Proarrhythmic Effects of Flecainide

Experimental Evidence for Increased Susceptibility to Reentrant Arrhythmias

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Background. The goal of this study was to investigate the nature and electrophysiological mechanisms of the proarrhythmic effects of flecainide in Langendorff-perfused rabbit hearts. Methods and Results. A thin layer of epicardium was obtained by an endocardial cryotechnique in 10 Langendorff-perfused rabbit hearts. Six other hearts were kept intact. Programmed electrical stimulation using up to three closely coupled premature stimuli and burst pacing was used to test the inducibility of arrhythmias both during control and administration of 1 μg/ml flecainide. During control, in the thin layer of epicardium, application of one to three premature stimuli induced nonsustained ventricular tachycardia in one out of 10 hearts, and burst pacing induced nonsustained ventricular tachycardia in four hearts and sustained ventricular tachycardia in two hearts. During administration of 1 μg/ml flecainide, application of one to three premature stimuli induced sustained ventricular tachycardia in five hearts, and burst pacing induced sustained ventricular tachycardia in nine hearts. All tachycardias were based on circus movement of the impulse around arcs of functional block. During administration of flecainide, different locations of the arc of block could be found in the same heart, leading to different reentrant circuits with different cycle lengths. In the control group of six intact hearts, application of up to three closely coupled premature stimuli in all cases induced ventricular fibrillation both during control and administration of flecainide. Conclusions. Flecainide alters propagation of the impulse in thin surviving layers of myocardium in a manner that facilitates the induction of functionally determined reentry. (Circulation 1991;84:1808–1818)

Proarrhythmia is the term used for either the aggravation of an existing arrhythmia or the facilitation of new arrhythmias by antiarrhythmic drugs.1 This phenomenon has been known for many years in clinical practice and has been documented for most currently used antiarrhythmic drugs,2 especially class Ic drugs like flecainide and encainide, which have been reported to possess a high degree of proarrhythmic effects.3,4 Although some hypothetical explanations of this adverse effect have been given,5,6 no direct evidence of the electrophysiological mechanism by which class Ic drugs might be proarrhythmic has been provided. The goal of this study was to investigate the nature and electrophysiological mechanism of the proarrhythmic effects of flecainide in thin sheets of perfused rabbit epicardium.

Methods

Sixteen Flemish rabbits weighing between 3.6 and 4.4 kg were used in this study. After heparinization (1,000 IU) the animals were killed by cervical dislocation. The thorax was opened by a midsternal incision and the heart was rapidly removed and placed in cold perfusion fluid (10°C). The aorta was cannulated and the heart was connected to a Langendorff perfusion system. The coronary arteries were perfused with a pressure of 50 mm Hg, resulting in a flow of 27±5 ml/min. The millimolar composition of the perfusion fluid was NaCl 130, NaHCO3 20.1, KCl 4.0, CaCl2 2.2, MgCl2 0.6, Na2HPO4 1.2, and glucose 12. The solution was saturated with a mixture of 95% O2–5% CO2 and pH was 7.35. In 10 of the hearts, an endocardial cryotechnique was used to freeze the complete right ventricle, the interventricular septum, and the endocardial and intramural layers of the free wall of the left ventricle.7,8 Briefly, a cryprobe was inserted through the pulmonary

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artery in the right ventricle, filled with liquid nitrogen (−192°C), and maintained in place until the right ventricle was completely frozen. The heart was then immersed in a tissue bath containing perfusion fluid at 30°C. The cryoprobe was installed in the left ventricular cavity through the left atrium and the coronary circulation was temporarily interrupted. The cryoprobe was filled with liquid nitrogen and maintained in place for 7 minutes. After this period, the coronary circulation was restored, the probe was removed, and the heart was removed from the tissue bath. During the rest of the experiment, the temperature of the heart was kept constant at 37°C. As a result of this procedure, only a thin epicardial layer about 1 mm thick of the free wall of the left ventricle survived, the rest of the myocardium being completely destroyed.7,8 In contrast to a model of anatomic reentry in the rabbit ventricle in which a fixed obstacle was created in the surviving epicardial layer,8 in the present series the whole left ventricular epicardium was kept intact. In six hearts, the endocardial cryoprobe procedure was not applied and the Langendorff-perfused rabbit heart was kept intact.

Recording and Stimulation

High resolution mapping of epicardial excitation was performed using a spoon-shaped electrode containing 248 unipolar electrodes at regular distances of 2.25 mm. The computerized mapping system allowed simultaneous recording, storage, and automatic analysis of all 248 electroggrams and on-line presentation of color-coded activation maps.8,9 Programmed electrical stimulation was performed using a programmable constant current stimulator delivering square impulses of 2-msec duration at twice diastolic threshold for regular stimulation and four times diastolic threshold for the induction of premature beats. Bipolar stimulation could be performed through any pair of electrodes in the spoon electrode. Both in the intact and the frozen heart, the stimulation protocol consisted of 1) application of one, two, and three premature stimuli (S2, S3, and S4, respectively) delivered with decreasing coupling intervals after 10 basic stimuli (S1–S1) at 300-msec intervals in the frozen heart and 10 msec shorter than the sinus cycle length in the intact heart, and 2) application of trains of 10 stimuli at a regular cycle length, which was progressively decreased at 10-msec steps until one-to-one capture of the ventricle failed. If no sustained arrhythmias were induced after completion of the stimulation protocol, it was repeated at a different pacing site (up to a maximum of six different sites). After the inducibility of ventricular arrhythmias was assessed during control, 1 μg/ml flecainide (Tambocor) was added to the perfusion fluid by continuous infusion close to the aortic cannula. After 30 minutes of infusion, inducibility of arrhythmias was tested again at the same sites by using the same protocol as described above.

Measurement of Conduction Velocity and Refractory Period

Pacing at the center of the thin surviving epicardial layer of the left ventricle produced an ellipsoidal spread of propagation with fast conduction parallel to the fiber axis (longitudinal conduction) and slow conduction perpendicular to it (transverse conduction). In each experiment, longitudinal ($\theta_L$) and transverse conduction velocity ($\theta_T$) were measured both during control and 30 minutes after administration of 1 μg/ml flecainide. Conduction velocity was measured from the distance traveled by the wave front normal to the isochrones per unit of time.

The ventricular effective refractory period was defined as the shortest S1–S2 interval still resulting in a propagated premature impulse during regular pacing with an S1–S1 interval of 300 msec. The effective refractory period was determined by decreasing the coupling interval of the premature stimulus in steps of 2 msec. The refractory period was measured at the same sites in the free wall of the left ventricle that were used to test inducibility of ventricular arrhythmias both during control and during administration of 1 μg/ml flecainide. The longitudinal and transverse wave length of the impulse was defined as the mean ventricular effective refractory period times the $\theta_L$ and $\theta_T$, respectively.

Results

Effects of Flecainide on Inducibility of Arrhythmias in the Intact Heart

During control, in the series of six intact isolated rabbit hearts, programmed electrical stimulation did not induce ventricular tachycardia (sustained or nonsustained). However, application of two closely premature stimuli induced ventricular fibrillation in two hearts and application of three closely premature stimuli induced ventricular fibrillation in the remaining four hearts. Ventricular fibrillation was terminated by administration of a single dose of potassium, and after a washout period of 30 minutes, infusion of flecainide was initiated. After 30 minutes of infusion of 1 μg/ml flecainide, a similar pacing protocol was used. As during control, no ventricular tachycardias could be induced and ventricular fibrillation was induced in the same two hearts by two closely coupled premature beats and by three premature beats in the remaining four hearts (see Table 1). In Figure 1, an example is presented in which no arrhythmias could be induced by one or two shortest possible premature beats both during control (upper panel) and administration of flecainide (lower panel). However, application of three closely coupled premature stimuli induced ventricular fibrillation in both cases.

Effects of Flecainide on Inducibility of Arrhythmias in Thin Layers of Epicardium

In the series of 10 frozen hearts, during control no arrhythmias were induced by application of one or two premature stimuli. In one out of 10 hearts, a short period of nonsustained ventricular tachycardia was induced after the application of three premature stimuli. During administration of 1 μg/ml flecainide, in three out of 10 hearts sustained, regular ventricular...
lar tachycardias could be induced by two closely coupled premature beats (upper panel, Figure 2). In two additional hearts, sustained ventricular tachycardia was induced by three early premature beats. Thus, during administration of flecainide in five out of 10 hearts, sustained ventricular tachycardia could be induced by multiple premature beats compared with only a single case of nonsustained ventricular tachycardia during control (Table 1). Moreover, during control, application of burst pacing induced nonsustained ventricular tachycardia in four hearts and sustained ventricular tachycardia in two hearts, compared with induction of sustained ventricular tachycardia in nine out of 10 hearts by the same pacing protocol during administration of flecainide. In the

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VF, ventricular fibrillation; SVT, sustained ventricular tachycardia; NSVT, nonsustained ventricular tachycardia.

Figure 1. Lack of effects of flecainide on the inducibility of ventricular fibrillation in the intact heart. Both during control and during administration of flecainide, no arrhythmias were induced by application of one or two closely coupled premature stimuli (S2–S3). However, in both cases, ventricular fibrillation was induced by three closely coupled premature stimuli (S2–S4). Interstimulus intervals are given in milliseconds.

Figure 2. Proarrhythmic effects of flecainide in the frozen heart model. Upper panel: During control, application of three closely coupled premature stimuli (S2–S4) did not induce ventricular tachycardia or ventricular fibrillation. During administration of flecainide, the application of two premature stimuli induced a regular, sustained ventricular tachycardia with a cycle length of 162 msec. Lower panel: In another heart, application of three closely coupled premature stimuli during control induced a short episode of nonsustained ventricular tachycardia with a slightly irregular cycle length of 113 msec. During administration of flecainide, the same number of premature stimuli induced a sustained ventricular tachycardia with a cycle length of 199 msec. Numbers indicate interstimulus interval and cycle length of ventricular tachycardia in milliseconds.
induced by application of three closely coupled premature stimuli. During administration of flecainide, a regular sustained ventricular tachycardia with a cycle length of 199 msec resulted from the same number of premature stimuli.

**Characteristics of Ventricular Tachycardia**

The only two episodes of sustained monomorphic ventricular tachycardia induced by burst pacing during control had cycle lengths of 116 and 121 msec. In four other hearts, only short-lasting episodes of self-terminating polymorphic ventricular tachycardia with a mean cycle length of 108±6 msec were induced.

Tachycardias induced during administration of flecainide were all sustained, monomorphic, and regular. The cycle length ranged from 118 to 203 msec (mean 163±16 msec, n=17). Epicardial mapping demonstrated that the tachycardias were all based on continuous reentry of the impulse around a line of functional block. In Figure 3, the epicardial activation map and 11 unipolar electrograms recorded along the reentrant circuit during sustained ventricular tachycardia (right) is compared with the excitation of the epicardium of the left ventricle during regular pacing (left). During tachycardia, the impulse propagated in a counterclockwise direction with a cycle length of 171 msec around an arc of functional block located at the anteroinferior part of the left ventricle. The functional nature of the arc of block is demonstrated by the smooth and continuous propagation of the impulse through this area during regular pacing.

During flecainide administration, different tachycardias could often be induced in the same heart,
each one being sustained and regular with the impulse reentering around a different arc of block with a different cycle length. In one heart, four different tachycardias and in five hearts, two different tachycardias were induced. In the remaining three hearts, only a single tachycardia could be induced. In Figure 4, the experiment is shown in which four different tachycardias were obtained. The cycle length of the ventricular tachycardias ranged from 124 to 187 msec. It should be noted that the arc of block present during one tachycardia was absent during other tachycardias, emphasizing the functional nature of the conduction block. It should be stressed that during the slowest tachycardia (Figure 4, right lower panel), the impulse was circulating at a regular revolution time of 187 msec in an area that could respond in a one-to-one way during a faster tachycardia with an interval of 124 msec originating from the apex of the left ventricle (Figure 4, left upper panel). In the two hearts in which sustained reentry was induced both during control and administration of flecainide, the cycle length of the tachycardia was longer during flecainide compared with control (177 and 198 msec versus 109 and 116 msec, respectively). However, in both cases, the arc of conduction block was shorter during flecainide compared with control. In Figure 5, sustained ventricular tachycardia induced by burst pacing during control is compared with sustained ventricular tachycardia induced in the same heart by application of two premature stimuli during administration of flecainide. During control, the impulse propagated at a regular cycle length of 116 msec around an arc of conduction block that extended for about 18 mm along the mid left ventricular wall. During flecainide, sustained reentry at a regular cycle length of 198 msec occurred around an arc of conduction block situated in a similar position in the left free wall (as during control) but it measured only about 10 mm.

Initiation of Ventricular Tachycardia

In Figure 6, the complete sequence of activation during initiation of sustained reentrant ventricular tachycardia by application of two premature stimuli during administration of flecainide is shown. During regular pacing (S1–S1=300 msec), an area of localized conduction delay that was absent during control (not shown) was present in the center of the free wall of the left ventricle (local crowding of isochrones). During the first premature beat (S2) given at a coupling interval of 148 msec, this crowding of isochrones was exaggerated at different sites of the ventricle. However, the fragmented impulse was still able to propagate through these areas of local conduction delay, and collision of the various wave fronts occurred at time 118 msec. During the second premature beat (S3) given at a coupling interval of 114 msec, two lines of conduction block appeared. One line of block was located at the left part of the map at isochrone 80 msec. The second line of block was very long and extended from the midwall to the posterior border of the left ventricle (isochrones 40–50 msec). The impulse could, however, propagate through a narrow isthmus between both lines of block. As a result, the impulse arrived at the right part of the map at time 130 msec and reentered the area proximal to the line of conduction block at time 159 msec. At this site of reentry, the interval between the antegrade and retrograde activation was 120 msec. Obviously, this time period was sufficient for the cells to recover their excitability, and a continuous regular circulating activation wave with a cycle length of 145 msec was initiated around this arc of block (VT1).

Effects of Flecainide on Epicardial Conduction

At a pacing rate of 300 msec, flecainide depressed both \( \theta_L \) and \( \theta_T \) to a similar extent (27% and 26%, \( p<0.001 \); Table 2). The mean effective ventricular refractory period was prolonged by 8% (\( p<0.003 \)). Local differences in effective ventricular refractory period at the different measuring sites were small both during control (±6 msec) and after administration of flecainide (±8 msec) in a given experiment. The longitudinal and transverse wave length of the impulse were both equally shortened by flecainide (21%, \( p<0.002 \); Table 2).

In Figure 7, the activation maps during pacing at the center of the free wall of the left ventricle both during control and administration of 1 \( \mu \)g/ml flecainide are shown. In both cases, during regular pacing (upper panels, S1–S1=300 msec) the impulse propagated in an ellipsoidal pattern with fast conduction parallel to the fiber axis and slow conduction perpendicular to it. During control, \( \theta_L \) and \( \theta_T \) were 57 and 37 cm/sec, respectively. During administration of flecainide, \( \theta_L \) and \( \theta_T \) both decreased to 49 and 17 cm/sec, respectively. In the lower panels of Figure 7, the activation maps during early premature beats are given. During control (Figure 7, left panels), \( \theta_L \) and \( \theta_T \) of a first shortly coupled premature beat (S4) were 38 and 20 cm/sec, respectively. No areas of conduction delay were present, and the spread of activation remained ellipsoidal. In the right lower panel of Figure 7, the activation map of a second early premature beat (S3) is given during administration of flecainide. During this second premature beat, \( \theta_L \) and \( \theta_T \) were considerably depressed to 33 and 13 cm/sec, respectively. In addition, multiple areas of conduction delay and block occurred that disrupted the uniform ellipsoidal activation pattern.

| Table 2. Effects of Flecainide on Electrophysiological Parameters |
|------------------|----------|----------|---------|---------|---------|
|                  | \( \theta_L \) | \( \theta_T \) | ERP     | WLT     | WLT     |
| Control          | 67±10    | 31±2     | 135±7   | 9.0±1.2 | 4.3±0.3 |
| (n=10)           |          |          |         |         |         |
| Flecainide       | 49±6     | 23*±4    | 146*±9  | 7.1*±1.0| 3.4±0.5 |
| \( 1 \mu g/ml \) |          |          |         |         |         |

\( \theta_L \), longitudinal conduction velocity (centimeters per second); \( \theta_T \), transverse conduction velocity (centimeters per second); ERP, ventricular effective refractory period (milliseconds); WLT, longitudinal wave length (centimeters); WL_T, transverse wave length (centimeters). *\( p<0.003 \) vs. control.
FLECAINIDE 1 μg/ml

During each tachycardia, the impulse circulated in a different segment of the free wall of the left ventricle around arcs of conduction block. The cycle lengths of the different tachycardias were 124, 151, 164, and 187 msec, respectively. Numbers indicate local activation times in milliseconds. Isochrones are drawn at 10-msec intervals. Arrows indicate direction of propagation of the circulating impulse around the arc of functional block. LAD, left anterior descending coronary artery.
Discussion

Effects of Flecainide on Inducibility of Ventricular Arrhythmias

In the intact heart, ventricular tachycardia could not be induced by programmed electrical stimulation. However, application of multiple closely coupled premature stimuli induced ventricular fibrillation in all hearts. In the frozen heart model, burst pacing in two out of 10 experiments induced a sustained reentrant ventricular tachycardia and in four out of 10 hearts induced short-lasting episodes of nonsustained reentrant ventricular tachycardia. Ventricular fibrillation was not observed. The inability to induce ventricular fibrillation is probably related to the fact that elimination of 80% of the left ventricular wall by the cryoprocedure diminished the ventricular mass to an extent that multiple reentering wavelets could no longer be sustained.\textsuperscript{10,11} Administration of flecainide did not modify the type and mode of induction of ventricular arrhythmias in the intact heart. In all hearts, ventricular fibrillation was induced with the same number of premature stimuli as during control.

In contrast, in the frozen heart model, administration of flecainide strongly enhanced the inducibility of ventricular tachycardia and modified its mode of induction. In three out of the four hearts in which tachycardia (sustained or nonsustained) was not induced during control, sustained ventricular tachycardia was induced during administration of flecainide. In four hearts in which only nonsustained ventricular tachycardia was induced during control, sustained ventricular tachycardia was induced during administration of flecainide. In two hearts in which burst pacing was needed to induce sustained tachycardia during control, application of premature stimuli induced sustained tachycardia during flecainide administration. Thus, induction of arrhythmias in hearts without previously documented tachycardia, transformation of nonsustained tachycardias into sustained, and facilitation of the mode of induction of sustained tachycardia occurred in nine out of 10 hearts under the influence of flecainide. The tachycardias induced during flecainide were based on reentry around an arc of functional block without the involvement of a fixed anatomical obstacle. This is clearly illustrated in Figures 3 and 6, which show that the arc of block during reentrant tachycardia was not present during regular pacing. Also, in Figure 4, the functional nature of the reentrant circuits is demonstrated by the different locations of arcs of conduction block during different tachycardias in the same heart.
Figure 6. Initiation of sustained reentrant ventricular tachycardia during administration of flecainide. Four consecutive activation maps are given showing the spread of activation during regular pacing (S1), two closely coupled premature beats (S2–S3), and the first beat of a resulting sustained ventricular tachycardia (VT). All maps represent the same frontal view of the heart. Numbers indicate local activation times in milliseconds. Isochrones are drawn at 10-msec intervals. Arrows indicate direction of activation. Double bars indicate conduction block. LAD, left anterior descending coronary artery. See text for description.
Figure 7. Slowing of conduction and induction of local conduction block by flecainide. Left panels: Control maps during regular pacing (S1) and the third shortest possible premature beat (S4). Right panels: Activation maps during regular pacing (S1) and a second early premature beat (S3) during administration of 1 μg/ml flecainide. The respective interstimulus intervals are given below the electrogram. Isochrones are drawn at 10-msec intervals. The thick isochronous in the right lower map indicate local conduction block. $\theta_T$, longitudinal conduction velocity (centimeters per second); $\theta_L$, transverse conduction velocity (centimeters per second). The encircled activation times indicate the sites between which $\theta_T$ and $\theta_L$ were measured. LAD, left anterior descending coronary artery. See text for description.
From the present data, it appears that a higher incidence of local functional conduction block was responsible for the proarrhythmic effects of flecainide. During control, shortly coupled premature impulses propagated smoothly in all parts of the left ventricular epicardium. During flecainide, multiple arcs of conduction block that could be used as a substrate for reentry developed. The effects of flecainide on $g_{Na}$, threshold potential, and conduction velocity might lead to a general decrease in the capability for conduction of the impulse. Because of a general decrease in stimulating efficacy of the depolarization wave by flecainide, propagation of early premature impulses may fail at regions with a relatively low capability for conduction. Thus, flecainide may unmask the natural spatial inhomogeneities in conduction properties, resulting in areas of long conduction delays and arcs of conduction block.

In the present series of experiments, no particular areas were identified as being especially prone to conduction block, and the location of the arc of block varied in different hearts and during different tachycardias obtained in the same heart. An additional factor to be considered in the study of the mechanisms of proarrhythmia by flecainide is the shortening of the wave length of the impulse. During administration of flecainide, conduction velocity was affected to a larger extent than the refractory period, resulting in a shortening of the wave length by 21%. However, these data should be regarded with caution because the measurements were performed during regular pacing and not during tachycardia. As shown in Figure 5, because of the relatively fast conduction velocity of the impulse during control, sustained tachycardia occurred only if a very long arc of block determined a long path length of the circuit. Only in this case, the revolution time of the circuit could be longer than the refractory period of the cells involved on it. However, because of the marked depression in conduction velocity during administration of flecainide, the revolution time of the circuit was prolonged, and sustained reentry occurred in the presence of a much shorter arc of conduction block.

**Cycle Length of Ventricular Tachycardia**

In several experiments during administration of flecainide, different tachycardias with markedly different cycle lengths were induced in the same heart. In the leading circle type of reentry, the revolution time of the circuit is determined by the refractory period of the cells involved in the circuit. However, the minor differences in local refractory periods as observed in the present experiments cannot adequately explain these differences in ventricular tachycardia cycle length. During flecainide, sustained reentrant tachycardias with a cycle length considerably longer than the shortest possible pacing interval were induced. In the example given in Figure 4, the whole epicardium was activated at a regular cycle length of 124 msec during a tachycardia originating from the apex (left upper panel). Three other ventricular tachycardias occurring in the same heart all had longer cycle lengths of 151, 162, and 187 msec, respectively, indicating that the revolution time of the circuit actually was longer than the refractory period. It has been previously suggested that in anisotropic myocardium, functionally determined circuits have a small excitable gap of 20–30 msec caused by impedance mismatch and electrotonic prolongation of the action potential at the pivot points of the circuit. It is likely that the depression of the amount of membrane current generated by flecainide will enhance such a mismatch between current sources and sink at the pivot points of anisotropic circuits. This will prolong the revolution time of the circulating impulse and create a larger excitable gap in the circuit.

**Clinical Implications**

The dose of flecainide used in this experimental study is well within the therapeutic range. However, binding of flecainide by plasma proteins may result in a lower free concentration in patients. The dosage of 1 μg/ml used in the present series decreased conduction velocity by about 25% and prolonged refractoriness by 8%, which is similar to the effects observed at therapeutic doses of flecainide in clinical practice.

The possible clinical implications of our results should be regarded with caution. Although it has been shown that after myocardial infarction, thin layers of endocardium or epicardium may survive, the pathophysiological substrate after myocardial infarction is much more complex than in the thin layers of normal epicardium used in the present studies. In at least 40% of patients after myocardial infarction, a possible substrate for reentrant ventricular tachycardia is present. In a population of post–myocardial infarction patients, administration of flecainide has been recently shown to increase the incidence of sudden death. In the present study, we found that flecainide was proarrhythmic by facilitating the induction of functional reentrant circuits in thin sheets of normal epicardium. Administration of flecainide in patients after myocardial infarction might modify the conduction of the cardiac impulse in thin surviving layers in a similar way, thus favoring the initiation of small reentrant circuits and resulting in rapid ventricular tachycardias and sudden death.

**References**


**KEY WORDS** • flecainide • proarrhythmia • ventricular tachycardia • functional circuit
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