Flecainide-Induced Arrhythmia in Canine Ventricular Epicardium
Phase 2 Reentry?

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Background. We recently reported that sodium channel block can produce opposite effects on action potential duration (APD) and refractoriness in epicardial versus endocardial tissues of the canine ventricle. In addition, strong sodium channel current inhibition was found to cause loss of the action potential dome in epicardium but not endocardium, thus inducing a marked dispersion of repolarization and refractoriness between epicardium and endocardium as well as among neighboring epicardial sites. The marked heterogeneity that evolves under these conditions provides a substrate for the development of arrhythmias. Flecainide was found to induceextrasystolic activity more readily than other sodium blockers. The present study contrasts the electrophysiological actions of flecainide in canine ventricular epicardium and endocardium and examines the characteristics of flecainide-induced arrhythmias in epicardial sheets of canine ventricle.

Methods and Results. Standard microelectrode techniques were used. Flecainide (10–20 μM) produced either prolongation or marked abbreviation of APD in epicardium but only minor changes in the APD of endocardium. Marked abbreviation of APD in epicardium was due to loss of the action potential dome (plateau phase). Arrhythmias displaying characteristics of reentry could be readily induced in flecainide-treated preparations either by increasing the stimulation rate or by introduction of extrastimuli. Flecainide-induced slowing of conduction, more accentuated at the faster stimulation rates, appeared to act synergistically with the drug-induced dispersion of repolarization to generate reentry in these relatively small sheets of epicardium. 4-Aminopyridine, a transient outward current (I_{to}) blocker, reversed the flecainide-induced marked abbreviation of APD in epicardium and abolished reentrant activity in all cases. Flecainide failed to induce reentry in preparations pretreated with 4-aminopyridine.

Conclusions. Our data suggest that the presence of a prominent I_{to} in epicardium contributes the development of marked electrical heterogeneity in the ventricle after exposure to flecainide. Flecainide-induced dispersion of repolarization, especially when accompanied by prominent conduction delays, results in extrasystolic activity via a mechanism that we have termed “phase 2 reentry.” Our results also suggest a role for I_{to} blockers in the treatment of reentrant arrhythmias. (Circulation 1993;87:562–572)

Key Words • action potential duration • flecainide • arrhythmia

The recent Cardiac Arrhythmia Suppression Trial (CAST) served to highlight the proarrhythmic potential of class IC antiarrhythmic agents such as flecainide and encainide. The mechanisms responsible for the higher incidence of life-threatening arrhythmias in post-myocardial infarction patients treated with these drugs, although the subject of intense study, remain poorly understood.1

Recent studies from our laboratory have shown that inhibition of the sodium channel current can produce opposite effects on action potential duration (APD) and refractoriness in epicardial versus endocardial tissues of the canine ventricle. Moreover, strong sodium channel inhibition was found to induce a marked dispersion of refractoriness in the ventricle by causing loss of the action potential dome in epicardium but not endocardium.2 The presence of a prominent transient outward current (I_{to}) in epicardium but not endocardium was found to underlie these differences in the response of the two tissue types to sodium channel blockers as well as to other pharmacological agents.2–4

Loss of the action potential dome in epicardium after sodium blockade is usually nonhomogeneous; marked abbreviation of the action potentials is observed at some sites and prolongation at other sites. The marked dispersion of repolarization and refractoriness that evolves under these conditions provides an ideal substrate for the development of reentrant arrhythmias.2,4 A consistent observation stemming from our previous study was that flecainide induces reentry much more readily than other sodium blockers such as tetrodotoxin and propranolol (high concentration).

The present study was designed to contrast the electrophysiological actions of flecainide in canine ventricular epicardium and endocardium and to define the characteristics of and factors contributing to flecainide-induced arrhythmias in epicardial sheets of canine ventricle.

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Received March 11, 1992; revision received October 8, 1992.
**Methods**

Papillary muscles, right ventricular trabeculae, and right ventricular epicardial strips (approximately 2.0×1.5×0.2 cm) were isolated from hearts removed from anesthetized (sodium pentobarbital, 30 mg/kg body wt) mongrel male dogs (weight, 18–26 kg). The epicardial preparations were obtained by razor blade shavings (Davol Simon Dermatome Power handle 3293 with cutting head 3292) made parallel to the fiber orientation in the right ventricular free wall. Data from papillary muscles and trabeculae are grouped together in the presentation of results. No significant differences could be discerned between the activity or responsiveness to drug of intact papillary muscles and that of strips shaved from the surface of these muscles. The terms endocardial and epicardial in this report refer to the muscle cells on the respective surfaces of the ventricular wall representing the outermost subendocardial and subepicardial layers.

Epicardial and endocardial preparations from the same heart were placed in a tissue bath and allowed to equilibrate while superfused with an oxygenated (95% oxygen, 5% carbon dioxide) Tyrode’s solution (37±0.5°C; pH 7.35). Unless otherwise indicated, the composition of Tyrode’s solution was (in mM): NaCl 129; KCl 4; NaHPO₄ 0.9; NaHCO₃ 20; CaCl₂ 1.8; MgSO₄ 0.5; and d-glucose 5.5.

The tissues were stimulated at basic cycle lengths (BCL) ranging from 200 to 2,000 msec using rectangular stimuli (1–3 msec-duration, 2.5 times diastolic threshold intensity) delivered through silver bipolar electrodes insulated except at the tips. Transmembrane potentials were recorded from one or more sites with the use of glass microelectrodes filled with 2.7 M KCl (10–20-M Ω direct current resistance) connected to a high-input impedance amplification system (WPI). Amplified signals were displayed on an oscilloscope (Tektronix, Beaverton, Ore.) and photographed on a 35-mm kymographic camera (Grass) or recorded on FM tape (A.R. Vetter Co., Redersburg, Pa.). The maximal rate of rise of the action potential upstroke (dV/dtₘₚₜ or Vₘₚₜ) was measured with a differentiator adjusted for linearity within the range of 50–500 V/sec. The duration of the action potential was measured as the interval between the upstroke and 50% or 90% repolarization of the action potential (APD₅₀ or APD₉₀). Care was taken to avoid transitional cells in obtaining data representative of ventricular endocardium. In the case of papillary muscles, recordings were always made from the apical region, known to be devoid of Purkinje fibers.

Experiments were not started until the preparations were fully recovered and displaying stable electrophysiological characteristics. In the case of the epicardial sheets, this sometimes took 3 or more hours; the spike-and-dome morphology of the epicardial action potential was usually much attenuated when the tissue was first introduced into the bath and recovered slowly as the tissue hyperpolarized (washout of residual catecholamines leaking out of sympathetic nerve endings may have contributed to this).

Restitution of action potential variables (i.e., progressively changes in the action potential characteristics of premature beats as they are introduced progressively later in diastole) was determined with the use of single test pulses (S₂) delivered after every 15th basic beat (S₁). The S₁S₂ coupling interval was increased progressively from the end of the refractory period until the next basic beat. The effective refractory period was defined as the longest S₁S₂ interval at which S₂ failed to elicit a propagated response.

**Drugs**

4-Aminopyridine (Sigma Chemical Co., St. Louis, Mo.) was dissolved in distilled water and made soluble by warming to yield a stock solution of 0.5 M. The pH of the stock was adjusted to 7.4 with HCl. Because 4-aminopyridine has been reported to cause release of neurotransmitters from adrenergic and cholinergic nerve endings, the release of neurotransmitters from adrenergic and cholinergic nerve endings, the combination of propranolol (0.3 μg/ml), phentolamine (1.0 μg/ml), and atropine (1.0 μg/ml) was used in earlier studies. Use of these agents was discontinued when it was determined that they did not alter the actions of 4-aminopyridine. Flecainide acetate (3M, St. Paul, Minn.) was used in concentrations ranging from 5 to 20 μM.

**Results**

Figure 1 illustrates the differential effects of flecainide on isolated canine ventricular epicardium and endocardium. The right panel shows a progressive decrease in Vₘₚₜ, amplitude, and duration (at 50% repolarization) of action potentials recorded from a papillary muscle preparation during 40 minutes of exposure to flecainide (15 μM). In contrast to the abbreviation of APD₅₀ and slight prolongation of APD₉₀ in endocardium, flecainide produced a prominent prolongation of both APD₅₀ and APD₉₀ in epicardium after 30 min (Figure 1, left). Attending the prolongation of APD was an increase in the delay between the upstrokes of phases 0 and 2, a diminution of the amplitude of phases 0 and 1, and a decrease in Vₘₚₜ (bottom trace). After 40 minutes of exposure to flecainide, a further decrease in the amplitude of phase 1 of the epicardial action potential results in an all-or-none repolarization and loss of the action potential plateau or dome. The premature repolarization of the action potential at the end of phase 1 results in a marked abbreviation of the epicardial response.

The differential responsiveness of epicardium and endocardium to flecainide is thought to be due to a dissimilar response of the two tissue types to sodium blockade. In epicardium, drug-induced block of the sodium channels causes a diminution of phase 0. Because phase 1 begins at less positive potentials and because the contribution of net inward current is weaker, phase 1 proceeds to more negative potentials at which the availability of IC₅⁺ is diminished. As a consequence, the second upstroke giving rise to phase 2 (plateau) of the action potential may be slowed and the start of phase 3 may be delayed, resulting in a prolongation of APD.

With greater inhibition of IC₅⁺, the relative influence of IC₉⁺ would be greater, resulting in termination of phases 0 and 1 at still more negative potentials. Net outward current during phase 1 could overwhelm IC₅⁺ and any slowly inactivating sodium current (or sodium window current), thus causing an all-or-none repolarization. The failure of these inward currents to overcome the
Flecainide (15 μM) prolonged APD in endocardium more pronounced at faster rates of stimulation. After 30 minutes of exposure to 15 μM flecainide, endocardial APD prolonged 3.4% (6.1±9.2 msec, n=7) at a BCL of 1,000 msec and 9.9% (14.9±10.4 msec, n=7) at a BCL of 300 msec. The examples presented in Figure 2B illustrate the rate-dependent changes in APD in representative epicardial and endocardial preparations before and after 45 minutes of exposure to 6 μM flecainide. In endocardium (Figure 2B), flecainide caused a flattening of the APD-rate relation. In epicardium, flecainide prolonged APD at both slow and rapid stimulation rates (Figure 2A).

With higher concentrations of flecainide, an altogether different APD-rate relation was observed in epicardium (Figure 3). The APD-rate relation recorded from epicardial and endocardial tissues of the same heart 30 minutes after exposure to 15 μM flecainide are shown. In epicardium, an increase in the rate of stimulation led to a markedly abbreviated action potential caused by abolition of the action potential dome. Thus, flecainide caused a steepening of the APD-rate relation in epicardium (Figure 3C). In endocardium, however, APD became virtually rate independent. A

**FIGURE 1.** Traces show effects of flecainide (F, 15 μM) in isolated canine ventricular epicardial and endocardial tissues. Transmembrane recordings (top) and Vmax (bottom) traces obtained before (solid lines) and after exposure (dotted lines) to flecainide. Basic cycle length, 500 msec.

**FIGURE 2.** Graphs show rate dependence of action potential duration (APD) in isolated canine epicardium (panel A) and endocardium (panel B) in the absence and presence of 6 μM flecainide. APD measured at 90% repolarization is plotted as a function of the basic cycle length (BCL).
nearly flat APD-rate relation was observed in six of seven endocardial preparations exposed to similar concentrations of flecainide. A prominent dispersion of repolarization develops between the two tissue types at faster stimulation rates.

The dispersion of repolarization induced by high concentrations of flecainide is both rate and time dependent. Figure 4 illustrates restitution characteristics of transmembrane responses recorded from an epicardial and endocardial preparation after exposure to flecainide (15 μM) at two basic stimulation rates (basic cycle length [BCL], 500 or 2,000 msec). Panel C: Action potential duration measured at 90% repolarization in epicardium and endocardium is plotted as a function of the basic stimulating cycle length.

Loss of the dome in epicardium was usually heterogeneous, with different sites displaying distinctive rate- and time-dependent behavior. Figure 5 illustrates the restitution of APD at three sites within the same epicardial preparation. APD is plotted as a function of the S1S2 coupling interval (BCL, 2,000 msec) recorded after exposure of the preparation to 15 μM flecainide. During basic stimulation, all three sites showed brief action potentials in which the dome was absent. Restoration of the dome at the three neighboring sites occurred at S1S2 intervals ranging between 340 and 530 msec. A marked dispersion of repolarization was therefore observed after premature beats introduced during this window in time.

Flecainide-induced dispersion of repolarization between epicardium and endocardium as well as among
different epicardial sites sets the stage for a variety of arrhythmic manifestations, as illustrated in Figures 6–11.

Figure 6 contrasts the response of epicardium and endocardium to a change in stimulation rate after exposure to 15 μM flecainide. Acceleration from a BCL of 2,000 msec to 500 msec caused only a slight reduction in the amplitude of the action potential in endocardium. In epicardium, acceleration caused a large decrease in the amplitudes of phases 0 and 1 and loss of the dome at the recording site. An electrotonic deflection occurring during phase 3 of the abbreviated epicardial response suggests that neighboring epicardial sites may have retained the dome. The local circuit currents that would be expected to flow under these conditions are probably responsible for the appearance of the extrasystolic response.

In a series of nine experiments, we examined the characteristics of flecainide-induced arrhythmic activity in canine ventricular epicardial preparations using multiple simultaneous recordings from the same preparation. Flecainide (10–20 μM) induced extrasystolic activity in six of the nine preparations studied.

Figure 7 shows transmembrane recordings obtained from two sites along an epicardial sheet pretreated with flecainide (15 μM, 40 minutes). At a BCL of 1,000 msec, both sites displayed action potentials lacking a dome. A premature stimulus introduced at an S\textsubscript{1}S\textsubscript{2} of 145 msec elicited a response at the proximal site, which was devoid of a dome, but one at the distal site, which alternated between two morphologies: one in which the dome was partially restored (trace 1) and another in which the dome was fully restored (trace 2). The longer distal response (trace 2) was attended by the appearance of an extrasystole at the proximal site. Although the mechanism responsible for reexcitation of the proximal site cannot be definitively discerned from the limited data available, the results suggest that electrical heterogeneity in response to flecainide precipitates reentrant reexcitation of the tissue. The large voltage gradient that develops between the short and long APD sites would be expected to generate fairly significant local circuit currents that could act to electrotonically depolarize sites exhibiting brief refractory periods, thus effecting reentrant reexcitation of the tissue. The lack of a reentrant response after the shorter distal S\textsubscript{2} responses (trace 1) may be due to a weaker and briefer electrotonic influence expected under these conditions.

Figure 8 illustrates a variation of this phenomenon in which reciprocating reentry between two epicardial sites is precipitated by a closely coupled extrastimulus. Transmembrane recordings were obtained from two sites proximal and distal to the stimulating electrodes in an epicardial sheet exposed to flecainide (15 μM, 35 minutes). The first beat in each trace is the ninth of a train of 10 basic beats (BCL, 500 msec). The action potential dome is absent during basic stimulation. A premature stimulus (S\textsubscript{2}) introduced with a coupling interval of 150 msec elicits a response devoid of a dome at the proximal site but one with a fully restored dome at the distal site. A local reentry appears to occur at the proximal site. As a consequence of the reentry, time relations are altered such that the next basic beat (S\textsubscript{1}') elicits an action potential with a dome at the proximal site but not at the distal site. The dispersion of repolar-
The increase in rate caused a slowing of conduction and loss of the dome at the two proximal sites but not at the distal site. The delay in conduction of the impulse to the distal site coupled with the delay in the appearance of the second upstroke (dome) serve to facilitate reentrant reexcitation of the proximal site. Retrograde propagation of the dome of the distal response appears to be responsible for reexcitation of the proximal sites. Thus, the tachycardia-induced dispersion of repolarization and slowing of conduction appear to act synergistically to generate extrasystolic activity exhibiting reentrant characteristics in ventricular epicardium exposed to flecainide.

Distinguishing between circus movement and reflected reentry is difficult without very sophisticated mapping techniques. However, recordings such as those presented in Figure 10 suggest that a form of reflection may be responsible for some cases of flecainide-induced reentry. The three traces in Figure 10 were recorded from the same preparation illustrated in Figure 9: Panels A–D, recorded at a BCL of 450 msec, illustrate the sequential electrotonic interactions leading to the generation of reentrant excitation of the proximal sites (top traces). Panels A and B illustrate the electrotonic influence of the dome of the distal action potential on the proximal recording shown in the middle trace. The subthreshold depolarizations are temporally aligned, suggesting that they are electrotonic images of activity occurring at the distal site. When these electrotonic depolarizations achieve threshold, the proximal sites exhibit extrasystolic activity (Figures 10C and 10D). The electrotonic interactions manifest are similar to those seen in models of reflection and suggest that reentrant excitation under these conditions need not involve a circuitous pathway.

Figure 11 illustrates an example of a double reentry in an epicardial preparation pretreated with 20 μM flecainide and stimulated at a BCL of 300 msec. Here
again, slow conduction and heterogeneous repolarization give rise to complex electrotonic interaction that make possible multiple reentries in a relatively small strip of isolated canine epicardium. Two successive reentrant responses (R₁ and R₂) are observed at the proximal (top) epicardial site.

Our results suggest that the prominent presence of an Iₐ₉-mediated spike and dome morphology in epicardium but not endocardium may be responsible for the development of electrical heterogeneities within epicardium and between epicardium and endocardium after exposure to flecainide. Electrotonic forces thus engendered are thought to underlie drug-induced arrhythmogenesis. As a test of this hypothesis, we examined the effects of 4-aminopyridine (4-AP), an Iₐ₉ blocker. 4-AP, in concentrations known to selectively block Iₐ₉ (0.5 mM), promptly restored the action potential dome in epicardium, thus eliminating the flecainide-induced dispersion of repolarization (Figure 12). 4-AP (0.5 mM) readily abolished flecainide-induced extrasyystolic activity in two of two preparations and prevented flecainide-induced arrhythmogenesis in two other preparations (two of two).

**Discussion**

Flecainide has been shown to be effective against a wide variety of arrhythmias including those induced by coronary artery occlusion, ouabain, chloroform-epinephrine, and aconitine.5,6 Its potent antiarrhythmic efficacy notwithstanding, flecainide has been shown to be among the most arrhythmogenic or proarrhythmic of agents.7-13 The electrophysiological mechanisms underlying the proarrhythmic actions of flecainide and other class IC agents unfortunately are not well understood.

The ability to inhibit sodium channel current in cardiac tissues is a property shared by many antiarrhythmic drugs, class I agents in particular. Class I antiarrhythmics are generally divided into three categories, IA, IB, and IC, based largely on the rates at which they bind and unbind from the sodium channel. Class IC drugs are the slowest to dissociate (unblock); flecainide falls into this group. Binding primarily to activated sodium channels,14 flecainide is capable of producing strong use-dependent block of the sodium channel.15-17

Sodium current inhibition has been shown to produce different and in some cases opposite electrophysiological responses in canine ventricular epicardium and endocardium.2 Sodium blockade with tetrodotoxin and propranolol abbreviates the action potential in endocardium but prolongs it in epicardium. The paradoxical prolongation of APD in epicardium was suggested to be due largely to a decrease in the amplitude of phases 0 and 1 (secondary to sodium channel block), which in turn alters the intensity and kinetics of some ionic currents, causing subsequent phases of the epicardial response to be shifted with respect to time and voltage. In this schema, a decrease of inward current in the early phases of the action potential would cause termination

**Figure 10.** Traces of sequential electrotonic interactions underlying the development of epicardial reentry. Transmembrane responses from three sites in an epicardial preparation pretreated with flecainide (20 μM) are shown (basic cycle length, 450 msec). See text for further description.

**Figure 11.** Traces of double reentry induced by flecainide. Transmembrane activity recorded from two sites proximal (top traces) and one distal (bottom trace) to the stimulating electrodes in an epicardial preparation pretreated with flecainide (20 μM). Basic cycle length, 300 msec. Tachycardia-dependent slowing of conduction and heterogeneity caused two consecutive reentrant responses (R₁ and R₂) at the proximal site.
of phase 1 at more negative potentials. The diminished availability of calcium current at these more negative potentials would slow the emergence of the second upstroke. Inhibition of the slowly inactivating “window” sodium currents by the sodium blockers may also contribute. The delay in the development of the second upstroke and the increased plateau height sometimes observed under these conditions would then cause a delay in the start of final repolarization, resulting in a prolongation of APD.

Flecainide differs from tetrodotoxin and propranolol in that accentuation of the spike and dome is not accompanied by an increase in the voltage of the peak plateau (possibly caused by an effect of the drug on calcium currents at concentrations >10 μM).  

Stronger inhibition of sodium current leads to loss of the action potential dome and marked abbreviation of the action potential of epicardium but not endocardium (Figures 1, 3, 4, and 6). The same basic mechanism outlined above may explain this action of flecainide. As termination of phase 1 shifts to more negative potentials, the availability of ICa is diminished, and outward currents may overwhelm the inward currents active at the end of phase 1, resulting in an all-or-none repolarization and marked abbreviation of APD.

Thus, flecainide causes either prolongation or marked abbreviation of APD90 in epicardium (Figure 1) but only a slight prolongation (Figure 1) or abbreviation (Figure 3) in endocardium. Flecainide has been reported to produce a dose-dependent prolongation of APD90 in mammalian ventricular myocardial tissues16,18,19 and in human, guinea pig, rabbit, and dog atrial tissues20-22 but a dose-dependent abbreviation of APD90 in canine Purkinje fibers.18  

Our observation of greater flecainide-induced prolongation of APD at faster stimulation rates or with premature beats is consistent with previous reports.21,22 Flecainide is somewhat unique among antiarrhythmic drugs in producing a tachycardia-dependent prolongation of the action potential; most drugs that prolong APD show bradycardia dependence (e.g., quinidine, 4-AP, clofilium, amiloride). Amiodarone is the only other agent known to cause greater prolongation of APD at faster rates.23 This behavior is unexpected because the profound use-dependent block of the sodium channels produced by flecainide would be expected to abbreviate rather than prolong the action potential after acceleration of the stimulation rate. These effects of the drug suggest that flecainide blocks more than just sodium channels. Indeed, Follmer and Colatsky24 recently demonstrated that flecainide also blocks the delayed rectifier potassium current (IK) in cat ventricular myocytes. A possible explanation for the tachycardia dependence of flecainide’s effect of prolonging APD may be that the drug preferentially binds to the open (activated) state of the potassium channel.25

Our observation of a greater prolongation of APD in ventricular epicardium compared with endocardium is concordant with the findings of Le Grand et al25 showing that flecainide-induced APD prolongation is greater in human atrial fibers displaying a spike-and-dome action potential configuration. In that study, as in ours, elimination of the notch (spike and dome) using the transient outward current blocker 4-AP greatly reduced the flecainide-induced prolongation of APD.

In a previous study, we described the ability of flecainide and other sodium channel blockers to induce postrepolarization refractoriness and to markedly depress excitability in a use-dependent manner in epicardium but not endocardium.2 This effect of the sodium channel blockers produced an inversion of the normal effective refractory period–rate relation in epicardium; refractoriness was observed to increase dramatically at faster stimulation rates. This effect of flecainide in epicardium and its effect of flattening the APD–rate relation in endocardium (Figures 2 and 3) approach the behavior expected from an “ideal” antiarrhythmic drug.25

Sodium channel inhibition appears to contribute to both the antiarrhythmic as well as proarrhythmic actions of flecainide, since drug-induced block of the sodium current is the primary factor responsible for loss of the action potential dome and the development of electrical heterogeneity in epicardium. A proarrhythmic effect of sodium channel blockade has been demonstrated in other in vitro (guinea pig) and mathematical models.13,26 Reduction in sodium channel availability was shown to increase the vulnerable period during which a premature stimulus could elicit repetitive activity.

**Electrical Heterogeneity and Arrhythmias**

Flecainide-induced abolition of the action potential dome in canine ventricular epicardium but not endocardium leads to the development of a prominent dispersion of repolarization in tissues spanning the ventricular wall (Figure 3). Dispersion of repolarization also occurs in epicardium because of the loss of the dome at some sites but not others (Figure 5). This heterogeneity contributes importantly to the arrhythmogenicity of the drug (Figures 6–11).

Extrasystolic activity is much more easily induced with flecainide than with other sodium blockers in isolated epicardium.2 This may be due to the fact that profound sodium channel block and thus marked dispersion of repolarization can occur at relatively slow stimulation rates. This is possible because flecainide's
strong use-dependent block of the sodium current allows for the development of potent sodium channel block at rates that permit ample time for recovery of the transient outward current. The combination of potent 1Na block and high availability of 1Na strongly favors the loss of the dome and the development of electrical heterogeneity and arrhythmic activity. The degree to which flecainide’s inhibition of 1Na and 1K contributes to these phenomena remains to be determined. Block of 1K could serve to further intensify the differences in repolarization times by prolonging APD in endocardium at a time when the epicardial action potential is markedly abbreviated because of loss of the dome.

To explain the differential effects of flecainide on epicardium and endocardium, we considered the hypothesis that differences in the responsiveness of the two tissues to the drug were due largely to the presence of an 1La-mediated spike and dome (notch) in epicardium but not endocardium. The time and rate dependence of the flecainide-induced effects (Figures 3 and 4) and the elimination of major differences in the responsiveness of the two tissues to flecainide after treatment with the 1La blocker 4-AP (Figure 12) provide strong evidence in support of this hypothesis. Variations in the intensity or availability of 1La may also underlie differences in the responsiveness of different epicardial sites to flecainide. Consistent with this hypothesis is the observation that flecainide-induced dispersion of APD was greatly reduced and arrhythmias suppressed after the introduction of 4-AP.

Epicardial preparations exposed to relatively high concentrations of flecainide show two prominent changes in response to acceleration of the stimulation rate: 1) rate-related slowing of conduction accompanied by activation delays at discrete sites and 2) development of large differences in repolarization times among neighboring sites. Slowing of conduction in the absence of dispersion of repolarization was never observed to give rise to arrhythmic activity in our preparations. Slowed or delayed conduction, however, appeared to contribute importantly to the induction of reentrant activity when dispersion of repolarization was present. This synergism between delayed conduction and heterogeneous repolarization would be expected to be especially important in diseased hearts. Indeed, clinical reports describe an increased predisposition for development of flecainide-induced arrhythmias in patients with structurally diseased hearts.10,11

Physiological and Clinical Implications

The mechanisms responsible for cardiac arrhythmias have generally been categorized under two major headings: 1) enhanced or abnormal impulse formation and 2) reentry. Reentry occurs when a propagating impulse fails to die out after normal cardiac activation but persists to reexcite the heart after the expiration of the refractory period.27 The flecainide-induced extrasystolic activity observed in our epicardial preparations appears most consistent with a reentrant mechanism. Although the precise mechanism responsible cannot be discerned from the limited data available in this study, our results suggest that flecainide-induced dispersion of repolarization gives rise to electrotonic currents that cause reentrant excitation via a circus movement mechanism or a mechanism akin to reflection.

In typical reflection, delayed conduction of the impulse permits local circuit (electrotropic) current generated by activation of distal sites to depolarize the proximal tissue and thus reexcite the preparation.28-32 In the case of flecainide-induced reentry, it is the appearance of a prominent action potential dome at some sites but not others that generates local circuit currents that cause reexcitation. In other words, it is the propagation of the action potential plateau across the same pathway (reflection) or alternate pathway (circus movement) used for propagation of phase 0 that is responsible for reentry. This is a novel mechanism that we have termed “phase 2 reentry.”

It is noteworthy that we have observed similar phenomena in canine ventricular epicardial sheets exposed to simulated ischemia or pinacidil.4,33,34 A more definitive assessment as to whether and to what extent reflection or circus movement mechanisms are involved must await high-resolution mapping.

The contribution of other mechanisms, namely enhanced and abnormal impulse formation, are discounted based on our failure to observe activity consistent with early or delayed afterdepolarizations or any form of pacemaker activity in hundreds of microelectrode impalements performed in the course of this study. This is not surprising, in view of the fact that flecainide is thought to be quite effective in suppressing rather than promoting arrhythmias caused by triggered activity and abnormal automaticity.

The concept of heterogeneous repolarization as the basis of arrhythmogenesis is by no means a new one (see References 35-39). When repolarization of transmembrane activity at some site within a syncytium outlasts repolarization at an adjacent site, local circuit current flows in proportion to the voltage gradient between the two sites. If of sufficient magnitude, this electronic current can reexcite the earlier repolarizing site by bringing local cells to their threshold potential. When late repolarization at a distal site is due to conduction delay between proximal and distal tissues, reexcitation of the proximal tissue is said to be due to reflection or reflected reentry.28,32,40-46 When delayed repolarization is secondary to the development of early afterdepolarization–induced active responses, reexcitation is said to be due to triggered activity. Finally, when caused by marked differences in APD, “focal reexcitation”38,47,48 and “prolonged repolarization-dependent reexcitation”49 have been suggested. Direct evidence for the last mechanism has long been lacking, and the concept itself has been the subject of some controversy. Moe and Mendez20 argued that major differences in APD could not occur between well-coupled cells because electrotonic forces would act to equalize intrinsic differences in action potential morphology. They considered abrupt transitions in APD to be possible only in poorly coupled cells and suggested that if electrotonic currents are too weak to equalize APD, they are also likely to be too small to effect reexcitation. Indeed, this type of reexcitation has not been demonstrated previously in tissues known to be devoid of pacemaker (phase 4 depolarization) or afterdepolarization activity.

A mere difference in APD (within limits) between adjacent cells does not appear to be sufficient to induce this type of focal reexcitation. Additional factors probably contribute to the reexcitation observed in our
flecainide-treated epicardial preparations. Chief among these is the depolarizing influence of a prominent second upstroke that is unique to the epicardial action potential. The voltage gradient between heterogeneous epicardial sites does not simply decay with time as in other tissues but increases transiently during the development of the action potential plateau; the result is an additional burst of depolarizing current that can reexcite the site at which a plateau has failed to develop. The development of a distinct phase 2 is therefore critical to the process we termed phase 2 reentry. Another factor that may facilitate the process, although not a prerequisite, is a slowing of conduction. Such slowing, commonly seen with flecainide, accentuates the dispersion of repolarization but also allows for the development of phase 2 later, after full repolarization and recovery of excitability at the site at which the plateau has failed to develop.

It has been suggested that many out-of-hospital cardiac arrest events recorded each year may be related to the use of drugs intended to prevent arrhythmias. In the CAST study, patients randomized to treatment with encainide and flecainide experienced arrhythmic death or nonfatal cardiac arrest more often than those given placebo. The proarrhythmic effects of encainide and flecainide were thought to play an important role in the unfavorable outcome.

The present study demonstrates the ability of flecainide to induce extrasystolic activity in relatively small segments of “normal” cardiac tissue. The concentrations of flecainide used to produce these effects (5–15 μM), however, are considerably greater than those encountered in the plasma of human patients receiving the drug. This disparity calls into question the applicability of our findings to humans. Several important issues not directly addressed in this study need to be investigated before a determination can be made. First is the matter of time course of development of drug effects. Although not a focus of our study, it was our observation that lower concentrations of flecainide are much slower to act. We have previously demonstrated a time course on the order of hours with respect to the effects of other agents to block sodium and other channels. Over a period of several hours or days, much lower concentrations of flecainide may produce effects similar to those that we demonstrated with short exposure to high concentrations of drug. Second, a recent study by Wang and coworkers suggests that flecainide is considerably more potent in human atrial tissues when compared with canine and guinea pig atrial tissues. Similar quantitative species differences in the sensitivity of ventricular tissues to flecainide, if they exist, may further close the gap. Finally, parallel studies at our laboratory indicate that marked electrophysiological heterogeneity between epicardium and endocardium as well as among different epicardial sites results in response to a wide variety of agents, including acetylcholine, pinacolind, and calcium blockers and conditions such as hypoxia and ischemia. It seems justified to speculate that these agents and conditions may act synergistically with flecainide and other potent sodium channel blockers to produce heterogeneity and proarrhythmia. Thus, in the presence of ischemia or high vagal tone, the concentrations of flecainide required to induce extrasystolic activity may be more clinically relevant.

The applicability of the flecainide-induced changes observed in canine hearts to humans also presumes the presence of similar electrophysiological distinctions between epicardium and endocardium in human ventricles as in the dog or at least the presence of a similar INa-mediated spike and dome in epicardium. Whereas direct evidence for electrophysiological distinctions between human ventricular endocardium and epicardium is lacking, indirect evidence for the presence of an INa-mediated (4-AP-sensitive) spike-and-dome action potential morphology in human ventricular epicardium has recently been described in a preliminary report by Chiamvimonvat and coworkers.

Our data suggest that rate-dependent depression of the sodium channel current can lead to prominent electrical heterogeneities in which conduction delays and dispersion of repolarization act synergistically to induce arrhythmic activity. The tachycardia dependence of arrhythmic manifestation in our preparations is consistent with clinical reports that proarrhythmic effects of flecainide and other sodium blockers often appear to be rate related, occurring during exercise or during rapid atrial or ventricular pacing.

Our results also suggest that it might be possible to diminish flecainide-induced ventricular arrhythmias by preventing or reversing the heterogeneity that develops through use of pharmacological agents (Figure 12) that selectively inhibit INa in cardiac tissues.

Acknowledgments

We wish to thank Judy Hefferon and Robert Goodrow for their skilled technical assistance. We are grateful to Dr. Di Diego for assistance with some of the experiments. Flecainide acetate was generously provided by the 3M Company.

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Flecainide-induced arrhythmia in canine ventricular epicardium. Phase 2 reentry?
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_Circulation_. 1993;87:562-572
doi: 10.1161/01.CIR.87.2.562
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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