal lines) corresponding to the cycle shown by the vertical lines in A. Panel A shows electrograms from nine electrode sites activated sequentially during one functional reentrant circuit during the cycle indicated. The locations of these electrodes are indicated by the letters A through I in panel B. Corresponding data from a dog with sustained atrial fibrillation are shown in panels C and D. Note that atrial activity is much more heterogeneous in the dogs with sustained atrial fibrillation. Many more isochrones are present, and there are a larger number of apparent reentrant circuits (arrows).

These differences in activation pattern were seen consistently, as indicated by the quantitative analyses of activation pattern during atrial fibrillation shown in Figure 6. The number of simultaneous reentrant circuits during atrial fibrillation in dogs with sustained atrial fibrillation averaged 6.3 ± 0.4 and was significantly greater than that in control dogs (2.8 ± 0.5, $p < 0.01$, vs. dogs with sustained atrial fibrillation). The index of inhomogeneity averaged 0.0090 ± 0.0005 during sinus rhythm in dogs with sustained atrial fibrillation and increased

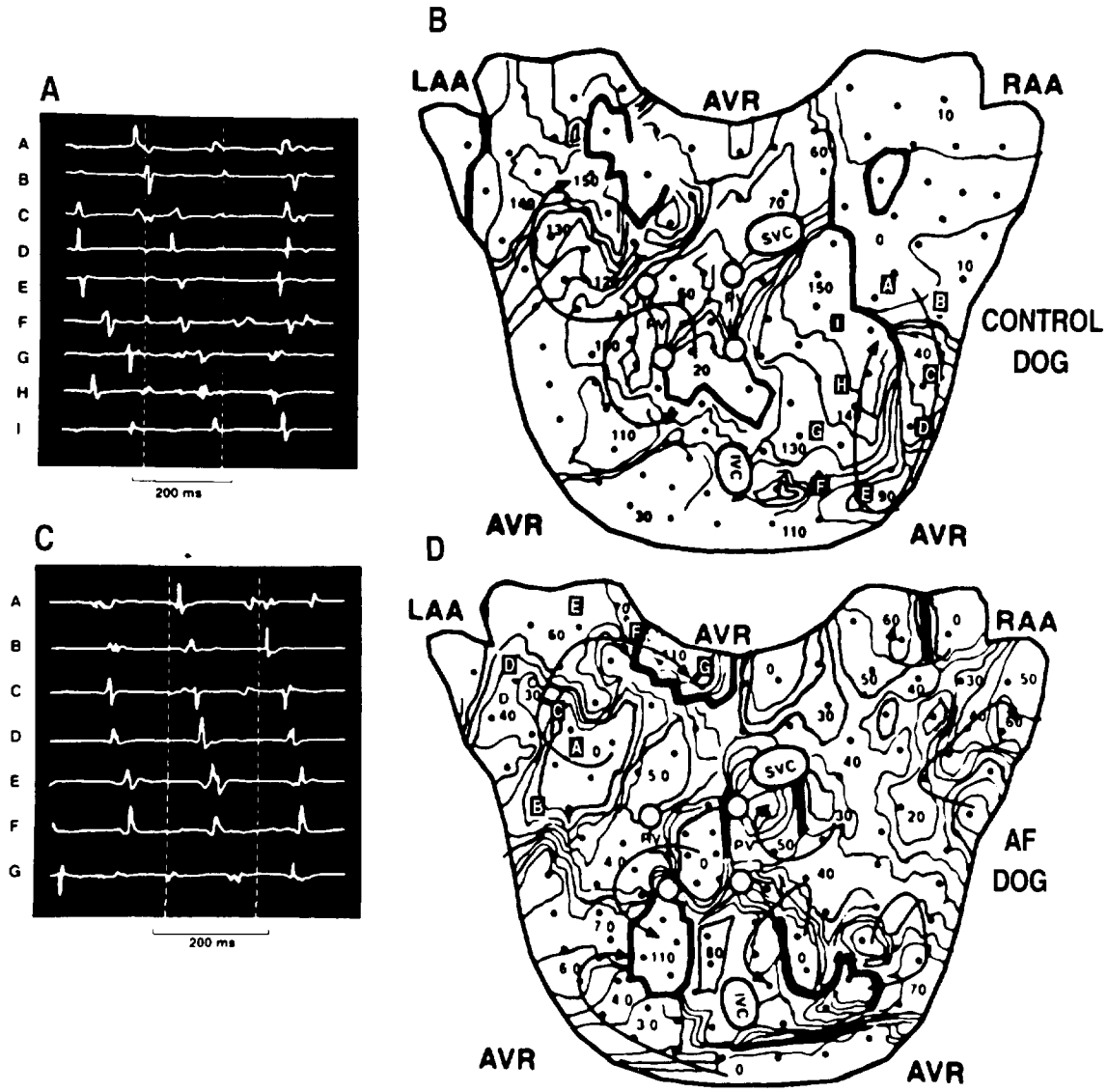

Figure 5. Electrical activity during atrial fibrillation in a control dog **(top, panels A and B)** and a dog with atrial fibrillation **(bottom, panels C and D).** Recordings from selected electrode sites are shown in **A** and **C,** and the activation maps corresponding to the cycles defined by the **vertical dashed lines** in **A** and **C** are shown in **B** and **D,** respectively. **Arrows in B** and **D** correspond to functional reentrant circuits; **lighter lines** define consecutive 10-ms isochrones, and **bolder lines** indicate zones of functional conduction block. **Numbers** are the activation time range of given isochrones, and **letters** correspond to positions of electrodes whose recordings are shown in **A** (for **letters** on activation map **B**) or **C** (for **letters** on map **D**). **Isochrones** were traced from computer-derived printouts. Abbreviations as in Figure 1.

to 0.171 ± 0.022 during atrial fibrillation ($p < 0.01$ vs. sinus rhythm). During atrial fibrillation in control dogs, the index of inhomogeneity averaged 0.050 ± 0.016, a value significantly less ($p < 0.01$) than that in dogs with sustained atrial fibrillation. These quantitative analyses indicate that atrial activation was substantially more heterogeneous in dogs with sustained atrial fibrillation than in control dogs and that the number of simultaneous reentrant circuits was considerably greater in dogs with sustained atrial fibrillation.

Efficacy of flecainide in atrial fibrillation. Flecainide converted atrial fibrillation in all dogs with sustained atrial fibrillation after a mean time of 10 min (range 7 to 14) and at a mean concentration of 1.7 ± 0.3 mg/liter, with termination of atrial fibrillation always occurring during the administration of the loading dose. After termination of atrial fibrillation, electrophysiologic variables were measured during the maintenance infusion, and then the maintenance infusion was stopped. Atrial fibrillation reinduction was attempted every 10 min after the end of the maintenance infusion, and blood samples were obtained to correlate drug concentrations with the inducibility of atrial fibrillation. During the maintenance infusion, the arrhythmia could not be induced in any dog (mean concentration 1.4 ± 0.3 mg/liter). After discontinuation of drug infusion, nonsustained atrial fibrillation became induc-

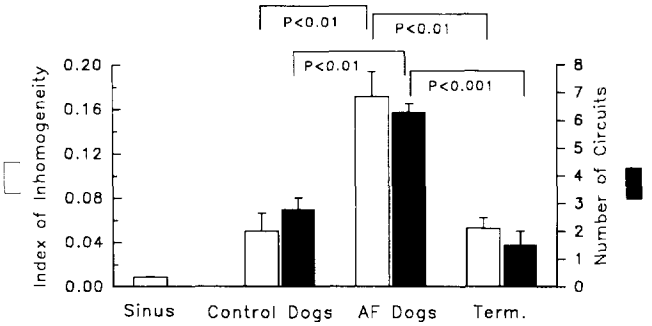

Figure 6. Index of inhomogeneity **(open bars, scale at left)** during sinus rhythm in dogs with atrial fibrillation (Sinus), during atrial fibrillation in control dogs, during atrial fibrillation in dogs with atrial fibrillation and just before flecainide-induced termination (Term.) in dogs with atrial fibrillation. Mean (±SE) number of functional reentrant circuits during a cycle of atrial fibrillation under each condition is shown by **solid bars (scale at right).**

ible at a mean concentration of 0.6 ± 0.2 mg/liter. Sustained atrial fibrillation could eventually be maintained at a concentration of 0.3 ± 0.1 mg/liter. In three dogs, sustained atrial fibrillation began spontaneously during drug washout, but in the others it was induced by burst pacing.

Effects of flecainide on activation during atrial fibrillation. Flecainide slowed atrial activation during atrial fibrillation. The mean cycle length of atrial fibrillation, determined as reported previously (7), was increased by the drug from 67 ± 7 to 123 ± 16 ms before atrial fibrillation termination ($p < 0.001$). Flecainide increased the organization of atrial activation and reduced the number of functional reentrant circuits (Fig. 6). The mean number of reentrant circuits was reduced to 1.5 ± 0.3 ($p < 0.001$) immediately before termination of the arrhythmia. The index of inhomogeneity was decreased by flecainide from 0.171 ± 0.022 before the drug to 0.053 ± 0.010 ($p < 0.01$) before termination.

The changes in atrial activation associated with flecainide-induced atrial fibrillation termination are illustrated by results from one dog in Figure 7. Panel A shows electrograms from sites corresponding to positions A to J in panels B and C. Panels B and C show activation patterns during the last two cycles of atrial fibrillation during flecainide-induced rhythm reversion. Note that overall activation is more homogeneous than before flecainide (compare with results from the same dog in Fig. 5D). Activation during the penultimate cycle (panel B) is dominated by a single figure-of-eight macroreentrant circuit. Reactivation from sites I and J to the region of sites A to C initiates the final cycle (panel C). The cycle shown in C terminates because of block in the cross-hatched zone in the lower right atrium adjacent to the atrioventricular ring (AV) (note the lack of activation at site J during the last cycle in panel A). In all cases, the termination of atrial fibrillation by flecainide was associated with an increase in the homogeneity of atrial activation and a reduced number of reentrant circuits, with activation in the final circuits terminating either by block (as in Fig. 7) or by collision of wavefronts as previously shown (8).

Effects of flecainide on electrophysiologic determinants of reentry. The rate-dependent effects of flecainide on atrial effective refractory period, conduction velocity and the minimal wavelength for reentry are shown in Figure 2. Flecainide produced rate-dependent reductions in atrial conduction velocity (panel B) and increases in atrial effective refractory period (panel A). Drug-induced changes in refractoriness exceeded those in conduction velocity, causing important increases in wavelength (panel C). Drug-induced changes in wavelength increased with decreasing cycle length (panel D), and at the shortest cycle length (150 ms) the wavelength in the presence of flecainide equaled the value in control dogs.

Regional effects of flecainide on conduction and refractoriness. Flecainide increased the effective refractory period and slowed conduction in all regions of the atria (Fig. 3). Flecainide increased refractoriness the most in zones that had the shortest refractoriness before the drug. Consequently, atrial refractoriness showed much less regional variation after flecainide (Fig. 3A), with the standard deviation of effective refractory period decreasing from 17 ± 1 to 8 ± 2 ms ($p < 0.01$). As a result of the homogenization in regional refractoriness, the wavelength became less variable, and regional wavelengths after the drug were similar to control values (Fig. 3C).

Discussion

We showed that in a subset of dogs the atria can support sustained atrial fibrillation despite bilateral vagotomy and beta-adrenoceptor blockade. The underlying electrophysiologic substrate includes reduced refractoriness and wavelength at rapid rates and a greater dispersion in atrial refractoriness. These result in increased heterogeneity of activation during atrial fibrillation, associated with a larger number of simultaneous functional reentrant circuits. Flecainide terminated atrial fibrillation by causing a tachycardia-dependent increase in atrial effective refractory period, reducing the number of reentrant circuits and the heterogeneity of atrial activation.

Factors associated with ability to manifest sustained atrial fibrillation. The importance of the reentrant path length in the physiology of atrial fibrillation was first discussed by Lewis et al. (18), who agreed with Rothberger and Winterberg (19) that short refractory periods were important to the ability to produce atrial fibrillation. Rensma et al. (1) showed that the wavelength was a critical determinant of reentrant atrial arrhythmias. A subsequent study from the same group reported a duration of atrial fibrillation in conscious (autonomically intact) dogs between 4 s and 66 min, with a mean of 211 s (2).

Vagal stimulation results in the ability to sustain atrial fibrillation as long as vagal stimulation continues and is associated with a reduced wavelength for reentry and an increased regional dispersion in atrial refractoriness (7,20–22). In the present experiments, we studied dogs that had the unusual property of supporting sustained atrial fibrillation in the absence of vagal nerve input. Two electrophysiologic

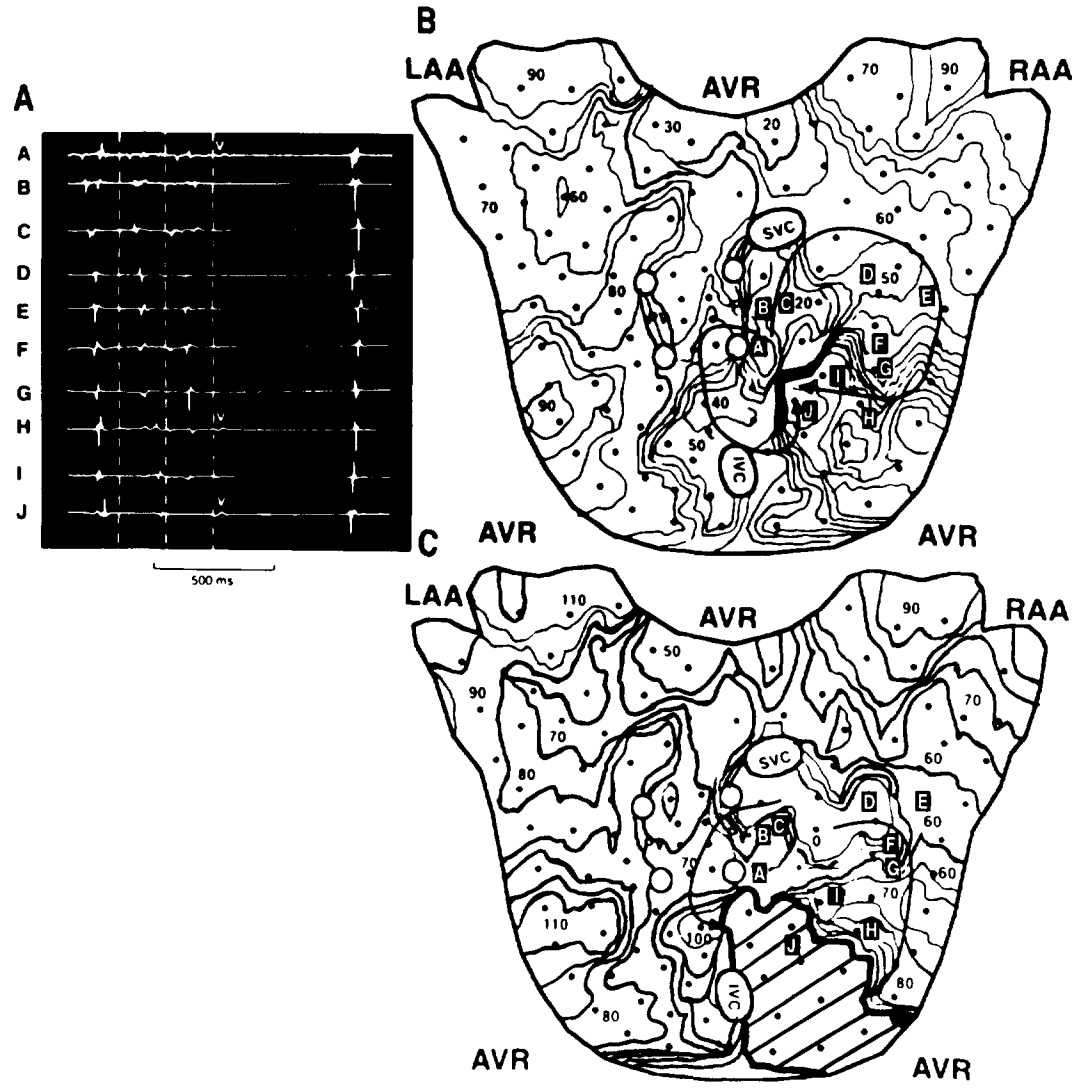

Figure 7. Selected electrograms (**A**) at time of atrial fibrillation termination by flecainide in the same dog whose activation during atrial fibrillation before flecainide is shown in Figure 5D. **B** and **C**, Activation during the last two cycles of atrial fibrillation, corresponding to intervals delineated by **dashed vertical lines** in **A**. Locations of electrode sites at which the recordings shown in **A** were obtained are indicated by **corresponding letters** in **B** and **C**. Reentry followed a figure-of-eight pattern in the cycle shown in **B**. During the last cycle (**C**), reentry is terminated by block in the **hatched area. Isochrones** were traced from computer-derived printouts. V = ventricular electrograms recorded by atrial electrodes (**A**); other abbreviations as in Figure 1.

characteristics of these dogs may have contributed to their ability to sustain atrial fibrillation: 1) These dogs manifested greater rate-dependent effective refractory period abbreviation. Consequently, they had small wavelengths for reentry at short basic cycle lengths, with a wavelength at a cycle length of 150 ms that was substantially smaller than that in control dogs (Fig. 2C) and in the same range as the wavelength of control dogs during vagal stimulation (Table 1). Activation mapping showed that during fibrillation, multiple small zones of atrial reentry coexisted in sustained atrial fibrillation dogs (Fig. 5), which requires a short wavelength according to the leading circle hypothesis (23). Multiple small circuits are essential for the maintenance of atrial fibrillation, as first proposed in Gordon Moe's "multiple wavelet" hypothesis (24,25) and subsequently demonstrated by Allessie et al. (26).

2) Increased dispersion of atrial refractoriness may have contributed to sustained fibrillation (Fig. 3 and 4). Variability in regional refractoriness may have contributed to the greater heterogeneity of activation during atrial fibrillation in dogs with atrial fibrillation, which increases the likelihood that recently excited tissue will be located near tissue recovering excitability and thus available for reactivation. Lammers et al. (27,28) have shown that inhomogeneities in conduction are important in the initiation of atrial reentry in isolated rabbit atria.

The mechanisms accounting for enhanced rate-dependent atrial refractory period abbreviation and dispersion in refractoriness in dogs with atrial fibrillation are unclear. Dogs with

atrial fibrillation showed more rate-dependent refractoriness abbreviation and regional variation than control dogs, but both groups showed the same basic qualitative properties. Thus, dogs with atrial fibrillation may present the extreme of a continuum of normal atrial refractory properties.

Mechanism of flecainide action in atrial fibrillation. Flecainide has been shown to be effective in the conversion of atrial fibrillation to sinus rhythm (29–32), in the maintenance of sinus rhythm after cardioversion (33,34) and in the prevention of atrial fibrillation paroxysms (35,36). The efficacy of class Ic drugs in atrial fibrillation appears paradoxic because this class of agents is considered to slow conduction without altering refractoriness (37), changes that would be expected to decrease the wavelength and increase the likelihood of reentry (1,23). We previously showed that flecainide reduces rate-dependent atrial action potential duration and refractoriness abbreviation, causing tachycardia-dependent increases in atrial refractory period (10,16). The present study shows that flecainide terminates sustained atrial fibrillation in the absence of cardiac vagal input by mechanisms similar to those previously described in the vagotonic model (7).

The potential ionic mechanism of the actions of flecainide on atrial tissue are incompletely understood. The drug inhibits the delayed rectifier (38) and the transient outward current (39), both of which can play a role in atrial repolarization (40,41). The rate dependence of drug action on atrial repolarization in dog atrium appears to result from sodium channel blockade, which reduces tachycardia-dependent cellular sodium loading and sodium/potassium-adenosine triphosphatase stimulation (39). Rate-dependent sodium channel block could also prolong refractoriness independently of changes in repolarization by depressing atrial excitability.

Novel aspects and potential significance of our observations. To our knowledge, the present study is the first to show that sustained atrial fibrillation can be induced reproducibly in the absence of vagal tone and beta-adrenoceptor stimulation in a subset of dogs and to study the electrophysiologic properties that account for their ability to sustain atrial fibrillation. In addition, we believe that this study is the first to evaluate the electrophysiologic mechanisms by which flecainide alters atrial activation to terminate atrial fibrillation in a model lacking enhanced vagal tone. Because the latter is unusual in patients with atrial fibrillation, these results are relevant to understanding the drug's ability to terminate atrial fibrillation in humans.

The mechanisms of idiopathic or "lone" atrial fibrillation in humans are uncertain. The majority of patients present with paroxysmal atrial fibrillation (42), and patients with drug-resistant atrial fibrillation may have a variety of focal histopathologic findings despite the absence of clinically detected cardiac disease (43). Patients with lone atrial fibrillation have a shorter atrial refractory period (44,45) and a greater dispersion of atrial refractoriness (45) than normal subjects. The ability to sustain atrial fibrillation in humans is associated with evidence of a reduced wavelength (46). Our atrial fibrillation group of dogs had a number of features in common with patients with lone atrial fibrillation. They had shorter refractory periods at rapid rates, smaller wavelengths and greater regional dispersion in atrial refractoriness than control dogs. The mechanisms permitting atrial fibrillation to be sustained in these animals may thus give insights into the mechanisms of idiopathic atrial fibrillation in humans. Dogs with atrial fibrillation showed a similar pattern but greater magnitude of rate-dependent refractoriness abbreviation and variability than control dogs. This finding raises the intriguing possibility that, at least in some patients, idiopathic atrial fibrillation may occur when atrial electrophysiologic properties are at one end of the spectrum of normal, with combinations of regional refractoriness and conduction velocity that allow atrial fibrillation to be sustained. By contrast, in at least one study (47), patients predisposed to reentrant atrial arrhythmias showed attenuated rate-dependent changes in atrial refractory period.

Limitations of the model. Although the vagus nerves were transected in all our dogs, vagal nerve endings could have released acetylcholine and contributed to the electrophysiologic properties of dogs with atrial fibrillation. Two pieces of evidence weigh against this possibility. First, although dogs with atrial fibrillation had shorter atrial refractory period and wavelength values than control dogs, their sinus rate and Wenckebach cycle length were similar to those of control dogs without vagal stimulation (Table 1); that is, there was no evidence of enhanced cholinergic action on the sinus and AV nodes. Second, vagal activation results in the shortest effective refractory period values in the right atrium and longest in the left atrium (7,20–22). In dogs with atrial fibrillation (Figs. 3 and 4), refractory periods were shortest in the left atrium (sites 6 and 7 [Fig. 1]) and longest in the right atrium (sites 2, 3 and 4 [Fig. 1]).

The ability to manifest sustained atrial fibrillation is unusual in normal dogs, as is the inducibility of sustained atrial fibrillation in patients without organic heart disease. We were therefore limited to a small study group of dogs with atrial fibrillation. Although there was no gross cardiac pathologic findings in these animals, the possibility of focal, microscopic heart disease, as noted in patients with idiopathic atrial fibrillation (43), cannot be excluded because microscopic examination of cardiac tissue was not performed.

It would have been interesting to calculate the wavelength by directly measuring the effective refractory period and conduction velocity during atrial fibrillation. Unfortunately, neither can be measured precisely during atrial fibrillation because of the nature of the arrhythmia. We assume that the wavelength at a short pacing cycle length (150 ms) is closely related to the wavelength during atrial fibrillation.

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