Intracoronary Flecainide Induces ST Alternans and Reentrant Arrhythmia on Intact Canine Heart: A Role of 4-Aminopyridine–Sensitive Current

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Background—The electrical alternans shown on an ST segment, ST alternans, is known as one of the most important predictors of ventricular fibrillation (VF). It has also been reported that sodium channel inhibition changes action potential configuration, especially on the repolarization phase. Thus, the sodium channel blocker may produce ST alternans and trigger reentrant arrhythmia.

Methods and Results—A sodium channel blocker (disopyramide, lidocaine, or flecainide) was infused selectively into the left anterior descending coronary artery in anesthetized, open-chest dogs. Sixty unipolar electrograms were simultaneously recorded from the entire cardiac surface of the heart. The amplitude of ST alternans (ST_a) was determined as the difference in the ST-segment magnitude between 2 consecutive electrograms. We accepted the greatest ST_a among 60 leads for evaluation. High-dose flecainide (100 μg·kg⁻¹·min⁻¹) increased ST_a and evoked a spontaneous VF. The ST_a in high-dose flecainide loading (8.7 ± 3.4 mV; mean ± SEM) was significantly greater than that in disopyramide or lidocaine (0.9 ± 0.4 and 0.8 ± 0.2 mV, P < 0.05). Treatment of 4-aminopyridine (4-AP) suppressed the increase in ST_a and the occurrence of VF evoked by flecainide, while E4031 or verapamil did not inhibit those.

Conclusions—Flecainide caused the ST alternans that was closely correlated to the occurrence of VF. Because the ST alternans was suppressed by 4-AP treatment, a 4-AP–sensitive current such as I_{to} or I_{sus} may play an important role on this phenomenon. (Circulation. 1999;99:1637-1643.)

Key Words: flecainide • arrhythmia • reentry fibrillation

Alternation of the ECG waveform in a beat-by-beat manner is known as electrical alternans. The electrical alternans shown on an ST segment, ST alternans (ST_a), was frequently observed in severe myocardial ischemia1–3 and is known to be a predictor of life-threatening ventricular tachyarrhythmias.4–6 Pharmacological induction of ST_a was reported by Karagueuzian et al7 in quinidine loading on the intact canine myocardium. Quinidine has been used as an antiarrhythmic agent because of its sodium channel–blocking action.8 The modulation of a sodium channel is 1 of the candidates that trigger ST_a because several recent studies demonstrated that the sodium current inhibition induced the prominent changes in repolarization-phase action potentials.9–11

The aims of the present study were to determine (1) whether a sodium channel blocker produces the ST_a and (2) whether the pharmacologically induced ST_a triggers the reentrant arrhythmia. In addition, we examined the effects of verapamil (a calcium channel blocker), E4031 (a blocker of a rapidly activating component of delayed rectifier potassium current, I_{sk}), or 4-aminopyridine (blocking action on transient outward current, I_{to} or sustained outward current, I_{sus}) on the sodium channel blocker–triggered ST_a and the arrhythmia because ion channels, including calcium and potassium current, determine the repolarization properties of the action potential and may play a key role in ST_a.

Methods

Surgical Preparation

This study conformed to the guiding principles of animal experiments at our institution. Adult mongrel dogs were anesthetized with an intravenous administration of 30 mg/kg sodium pentobarbital. Under positive pressure ventilation with room air supplemented with oxygen (3 to 5 L/min), the thorax was opened in the fifth intercostal space, the pericardium was opened, and a pericardial cradle was made to support the heart at an appropriate position. Arterial pressure, blood gases, and pH were monitored. The PO_2, PCO_2, and pH of the arterial blood were maintained within the physiological range. After the sinus node was crushed, the right atrium was paced at a cycle length of 400 ms.

Mapping of Epicardial Electrograms

The entire right and left ventricles were wrapped up with a sock implemented by an array of 60 electrodes. These electrodes were...
made of fine silver wires (0.008-in diameter) and insulated except at the point of attachment. The electrode array had 6 rows and 10 columns. The distance between adjacent electrodes was 7 to 10 mm. All unipolar electrograms were referenced to a Wilson’s central terminal. Data were digitized at a sampling frequency of 1000 Hz in each electrogram (CD-G015; Chuncini Denshi) and was stored on magneto-optical disks for later analysis as described in the previous study.1,12

Experimental Protocol

Protocol 1: Induction of STₐ by Disopyramide, Lidocaine, or Flecainide

After heparin (10 000 IU) was administered intravenously, a 24-gauge plastic cannula was inserted into the left anterior descending coronary artery (LAD) at the distal site of the second diagonal branch.13 Saline (n=6), disopyramide (low dose, 20 μg · kg⁻¹ · min⁻¹; high dose, 200 μg · kg⁻¹ · min⁻¹; n=8), lidocaine (low dose, 0.12 mg · kg⁻¹ · min⁻¹; high dose, 0.6 mg · kg⁻¹ · min⁻¹, n=7), or flecainide (low dose, 10 μg · kg⁻¹ · min⁻¹; high dose, 100 μg · kg⁻¹ · min⁻¹, n=7) was given via intracoronary infusion through a cannula.13 A lower dose of disopyramide, lidocaine, or flecainide was almost 1% of what was used intravenously in previous experimental studies, and a higher dose was 5% to 10%.14-16 After the control measurement, the low dose was loaded during the first 10 minutes, and the high dose was continued for the next 10 minutes. Sixty epicardial electrograms were simultaneously recorded at control, 10 minutes after the low dose, 10 minutes after the high-dose infusion, and just before ventricular fibrillation (VF), if VF occurred. In addition, the therapeutic dose of flecainide (0.2 mg/kg over 15 minutes)17 was investigated with the intravenous infusion because the sodium channel blockers; there was greater STₐ in flecainide-loaded dogs, whereas none of the disopyramide- or lidocaineloaded dogs developed VF. Two of 7 flecainide-loaded dogs, whereas none of the disopyramide- or lidocaineloaded dogs developed VF. Two of 7 flecainide-loaded dogs, whereas none of the disopyramide- or lidocaineloaded dogs developed VF. The ST level was significantly greater in high-dose protocols than at the control state or in low-dose protocols of disopyramide, lidocaine, or flecainide (P<0.05 each; Figure 2A); however, there were no significant differences in ST levels among the sodium channel blockers. In contrast, there were significant differences in the ST, among the sodium channel blockers; there was greater ST, in flecainide loading compared with disopyramide or lidocaine (Figure 2B). However, ST, did not significantly increase with the therapeutic dose (0.2 mg/kg) of intravenous flecainide (control, 1.5±0.4 mV; flecainide, 2.4±0.4 mV).

We examined the activation sequence on the AT map of the regular beats and the initiation of VT beats, as shown in Figure 3. On the regular beat at the control state, the activation rapidly propagated through the entire surface, and clouded isochronal lines were not seen. On the other hand, after flecainide infusion, the conduction of the regular beat was delayed around the perfused area; isochronal lines between B3 and C3 were particularly clouded. The spontaneous ventricular activity, VT1, was initiated at the proximal site of the dense lines. This excitation rotated around the arc of the conduction block, coalesced, and reached the opposite activation time (AT) of each electrogram was defined as the minimum derivative of the QRS signal.22 The earliest activation during the atrial pacing wave was defined as time zero. A recovery time (RT), defined as the maximum derivative of the T wave in the unipolar electrogram, was used as a measure of local repolarization. The activation-recovery interval (ARI), defined as the interval between AT and RT, was used as a measure of local action potential duration.23,24 The dispersion of AT, RT, or ARI was defined as the difference between the maximum and minimum values among 60 epicardial leads. Isochronal maps were constructed with isochrones delineated at 10-ms intervals. It was decided that a possible conduction block was present when the difference in activation time between 2 adjacent leads exceeded 100 ms.25

Statistical Analysis

Quantitative data were expressed by mean±SEM. The comparison of group mean values was performed with ANOVA followed by Student’s t test with Bonferroni correction as appropriate. Differences were considered significant at P<0.05.
side of the block. The earliest activation of VT2 was located on lead B3, and the activation sequence was similar to that in VT1. These results suggested that a reentrant circuit was formed. This excitation led to VF after the ventricular tachycardia (VT) continued for several seconds.

We also analyzed recovery sequence and the action potential duration through the use of RT and ARI maps just before VT/VF. This analysis allowed us to determine the instant of local recovery or action potential duration. Representative maps indicated that RTs delayed and ARI prolonged on the perfused area (Figure 4). VT/VF occurred with a combined appearance of activation delay and recovery dispersion. When we calculated the dispersion of ATs, RTs, and ARIs, all parameters increased significantly after flecainide infusion (P<0.05, Figure 5).

**Protocol 2: Effects of Verapamil, E4031, or 4-Aminopyridine on ST<sub>a</sub> Evoked by Flecainide**

We examined the effects of treatment with verapamil, E4031, or 4-aminopyridine on the flecainide-induced ST<sub>a</sub>. The treatment with each agent did not affect the mean aortic pressures. Flecainide-induced ST<sub>a</sub> was measured just before VF, if VF occurred, or after 30 minutes of flecainide infusion, if VF did not occur (Figure 6). The ST<sub>a</sub> was significantly smaller with 4-aminopyridine treatment than with saline, verapamil, or E4031 treatment (P<0.05 each). VF spontaneously occurred in all dogs that received treatments of saline, verapamil, or E4031. In contrast, VF developed in only 2 of 7 dogs that received 4-aminopyridine.

The ST<sub>a</sub> was examined on both epicardial and endocardial sites in a limited number of experiments (n=3, Figure 7). The

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**Figure 1.** Representative electrograms before and after disopyramide, lidocaine, or flecainide infusion. SVT indicates supraventricular tachycardia; VT1, first beat of VT; and VT2, second beat of VT.

**Figure 2.** Effects of saline, disopyramide, lidocaine, and flecainide on (A) amplitude of ST level (ST amplitude) and (B) ST<sub>a</sub>. #P<0.05 vs control. ¶P<0.05 vs low dose. *P<0.05 vs saline, disopyramide, and lidocaine in high dose.

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**Table 1.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ST amplitude (mV)</th>
<th>Control</th>
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<th>High Dose</th>
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<td>15</td>
<td>10</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Disopyramide</td>
<td>10</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lidocaine</td>
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<td>0</td>
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</tr>
<tr>
<td>Flecainide</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

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**Figure 2.** Effects of saline, disopyramide, lidocaine, and flecainide on (A) amplitude of ST level (ST amplitude) and (B) ST<sub>a</sub>. #P<0.05 vs control. ¶P<0.05 vs low dose. *P<0.05 vs saline, disopyramide, and lidocaine in high dose.
STa tended to be greater in the epicardial than in the endocardial sites. 4-Aminopyridine strongly suppressed the STa on both sites.

**Discussion**

The CAST study focused on the possible proarrhythmia of sodium channel blockers. Recently, genetic disturbance of sodium channels was found in patients with the Brugada form of idiopathic VF. Increased attention has been given to the relation between sodium channel suppression and arrhythmia. The present study demonstrated that (1) flecainide induced STa and triggered VF in the intact heart, whereas disopyramide and lidocaine did not produce STa; (2) 4-aminopyridine attenuated STa and suppressed the occurrence of VF; and (3) STa induced by flecainide tended to be greater in the epicardial than in the endocardial sites.

**ST Elevation Due to Sodium Channel Blockers**

In the present study, sodium channel blocker invariably elevated ST segments, which supports that sodium channel blockers alter the ventricular repolarization. This phenomenon may relate to the experimental study by Colatsky.

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**Figure 3.** Activation sequence during atrial pacing before and after high-dose flecainide infusion and at initiation of ventricular arrhythmia. Display format is apical polar projection of ventricles, with left ventricular apex in center. Isochronal lines are drawn every 10 ms. Bold lines indicate conduction block. *Earliest activation in each contraction. LAD indicates left anterior descending coronary artery; VT1, first beat of VT; and VT2, second beat of VT.

**Figure 4.** Recovery sequence and ARI distribution after high-dose flecainide. RTs are delayed in perfused area, and ARI is mildly prolonged in that area. In a RT map, earliest recovery was defined as time zero. Display format is same as Figure 3.
evaluated the effects of tetrodotoxin on rabbit Purkinje cells and showed that tetrodotoxin-sensitive window currents maintain the action potential plateau, which can be blocked by sodium channel blockers. Depletion of this current shortened the action potential duration and may induce ST elevation, as seen in the present study. Another possible mechanism of ST elevation is local conduction disturbance. Sodium channel blockers frequently cause widened QRS complex due to local conduction disturbances, which may induce the secondary ST-segment elevation.

Mechanism of STa Due to Flecainide

Regarding the mechanism of STa, primarily the calcium ion channel has been examined; calcium blockers such as verapamil and diltiazem suppressed T-wave alternans on ischemic hearts in experimental studies and in patients with Prinzmetal’s variant angina. The alternans in the calcium-dependent fluorescence transient was also reported in ischemic rabbit hearts. In this study, however, treatment with verapamil did not suppress the STa. This suggested that the other mechanism may work on the flecainide-induced STa.

Several reports demonstrated that alternans in action potential duration and configuration mainly occurs in the phase 2 or 3 state. We focused on the role of the potassium channel in the flecainide-induced STa. The contribution of potassium channels were examined through the use of E4031 (I_K blocker) and 4-aminopyridine. The results indicated that 4-aminopyridine strongly suppressed the amplitude of STa induced by flecainide, whereas E4031 did not have such effects. 4-Aminopyridine has blocking actions of transient outward (Ito), inward rectifier (I_k1), and delayed rectifier (I_kr) currents in a dose-dependent manner. The dose in the present study was chosen according to previous reports in which the effect of Ito action is prominent. Because the Ito blocker E4031 did not suppress the STa, and because Ito has a major effect on resting potential, we thought Ito was most responsible for the STa. Ito, the sustained depolarization-induced outward current, was recently reported to contribute to repolarization in action potential and to be sensitive to 4-aminopyridine, may also be responsible for this phenomenon.

Krishnan and Antzelevitch demonstrated that flecainide produced marked abbreviation of action potential duration mainly in epicardium and may increase the dispersion of repolarization. They also reported that 4-aminopyridine reversed these effects. These lines of evidence strongly suggested that the 4-aminopyridine-sensitive current may play a key role in the flecainide-induced STa and VF. Interestingly, we found that flecainide-induced STa tended to be less in the endocardial site than in the epicardial site. Several studies have also demonstrated that the Ito is more prominent in canine epicardium than in canine endocardium. The results in our study accorded with these findings.

The reason why flecainide, and not disopyramide or lidocaine, induced STa was not identified. Flecainide is classified as a slow kinetic drug and is known to have a strong sodium channel–blocking action. It is also reported that flecainide has a direct effect on Ito.

Mechanism of Ventricular Arrhythmia

The results showed a close correlation between STa, and ventricular arrhythmia. Analysis on activation sequence suggests that a reentrant mechanism is the most probable. The conduction block and dispersion of refractoriness induced by flecainide may be important factors for maintaining the reentry circuit. The present study provided new mechanisms of the arrhythmogenesis of sodium channel blockers (ie, ST alternans–related arrhythmia).

Krishnan and Antzelevitch reported another mechanism of flecainide-induced arrhythmia, “phase 2” reentry. They observed a marked dispersion of repolarization within a small perfused area of myocardium (~100 ms within a 2.0-cm² area) and concluded that the voltage gradient in phase 2 directly generated an ectopic activity. In the present study, however, RT maps did not show such severe dispersion (Figure 4). Moreover, the dispersion was seen gradually between perfused and nonperfused areas but not within the perfused area. These observations did not distinguish the
mechanism of arrhythmia, including phase 2 reentry. Further studies, including intramural mapping, will be needed to clarify the submechanism of reentry.

Study Limitations and Clinical Implication

A limitation of this study was the route of administration. We administered agents through an intracoronary route. This method was selected to investigate the effect of a strong sodium channel block in an in vivo heart. Otherwise, systemic hemodynamics will considerably alter and thus probably obscure the effect of this agent. Besides its merit, this may cause the nonuniform distribution of agents and may be a factor in proarrhythmia. We supposed, however, that the route of administration was not a determinant of proarrhythmias because only flecainide was proarrhythmic.

Intracoronary administration was chosen on the basis of the reported experimental studies of the intravenous use of sodium channel blocker in dogs or rabbits.14–16 Because these doses might be higher than those with therapeutic use in humans, our results cannot be directly extended to a clinical situation. In fact, the therapeutic dose of flecainide did not induce STa or VF. However, we should pay attention to the possibility of this type of proarrhythmias in patients who are treated with flecainide.

In conclusion, flecainide-induced electrical alternans of the ST segment correlated closely with the occurrence of VF. Because this STa was suppressed with 4-aminopyridine treatment, it is suggested that 4-aminopyridine-sensitive current plays an important role in this phenomenon.

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