Direct Effects of Class I Antiarrhythmic Drugs on Epicardial Electrograms in Dogs

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Summary
The effects of class I antiarrhythmic drugs on epicardial electrograms during regular atrial pacing were investigated in anesthetized, open-chest dogs. Lidocaine, flecainide or disopyramide was infused selectively into the distal site of the left anterior descending artery. Lidocaine produced a dose-dependent elevation of ST segment without changing the amplitude of R wave. Flecainide produced a dose-dependent increase of R-wave amplitude accompanied by the augmentation of negative T. The ST segment was elevated at the high dose. The QRS area did not change at the low dose but significantly increased at the high dose, indicating that the ST-T change at the low dose was secondary to changes in ventricular depolarization. The effects of disopyramide on R wave and ST segment were between those of lidocaine and flecainide. The major action of lidocaine was the acceleration of ventricular repolarization while that of flecainide was the deceleration of ventricular conduction. Disopyramide had an action that was intermediate between the two drugs.

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The common mechanism of class I antiarrhythmic drugs to suppress the occurrence of premature beats is their ability to inhibit fast Na⁺ current and thus to reduce the conduction velocity and block the premature impulses. There are great differences among class I drugs in the extent and characteristics of this action as well as in other actions such as on K⁺ currents. The effects of class I drugs on transmembrane action potential and specific ionic channels of isolated myocytes are well documented. However, the effects of these drugs at high concentrations on epicardial electrograms in vivo beating hearts have not been fully investigated because of the presence of negative chronotropic effects.

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negative inotropic effects and extracardiac effects such as potent local anesthetic effects on nerve.\textsuperscript{1} Recently, class Ic antiarrhythmic drugs have been reported to produce ST-segment elevation on 12-lead ECG in humans.\textsuperscript{2,3} We also reported that intracoronary infusion of class I drugs produced ST-segment elevation on epicardial electrograms in dogs, however, we did not analyze changes in the QRS complex which could be altered by slowing the conduction.\textsuperscript{3} Therefore, we conducted this study to elucidate the changes in ECG waveforms induced by class I antiarrhythmic drugs.

**METHODS**

**Surgical preparation:** This study conformed to the guiding principles of animal experiments in our institution. Eighteen mongrel dogs were anesthetized with an intravenous administration of 30 mg/kg sodium pentobarbital. Under artificial ventilation, the thorax was opened in the fifth intercostal space, the pericardium opened, and a pericardial cradle constructed to support the heart at an appropriate position. Arterial pressure, blood gases, and pH were monitored. The PO\textsubscript{2} and pH of the arterial blood were maintained at levels greater than 100 mmHg and between 7.35–7.45, respectively. The sinus node was crushed, and the right atrium was paced at a cycle length of 400 msec. A 24-gauge plastic cannula was inserted into the left anterior descending artery at the distal site of the second diagonal branch for the local injection of antiarrhythmic drugs. Heparin (10,000 IU) was given intravenously before the cannulation.

**Epicardial mapping:** The heart was wrapped up in an array of 60 unipolar electrodes. These electrodes were made of fine silver wires that were insulated except at the point of attachment. All recordings were referenced to a Wilson’s central terminal and recorded on a magneto-optical disk after analog-digital conversion with a sampling frequency of 1,000 Hz using a multichannel data recording system (CD-G015, Chunichi Denshi, Nagoya, Japan).\textsuperscript{5}

**Experimental protocol:** Lidocaine (low dose, 0.12 mg/kg/min; high dose, 0.6 mg/kg/min, \( n = 6 \)), flecainide (low dose, 10 \( \mu \)g/kg/min; high dose, 100 \( \mu \)g/kg/min, \( n = 6 \)), or disopyramide (low dose, 20 \( \mu \)g/kg/min; high dose, 200 \( \mu \)g/kg/min, \( n = 6 \)) was given via intracoronary infusion through a cannula.\textsuperscript{6} The lower doses of lidocaine, flecainide, and disopyramide were almost 1% of those used intravenously in previous experimental studies, while the higher doses were 5% to 10%.\textsuperscript{7–9} After the control recordings, the low dose was loaded during the first 10 minutes and the high dose was continued for the next 10 minutes.

**Analysis of epicardial electrograms:** The flat portion of the PR segment was defined as the zero level. The amplitude of the ST segment was measured at 0.08 seconds after the J point. QRST area was calculated by integrating the electro-
gram over the QRST interval. Epicardial activation time was determined using the time of minimum derivative of each QRS with reference to the earliest activation time among epicardial mapped electrograms (time = 0). For the analysis of drug effects, we selected one electrogram located at the center of the drug-perfusion area in each dog. The QRST area corresponds to the ventricular gradient and is hardly influenced by alterations of the ventricular activation sequence. Thus, the secondary ST-T change due to changes in activation is not accompanied by a change in the QRST area, while the change in QRST area indicates the presence of changes in repolarization properties. The increase or decrease in QRST area suggests a decrease or increase in action potential duration (APD). On the other hand, the prolongation of activation time directly reflects the delayed arrival of the depolarization wavefront to the electrode site.

Statistical analysis: Comparisons of values among the three groups (lidocaine, flecainide and disopyramide) were made by ANOVA followed by Scheffe’s test. Statistical significance of the change in values by the drug was assessed by the paired Wilcoxon test. Linear regression analysis was used to calculate the correlation coefficient. Quantitative data are expressed as mean ± SEM. Differences were considered significant at $p < 0.05$.

RESULTS

Figure 1 shows representative electrograms in a dog receiving lidocaine (A), flecainide (B) or disopyramide (C). The Table summarizes the effects of lidocaine, flecainide or disopyramide on R wave, ST segment, activation time and QRST area. Under baseline conditions, there were no significant differences in these parameters among groups.

The electrogram after lidocaine showed a dose-dependent elevation of ST segment without apparent changes in R-wave amplitude or QRS morphology (Figure 1-A). This ST-segment elevation was accompanied by the increase in QRST area (Table). Plots of the changes in QRST area versus changes in ST-segment amplitude for 6 dogs revealed a close correlation between the two ($r = 0.90$), as shown in Figure 2.

Flecainide produced an increase in R-wave amplitude, widening of QRS complex and augmentation of negative T in a dose-dependent manner (Figure 1-B). This R-wave increase was accompanied by prolongation of the activation time (Table). Plots of changes in activation time versus changes in R-wave amplitude for 6 dogs demonstrated a close relationship ($r = 0.77$, Figure 3). The QRST area and ST segment did not change at the low dose, but significantly increased at the high dose.

Disopyramide produced an increase in R-wave amplitude dose-dependently
with concomitant widening of the QRS (Figure 1-C). The degree of R-wave increase was much smaller than that after flecainide ($p < 0.01$ at the high dose). Although the increase in R-wave amplitude tended to be accompanied by an increase in activation time in each dog, there was no significant correlation be-
Figure 2. Plots of changes in QRST area (delta QRST) versus changes in ST-segment amplitude (delta ST) for all six dogs receiving lidocaine.

Figure 3. Plots of changes in activation time (delta AT) versus changes in R-wave amplitude (delta R) for all six dogs receiving flecainide.
between them for pooled data from 6 dogs. The level of ST segment did not change at the low dose, but did increase at the high dose. There was a significant correlation between the changes in QRST area and the changes in ST segment for pooled data from 6 dogs ($r = 0.61, p < 0.05$).

**DISCUSSION**

In this study, we investigated the direct effects of lidocaine, flecainide and disopyramide on epicardial electrograms during regular atrial pacing in anesthetized, open chest dogs. We demonstrated that each drug had a different effect on the electrogram, although the ST segment was invariably elevated at the high dose.

**Lidocaine:** The noticeable waveform change after lidocaine infusion was the elevation of ST segment without a significant change in R-wave amplitude. Thus, lidocaine predominantly alters the ventricular repolarization. At the high dose, however, there was a slight but significant increase in activation time, indicating the deceleration of conduction velocity. It is well known from experiments in cardiac muscle that lidocaine has little effect on fast Na⁺ currents at normal or low stimulation rates and decreases the APD which is attributed to the blockade of small Na⁺ currents that flow during the plateau of the action potential. The dose-dependent elevation of the ST segment is probably due to the blockade of this inward Na⁺ current.

**Flecainide:** The dominant change in the epicardial electrograms after flecainide administration was a marked increase in R-wave amplitude. Since there was a linear correlation between activation time and R-wave amplitude, the increase in R-wave amplitude was considered to be directly derived from the slowing of conduction velocity. The giant negative T wave observed at the low dose was secondary to the altered ventricular conduction because of the absence of QRST area change. At the high dose, the QRST area increased, significantly indicating the shortening of APD.

Flecainide binds tightly to Na⁺ channels and blocks fast Na⁺ currents and prominently decreases the conduction velocity. At concentrations of up to $10 \mu g/ml$, flecainide has been shown to lengthen the APD in ventricular muscle and shorten it in Purkinje fibers, while at higher concentrations ($30 \mu g/ml$) flecainide shortens the APD even in ventricular muscle. The fluctuation of APD may be the consequence of competition between the blocking actions of inward Na⁺ and outward K⁺ currents.

**Disopyramide:** The extent of the increase in R-wave amplitude and activation time was smaller than that of flecainide. This finding was compatible with electrophysiological data which indicated that the inhibition of fast Na⁺ currents by
disopyramide was less marked than that of flecainide. Class Ia drugs including disopyramide are supposed to prolong APD at therapeutic concentrations, but the increase in QRST area suggested the shortening of APD. This opposite effect may be due to the higher concentrations of disopyramide used in our study. Wyses et al. reported that in canine Purkinje fibers the prolongation of APD at low concentrations of disopyramide tended to reverse as the concentration was increased. 17

Conclusions: The predominant effects of lidocaine and flecainide on epicardial electrograms in regularly beating hearts were ST-segment elevation and the increase in R-wave amplitude, respectively. The underlying mechanisms of these changes are probably related to the block of slow inward Na+ currents in lidocaine and to the marked inhibition of fast Na+ currents in flecainide. Disopyramide has an action on the ST segment and R wave which appears to have aspects of both lidocaine and flecainide.

References


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