Utilization of an Isolated, Blood-Perfused Canine Papillary Muscle Preparation as a Model to Assess Efficacy and Adversity of Class I Antiarrhythmic Drugs

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ABSTRACT—To develop a model to predict the efficacy and adversity of class I antiarrhythmic drugs, intraventricular conduction time (IVCT), coronary blood flow (CBF), developed tension of papillary muscle (DT) and idioventricular automaticity rate (VR) were measured following drug administration in an isolated canine papillary muscle preparation cross-circulated with the heparinized blood of a donor dog. Tetrodoxin, the prototypic fast Na⁺ channel blocker, and class I drugs increased IVCT and CBF, but decreased DT and VR, in a dose-dependent manner. The profiles of known class I drugs, procainamide, disopyramide, lidocaine, mexiletine and flecainide were similar, but the potencies of each drug were different. Two new class I drugs, ME3202 and AN-132, were also tested and found to have effects that were similar to that of tetrodotoxin. There was a good correlation between the doses of drugs prolonging IVCT by 50% and the canine antiarrhythmic plasma concentrations in our previous study. This model can also be used to estimate the use-dependency and the kinetics of use-dependent sodium channel block; however, it is not suitable for extensive investigation of cellular and molecular mechanisms. Thus, the use of this model facilitates the comparison of multiple cardiac effects of class I drugs and may be an effective way to better assess new antiarrhythmic drugs.

Keywords: CAST (cardiac arrhythmia suppression trial), ME3202, Tetrodotoxin, Verapamil, Antiarrhythmic drug

The recent Cardiac Arrhythmia Suppression Trial (CAST), in which the patients who received class I drugs to suppress nonsustained ventricular arrhythmias after myocardial infarction, demonstrated a higher mortality in patients taking the drug compared with those given the placebo (1). Not only has CAST focused attention on the potential for late proarrhythmia as well as the negative inotropic action of antiarrhythmic drugs, but it has stimulated a renewed effort to better assess antiarrhythmic drug efficacy and adversity during the preclinical stages of drug development.

Based upon this need, we utilized an isolated, blood-perfused canine papillary muscle preparation to precisely study the direct cardiac effects of the class I antiarrhythmic drugs under physiologically stable conditions (2–8). An electrically paced preparation was used to measure intraventricular conduction time (IVCT), coronary blood flow (CBF) and developed tension of the papillary muscle (DT), while a spontaneously beating preparation was used to measure ventricular automaticity rate (VR). Tetrodotoxin (TTX), the prototypic Na⁺ channel blocker (9, 10), was studied initially. The effects of verapamil, a prototypic Ca²⁺ channel blocker (2, 8), was used for comparison with the class I agents. The effects and relative potency of well-established and new class I drugs were compared with responses observed with TTX and verapamil. We propose that this model for evaluating the multiple effects of a drug on cardiac muscle is an effective way to better assess class I agents during antiarrhythmic drug development.

MATERIALS AND METHODS

Experiments were carried out using papillary muscle preparations cross-circulated with the heparinized arterial blood of donor dogs as shown in Fig. 1, which was essentially the same as the previous reports (2–8). All experi-

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ments were performed in accordance with Guidelines for Animal Experiments, Yamanashi Medical University.

**Preparation**

The hearts were obtained from mongrel dogs of either sex, weighing approximately 10 kg, which were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and given calcium heparin (500 U/kg, i.v.). They were excised after exsanguination and plunged into cold Tyrode’s solution kept at about 4°C. The preparation consisted of the anterior papillary muscle of the right ventricle attached to the interventricular septum. The anterior septal artery, a nutrient artery of the His-Purkinje system and papillary muscle, was directly cannulated. Bipolar electrodes were sutured onto the His bundle region close to the tricuspid valves for the electrical stimulation, and other bipolar electrodes were attached on the apex of the papillary muscle for a record of the electrograms.

**Donor dog**

Adult mongrel dogs of either sex, weighing 14–23 kg, were used as donor dogs. Dogs were anesthetized initially with sodium pentobarbital (30 mg/kg, i.v.) and supplemented with 4–5 mg/kg every hour. At the start of cross-circulation, calcium heparin (500 U/kg, i.v.) was given, and 200 U/kg, i.v. was supplemented every hour. Respiration was controlled using a dog respirator (607; Harvard, Millis, MA, USA). The systemic blood pressure, heart rate and electrocardiograms were monitored continuously with a polygraph (361-6; NEC San-ei Instruments, Tokyo).

**Cross circulation**

The preparation was placed in a double-wall glass jacket maintained at 38°C by circulating warm water, and it was perfused with arterial blood from the carotid artery of the donor dog. Perfusion pressure was kept at 120 mmHg with a peristaltic pump (7553-00; Cole-Parmer, Chicago, IL, USA) and a Starling’s pneumatic resistance placed parallel to the perfusion circuit. Venous blood from the preparation and excess blood passing through the pneumatic resistance were collected in a blood reservoir and returned to the jugular vein of the donor dog.

**Effects of drugs on IVCT, CBF and DT**

After equilibration of 1 hr, the preparation was electrically driven by a stimulator (DHM-226-3; Dia Medical, Tokyo) and an isolation unit (DPS-110, Dia Medical). The stimulation pulses were rectangular in shape, 1–3 V (about 20% above the threshold voltage) and 5-msec duration at a cycle length of 500 msec for all drugs. Cycle lengths of 400 and 300 msec were also used for lidocaine and mexiletine to assess the use-dependent effect of drugs in this preparation. IVCT as an interval between the stimulus artifact and distal electrogram at the tip of the papillary muscle was measured continuously by an automatic interval meter (DHM-226-1, Dia Medical) with 1 msec of analysis pitch. The rate of CBF through the anterior septal artery was continuously monitored with an electromagnetic flowmeter (MVF1100; Nihon Kohden, Tokyo). DT preloaded with a 2-g weight was measured isometrically using a force displacement transducer (DRM-100S, Dia Medical). Effects of procainamide (1–3000 μg), disopyramide (1–1000 μg), lidocaine (1–1000 μg), mexiletine (1–1000 μg), flecainide (1–300 μg), ME3202 (1–1000 μg), AN-132 (1–1000 μg), TTX (0.1-10 μg) and verapamil (0.1–10 μg) on these three parameters were simultaneously assessed and were recorded on a rectilinear recorder (8K231S, NEC San-ei Instruments).

**Effects of drugs on VR**

As the papillary muscle preparation had an automaticity originating in the Purkinje fiber of the ventricular
It showed a spontaneous regular contraction when the electrical stimulation was stopped (4, 5, 7). Using this spontaneously beating papillary muscle preparation, VR was measured with a cardiotachograph (1321, NEC San-ei Instruments) triggered by bipolar electrograms of the papillary muscle. Effects of procainamide (1–3000 μg), disopyramide (1–1000 μg), lidocaine (1–1000 μg), mexiletine (1–1000 μg), flecainide (1–1000 μg), ME3202 (1–1000 μg), TTX (0.1–10 μg) and verapamil (0.1–10 μg) on VR were assessed and were recorded on a rectilinear recorder (8K231S, NEC San-ei Instruments).

Drugs

Drugs used in this study were as follows: procainamide hydrochloride (Dai-ichi, Tokyo), disopyramide phosphate (Roussel through Chugai, Tokyo), lidocaine hydrochloride (Fujisawa, Osaka), mexiletine hydrochloride (Böhringer Ingelheim through Tanabe, Osaka), flecainide acetate (Eisai, Tokyo), ME3202; 2-[2-(diisopropylamino) ethyl] - 4 - methyl - 2 - (2 - pyridyl) - pentanamide (Meiji, Tokyo), AN-132; 3-(diisopropylamino ethyl)amino)-2, 6-dimethylpropionanilide 2H3PO4 (Chugai, Tokyo), TTX (Sigma, St. Louis, MO, USA) and verapamil hydrochloride (Eisai, Tokyo). A 10-μl volume of drug solution was injected into the anterior septal artery over 4 sec with a microsyringe (Terumo, Tokyo). The blood containing the injected drug was discarded after going through the papillary muscle preparation. Given the relatively small doses of drugs administered to the preparations compared to those needed in a whole intact animal, multiple drug doses can be relatively rapidly studied in the same preparation.

Data analysis and statistics

The drug effect after intraarterial administration was assessed from both the peak response and its duration. Peak responses in each parameter are expressed as a percent of their basal values before injection. ED50(IVCT), the dose (μg) of drugs causing a 50% increase in IVCT; ED50(CBF), the dose (μg) causing a 50% increase in CBF; ED50(DT), the dose (μg) causing a 50% decrease in DT; ED50(VR), the dose (μg) causing a 50% decrease in VR, were calculated from dose-response curves by the least squares method. The pharmacodynamics of drugs was assessed using onset half time (OHT) and recovery half time (RHT), as follows: OHT is the time (sec) required to reach the peak effect from 1/2 peak effect in each cardiac variable. OHT(IVCT), OHT(CBF), OHT(DT) and OHT(VR) indicate the onset half time to increase IVCT and CBF and to decrease DT and VR, respectively. RHT is the time (sec) required to return to 1/2 peak effect from the peak effect in each cardiac variable. RHT(IVCT), RHT(CBF), RHT(DT) and RHT(VR) indicate the recovery half times from the maximum responses in IVCT, CBF, DT and VR, respectively. The statistical comparisons of mean values were evaluated by Student’s t-test, and correlation between two groups was assessed by analysis of variance. P values less than 0.05 were considered significant. The data are presented as the mean±S.E.M.

RESULTS

Baseline characteristics of the preparation

When paced at a cycle length of 500 msec, the preparations showed a basal IVCT of 41±1 msec, CBF of 5.4±0.3 ml/min and DT of 6.3±0.2 g (n=53). When paced at a cycle length of 400 msec, the preparations showed a basal IVCT of 44±1 msec, CBF of 4.1±0.3 ml/min, DT of 5.0±0.4 g (n=12). When paced at a cycle length of 300 msec, the preparations showed a basal IVCT of 45±1 msec (n=12), and 10 preparations out of 12 showed a pulsus alternans type contraction, which was a regular alteration of DT, despite a regular rhythm. As the distance between the pacing electrodes of the His bundle and papillary muscle electrodes was about 3–5 cm, the conduction velocity was estimated as about 1.2–2.0 m/sec.

Without pacing, the ventricle spontaneously depolarizes. The basal VR (beats/min) was 41±5 (n=6) before procainamide, 41±2 (n=6) before disopyramide, 40±6 (n=6) before lidocaine, 41±5 (n=6) before mexiletine, 39±4 (n=6) before flecainide, 39±3 (n=6) before ME3202, 36±3 (n=6) before TTX and 42±5 (n=6) before verapamil. There was no significant difference among the groups.

Effects of TTX and verapamil on IVCT, CBF and DT

Typical experiments showing the effects of TTX and verapamil are shown in Fig. 2, and dose-response curves are shown in Fig. 3. Administration of TTX resulted in a dose-dependent prolongation in the IVCT and produced broadening and diminution of amplitude of bipolar electrograms obtained from the papillary muscle. TTX caused an increase in CBF and a decrease in DT. Meanwhile, verapamil decreased IVCT slightly, increased CBF significantly and decreased DT followed by a transient increase in all preparations as shown in Fig. 2. These two drugs were used to establish a relative potency scale of cardiac direct effects for the class I drugs.

Evaluation of the effects of class I drugs on IVCT, CBF and DT in a blood-perfused canine papillary muscle preparation

Typical experiments showing the effects of procainamide, mexiletine, ME3202 and AN-132 on IVCT, CBF
and DT are shown in Fig. 4. Dose-response curves of mexiletine and flecainide on IVCT, CBF and DT are shown in Fig. 5.

As with TTX, seven class I drugs increased IVCT in a dose-dependent manner. The increase in the IVCT after the injection of lidocaine or mexiletine was enhanced by decreasing the cycle length, as shown in Fig. 5A. When paced at a 300-msec driving interval, a second degree conduction block was produced in 1 out of 6 preparations by 100 μg of lidocaine and no preparation by 100 μg of mexiletine, in 2 out of 6 by 300 μg of lidocaine and 1 out of 6 by 300 μg of mexiletine, and in 2 out of 6 by 1000 μg of lidocaine and 2 out of 6 by 1000 μg of mexiletine. The dose causing a 50% (approximately 20 msec) increase in IVCT, ED50(IVCT), is shown in Table 1, indicating that the effect of TTX on IVCT was 56–562 times more potent than those of class I drugs; the potency of the effect on IVCT of class I drugs was in the order of flecainide, AN-132, ME3202, disopyramide, lidocaine, mexiletine and procainamide, while lidocaine and mexiletine increased it.
at rapid driving. The onset half time for IVCT (OHT_{IVCT}), which indicates the onset rate after the highest dose of each drug, was extremely slow for flecainide and disopyramide; intermediate for procainamide, AN-132 and ME3202; and quite fast for mexiletine, TTX and lidocaine, as shown in Table 2. Recovery half time for IVCT (RHT_{IVCT}), which indicates the recovery rate after the highest dose of each drug, was slow for flecainide, disopyramide, ME3202 and AN-132; intermediate for procainamide; fast for lidocaine, mexiletine and TTX, as shown in Table 2.

The effect of class I drugs on coronary artery tone was similarly studied by measuring CBF. All class I agents studied increased coronary flow in a dose-dependent fashion. The ED_{50(CBF)} values are shown in Table 1, indicating that the vasodilator effect of verapamil was 68–1369 times more potent than those of class I drugs and that the potency of the coronary vasodilator effect of class I drugs was in the order of flecainide, lidocaine, mexiletine, AN-132, ME3202, disopyramide and

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**Fig. 3.** Dose-response curves of tetrodotoxin (TTX) and verapamil for IVCT (A), CBF (B) and DT (C). The data are presented as the mean±S.E.M. (n=6). *P<0.05, vs basal value. IVCT: intraventricular conduction time, CBF: coronary blood flow, DT: developed tension of papillary muscle.
procainamide. The onset half time for CBF (OHT$_{\text{CBF}}$), which indicates the onset speed of the response to the highest dose of each drug, was extremely slow for verapamil, intermediate for disopyramide and ME3202, and quite fast for other drugs, as shown in Table 2. The recovery half time for CBF (RHT$_{\text{CBF}}$), which indicates the recovery speed of the response to the highest dose of each drug, was extremely slow for verapamil, intermediate for ME3202 and disopyramide, and fast for other drugs, as shown in Table 2.

As with TTX and verapamil, the class I agents decreased DT in a dose-dependent manner, although procainamide produced a transient increase followed by a decrease in 4 out of 6 preparations as shown in Fig. 4. Decreasing the drive cycle length hardly affected the negative inotropic effects of lidocaine and mexiletine as shown in Fig. 5C. The ED$_{50(DT)}$ values are shown in Table 1, indicating that the potency of the negative inotropic effect of class I drugs was in the order of flecainide, mexiletine, lidocaine, disopyramide, AN-132, ME3202 and procainamide. The onset half time for DT (OHT$_{\text{DT}}$), which indicates the onset speed of the inotropic response to the highest dose of each drug, was slowest for disopyramide followed by verapamil and flecainide, and

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**Fig. 4.** Effects of intraarterial injection of class I drugs on the isolated, blood-perfused canine papillary muscle preparation paced at a cycle length of 500 msec. Original tracings of procainamide, mexiletine, ME3202 and AN-132. As the amplitude of electrograms was diminished after 1000 µg of AN-132 injection, trigger failure of the papillary muscle electrogram transiently occurred. IVCT: intraventricular conduction time, CBF: coronary blood flow, DT: developed tension of papillary muscle.
quite fast for other drugs, as shown in Table 2. The recovery half time for DT ($RHT_{DT}$), which indicates the recovery speed of the tension response to the highest dose of each drug, was extremely slow for disopyramide followed...
by flecainide; and it became faster in the order of verapamil, lidocaine, procainamide, ME3202, mexiletine, AN-132, and was the fastest for TTX, as shown in Table 2.

**Effects of TTX and verapamil on VR**

Typical experiments showing the effects of TTX and verapamil are shown in Fig. 6A, and dose-response curves are shown in Fig. 6, B and C, respectively. TTX decreased VR in a dose-dependent manner, but verapamil failed to produce a significant change in VR even in doses that produced significant vasodilator and negative inotropic effects.

**Evaluation of the effects of class I drugs on VR using this model**

Typical recordings of procainamide, disopyramide, mexiletine and ME3202 are shown in Fig. 7. Dose-response curves of class I drugs are shown in Fig. 8. As with TTX, all the class I drugs decreased VR in a dose-dependent manner. The ED_{50(VR)} values are shown in Table 1; and the order of the potency of the effect on VR of class I drugs was mexiletine, lidocaine, AN-132, ME3202, flecainide, disopyramide and procainamide. The onset half time for VR (OHT_{VR}), which indicates the onset velocity of the response to the highest dose of each drug, was fast for all drugs, as shown in Table 2. The recovery half time for VR (RHT_{VR}), which indicates the recovery speed of the responses to the highest dose of each drug, was also fast for all drugs, as shown in Table 2.

The correlation between the drug-induced change of each parameter and antiarrhythmic potency

We have previously described the use of the classical digitalis-induced and coronary ligation-induced arrhythmia models to assess the antiarrhythmic activity of class I drugs (11). Correlation between ED_{50(VICT)} in this study and antiarrhythmic effects on the in vivo canine digitalis arrhythmia of class I drugs expressed by the antiarrhythmic IC_{50} plasma concentrations from our earlier reports (11) is shown in Fig. 9. ED_{50(VICT)} correlated well with the antiarrhythmic concentrations of digitalis arrhythmias, while other ED_{50} values showed poor correlations. There was also a good correlation between ED_{50(VICT)} and the antiarrhythmic IC_{50} plasma concentrations of coronary ligation arrhythmia (data are not shown).

**DISCUSSION**

The present study was designed to test the potential utility of a blood-perfused papillary muscle preparation as a means to assess the pharmacological efficacy and adversity of the class I antiarrhythmic drugs. Although this preparation has been described previously, it has not been utilized as a tool to assess and compare the relative po-
tencies and differences within a class of antiarrhythmic drugs. The results of this study demonstrate that the relative potencies of the class I agents on IVCT, CBF, DT and VR can be readily assessed and varied significantly. Furthermore, the results demonstrate that specific properties of new agents, still in the developmental phase, can be readily and quantitatively assessed in a model in which the electrophysiological properties are known to be similar to those observed in humans (2-8).

Under physiologically maintained electrical and mechanical conditions, 1) use-dependency and pharmacodynamics of sodium channel block, 2) changes in contraction, coronary blood flow and idioventricular automaticity, and 3) correlation between cardiac direct effects and antiarrhythmic activity were assessed with this model.

Use-dependency: The use-dependent effects of lidocaine and mexiletine were assessed by using three different driving cycle lengths. The effects on IVCT were enhanced by higher stimulation frequency. These results are well in accordance with the previous in vitro and in vivo studies (3, 5, 6, 12-15). Since changes in $\dot{V}_{\text{max}}$ were
generally proportional to changes in the square of the conduction velocity (16), the use-dependency in the present experiment can be also interpreted within the framework of the "modulated receptor hypothesis" proposed by Hondeghem and Katzung to explain the interaction between class I antiarrhythmic drugs and the cardiac sodium channels (17).

Kinetics of use-dependent sodium channel block (pharmacodynamics): To estimate the onset and recovery rate of drugs in our preparation, we measured OHT and RHT, respectively. For example, disopyramide and flecainide showed slow onset and long-lasting effects on IVCT after bolus injections, while the reverse was true for lidocaine and mexiletine in this study. The order of speed estimated by OHT_{IVCT} and RHT_{IVCT} in the present study was in good accordance with that classified by the onset rate for the use dependent block and the recovery time constant from the use dependent block in previous reports, respectively (14, 18-20). Therefore, these findings indicate that the classification by the kinetics of binding and dissociation of class I drugs with Na⁺ channels is also valid in our preparation.
Fig. 8. Dose-response curves of six class I antiarrhythmic drugs for VR. The data are presented as the mean ± S.E.M. (n=6). *P<0.05, vs basal value. VR: ventricular automaticity rate.

Fig. 9. Correlation between ED_{50}(IVCT) in this study and the antiarrhythmic concentrations for digitalis arrhythmias. y=0.181x+0.004, r=0.778. Lidocaine and mexiletine were tested at two faster driving rates to examine effects on intraventricular conduction time. Other drugs were tested at 500-msec driving interval. Antiarrhythmic plasma concentrations were calculated from our earlier reports (11, 39, 40). P: procainamide, D: disopyramide, L4: lidocaine at 400-msec driving interval, L3: lidocaine at 300-msec driving interval, M4: mexiletine at 400-msec driving interval, M3: mexiletine at 300-msec driving interval, F: flecainide, ME: ME3202, AN: AN132.
Negative inotropic effects: Negative inotropic effects of antiarrhythmic drugs present a particular concern clinically, since it has been considered one of the risk factors for the higher mortality rate in the CAST trial. Seven class I antiarrhythmic drugs and TTX dose-dependently decreased DT, which is in good accordance with the previous reports (3, 5–7, 14, 21–24). The negative inotropic effect of class I antiarrhythmic drugs is considered to represent the sum of their Na⁺ channel blocking and additional drug-dependent inotropic properties (21, 25–27). The Na⁺ channel blocking effect of class I drugs has been thought to increase cardiac transmembrane Na⁺ concentration gradient, and this effect may increase the Na/Ca exchange mechanism, resulting in the decrease in the intracellular Ca⁺ concentration (21, 25–27). It has been suggested that the inhibition of slow inward Ca⁺ current (21) and inhibition of Ca²⁺ efflux from the sarcoplasmic reticulum (28) would be also responsible for their negative inotropic effects.

Procainamide and verapamil decreased the contraction of papillary muscle followed by a transient increase, which is in accordance with the previous report (7, 8). As shown in an earlier report (7), the positive inotropic phase of procainamide was not modified by pretreatment with 10–30 µg of propranolol, which is the sufficient dose to block the same degree of positive inotropic action by norepinephrine. The precise mechanism of this transient positive inotropic response by procainamide and verapamil is still unknown.

One example of the way this model can be used is to study more subtle yet potentially important negative inotropic effects of class I drugs. For example, lidocaine and mexiletine exerted negative inotropic action while the intraventricular conduction remained unaffected, although the negative inotropic actions of lidocaine and mexiletine are commonly said to be clinically insignificant (29, 30). As shown in this experiment, bolus administration of these drugs produced significant transient depression of ventricular contractility, which was comparable to that produced by disopyramide.

Effects on coronary blood flow: The class I antiarrhythmic drugs increase CBF (3, 5, 6, 12, 31), and these effects can be easily assessed in this model. To analyze further the effects of class I drugs on CBF, we compared their effects with TTX and verapamil. TTX slightly increased CBF, which is compatible with the conclusion by Lipsius et al. (32), while verapamil showed a potent and long-lasting coronary vasodilator effect. Although it is quite natural to expect that the coronary vasodilator effects of class I drugs may lead to cardioprotection as well as to antiarrhythmic activity (12, 33), the coronary effects by class I drugs may be less important, because the duration of the effects of class I drugs on CBF were transient compared with their effects on IVCT, DT and VR and much weaker than the coronary effect of verapamil.

Changes in idioventricular automaticity: Changes in the spontaneous VR were studied. Class I antiarrhythmic drugs and TTX used in this study decreased VR in a dose-dependent manner, whereas verapamil virtually did not affect it in doses that suppressed the DT and increased the CBF. Similar results were reported previously (2, 5, 7, 34–38). The ventricular automaticity observed in un-paced papillary muscle preparations has been thought to originate in Purkinje fibers in the ventricular septum (2). Consequently, the inhibition of the VR by TTX and class I drugs is most likely caused by suppression of the pacemaker current in Purkinje fibers manifesting “normal” automaticity. The mechanism of action of lidocaine responsible for this automaticity has been ascribed to their blockade of the pacemaker current activated by hyperpolarization (Iₜ) (34). This effect of class I drug may reflect its antiarrhythmic activity on the limited arrhythmias where “normal” automaticity of Purkinje fiber may play a significant role as an arrhythmogenic mechanism. Lidocaine and mexiletine should be administered with caution in patients with idioventricular rhythm without sinus beats, because a bolus administration of these drugs may produce potent depression of VR, as shown in these experiments.

Correlation between cardiac direct effects and antiarrhythmic activity: We examined the correlation between the intraarterial ED₅₀ doses in this study and the antiarrhythmic IC₅₀ plasma concentrations obtained in our previous canine arrhythmia model studies, namely digitalis- and coronary ligation-induced arrhythmias (11, 39, 40). Although these arrhythmias most likely are caused by triggered activity from delayed after depolarizations, abnormal automaticity and/or re-entrant excitation in very depolarized tissues (11, 39, 40), a good correlation was found only between ED₅₀(IVCT) in this current study and IC₅₀ of two different types of arrhythmia models. The results may indicate that the antiarrhythmic mechanism of class I drugs in the canine arrhythmia models is closely related to the suppression of the normal intraventricular conduction. However, caution must be taken on the interpretation of the in vitro results of the present study, which were obtained on “normal” cardiac tissue.

In summary, the canine isolated, blood-perfused papillary muscle preparation can be used to assess use-dependency, kinetics of sodium channel block, inotropic effects of class I drugs as well as the effects on coronary blood flow, intraventricular conduction and ventricular automaticity. Meanwhile, the model is not suitable for extensive investigation and molecular mechanisms because of mutual complex interactions of multiple parameters. Class I antiarrhythmic drugs have multiple pharma-
ological effects on ventricular tissue, including inhibition of conduction, automaticity and contraction and coronary vasodilator effects, which were similar to those of TTX and were in good accordance with previous reports using different species (13–16, 18, 19, 21, 26, 32, 34). Although these drugs may exert their antiarrhythmic effects through a combination of these actions, the effect on conduction may be the most relevant for the antiarrhythmic actions. Use of this model facilitates the comparison of direct cardiac effects of class I drugs and the data shown in this paper provide convenient guidelines in predicting possible effectiveness and potential adverse effects of the new antiarrhythmic drugs.

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