Full Paper

Effects of a Novel Cyclohexane Dicarboximide Derivative, ST-6, on Reperfusion-Induced Arrhythmia in Rats

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Received November 5, 2004; Accepted March 7, 2005

Abstract. The present study was designed to determine whether a novel cyclohexane dicarboximide derivative, ST-6, 2-[4-[4-(chlorophenyl)-4-hydroxy-1-piperidinyl]butyl]hexahydro-1*H*-isoindol-1,3(2*H*)-dione, prevents reperfusion-induced ventricular arrhythmias. Pentobarbital-anesthetized rats were subjected to left coronary artery occlusion for 4 min followed by 4-min reperfusion, and the incidence of their ventricular arrhythmias was examined. The coronary occlusion of control rats induced ventricular tachycardia and fibrillation, eventually leading to sudden death. The intravenous injection of 0.1 to 2 mg/kg ST-6 prior to the occlusion resulted in a dose-dependent suppression of the ventricular arrhythmias. The suppression of ventricular fibrillation was also observed on the intraperitoneal and intraduodenal administration of 2 to 10 mg/kg ST-6 15 min prior to coronary occlusion. Antiarrhythmic effects of this agent (0.5 mg/kg per min) were compared with those of other antiarrhythmic agents including lidocaine (0.1 mg/kg per min), sematilide (0.3 mg/kg per min), and diltiazem (0.5 mg/kg per min) by administering the agents from 1 min after the coronary occlusion to the end of 4-min reperfusion. Antiarrhythmic effects of ST-6 were similar in degree to those of lidocaine and diltiazem, whereas no significant prevention by sematilide was seen. The results suggest that ST-6 may be capable of suppressing reperfusion-induced arrhythmias following oral or intravenous administration.

Keywords: arrhythmia, rat heart, reperfusion, ST-6

Introduction

In previous studies, we have shown that a novel cyclohexane dicarboximide derivative, ST-6, attenuated hypoxia/reoxygenation-induced or ischemia/reperfusion-induced contractile dysfunction and enhanced reperfusion-induced restoration of myocardial high-energy phosphates in perfused rat hearts (1, 2). This was associated with prevention of ionic disturbances in ischemic/reperfused or hypoxic/reoxygenated hearts. Particularly, the agent attenuated ischemia- or hypoxia-induced Na⁺ accumulation. Furthermore, this agent showed a suppression of V dot max ($\dot{V}_{max}$) of the action

potential of the left ventricle (2). This implies that suppression of Na⁺ overload through Na⁺ channels in the ischemic heart plays an important role in the improvement of the ischemia/reperfusion injury, which was consistent with our previously proposed hypothesis (3, 4).

It is well recognized that ischemia and reperfusion induce various arrhythmias (5). In particular, reperfusion following a certain period of ischemia induces ventricular arrhythmias such as ventricular tachycardia and ventricular fibrillation (6), which are different from coronary occlusion-evoked arrhythmias (7). It has been shown that agents that have Na⁺ channel blockade are capable of preventing reperfusion-induced arrhythmias (8). In the present study, we determined whether ST-6

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might have an ability to prevent or reduce reperfusion-induced arrhythmias in the rat. Antiarrhythmic agents with different electrophysiological properties including the sodium channel blocker lidocaine, potassium channel blocker sotalolol, and calcium channel blocker diltiazem (9–11) were also tested in the present study for the purpose of comparison.

Materials and Methods

Animals

Eighty-six male Sprague-Dawley rats (300–450 g; Charles River Japan, Atsugi) were used in the present study. The animals were conditioned for one week at $23 \pm 1^\circ\text{C}$, with a constant humidity of $55 \pm 5\%$, under a cycle of 12 h of light and 12 h of dark and had free access to food and tap water according to the Guideline of Experimental Animal Care issued by the Prime Minister's Office of Japan.

Agents

2-[4-[4-(Chlorophenyl)-4-hydroxy-1-piperidinyl]butyl]hexahydro-1*H*-isoindol-1,3(2*H*)-dione (ST-6) was a gift from Sumitomo Pharmaceutical Company (Osaka). Lidocaine hydrochloride, sotalolol, and diltiazem hydrochloride were purchased from Sigma (St. Louis, MO, USA). Evans blue was purchased from Tokyo Chemical Product (Tokyo).

Induction of arrhythmias

Arrhythmias were induced as described previously (12). Animals were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). Their tracheae were cannulated and ventilated with room air at a rate of 5 ml/min using a respirator (SN-480-7; Shinano Seisakusho, Tokyo). The tidal volume was set at 10 ml/kg. Atelectasis was prevented by maintaining an expiratory pressure of 2 cmH₂O. Blood in the carotid artery was sampled and blood gases were measured with a gas analyzer (Model 288; Chiba-Corning, New York, NY, USA). The pO₂ and pCO₂ of the blood were adjusted to 95–110 and 35–40 mmHg, respectively, by changing the breathing rate from 40 to 60 cycle/min. Electrocardiograms (ECG-6303; Nihon Kohden, Tokyo) were measured via electrodes placed on the left thorax (apex of the heart) and the right scapula and recorded on a thermal pen recorder (TP-400T, Nihon Kohden). In some animals, ECGs (lead II) were analyzed by an ECG processor (Softron, Tokyo) to detect profiles of arrhythmias evoked during ischemia and reperfusion. The systolic blood pressure (SBP) was measured through a cannula inserted into the carotid artery. Heart rate (HR) was triggered from SBP (AT601G, Nihon Kohden). Values

for hemodynamic parameters were determined under open-chest conditions. The femoral vein was cannulated for administration of drugs. Rectal temperature was maintained at $36.5 \pm 0.5^\circ\text{C}$ with an infrared lamp.

The chest was opened and the heart was gently exteriorized after the pericardial incision. A ligature (5-0 TI-Cron; Sherwood Davis & Geck, St. Louis, MO, USA) was placed around the left coronary artery approximately 2 mm from its origin according to the method of Selye et al. (13). Then the heart was repositioned in the thoracic cavity. Both ends of the ligature were passed through a silicone tube (inside diameter, 4 mm; length, 50 mm) and exteriorized out of the thoracic cavity. Both ends of the ligature were pulled, which occluded the left coronary artery. The tube and ligature were clamped for 4 min together with a small hemostatic clamp during ischemic insults. Reperfusion was initiated by removing the clamp from the tube and ligature and confirmed by a color change in ventricular surface from cyanosis to hyperemia. Reperfusion was continued for 4 min regardless of the presence or absence of arrhythmias. The ligature was left in place in order to determine the ischemic area at the end of experiments.

It is generally believed that reperfusion after 3–10 min of ischemia results in a higher incidence of reperfusion-induced ventricular fibrillation in anesthetized rat hearts (14). We observed in a previous study that most of the reperfusion-induced arrhythmias were initiated within the first minute of reperfusion and rarely provoked longer than 4 min after coronary occlusion under the present experimental conditions (12). Accordingly, a 4-min period of ischemia followed by a 4-min period of reperfusion was employed for the study on ischemia/reperfusion arrhythmias in the present study. The mortality of animals was finally decided at the end of reperfusion. Since ventricular fibrillation was clearly discernible among ventricular arrhythmias, we focused on the incidence of ventricular fibrillation in the present study.

Treatment with agents

The purpose of the present study was to characterize the anti-arrhythmic effects of ST-6. The experimental protocol is shown in Fig. 1. In the first set of experiments, ST-6 at doses of 0.1 to 2.0 mg/kg was injected as a bolus into the femoral vein and the antiarrhythmic effects were examined. In the second set of experiments, the agents were intraperitoneally or intraduodenally administered 15 min prior to coronary occlusion and their antiarrhythmic effects were evaluated. In the third set of experiments, we compared the effects of ST-6 with those of several agents such as lidocaine,

Fig. 1. Experimental protocol is shown in Fig. 1. In the first set of experiments (1st Exp), bolus administration of ST-6 was performed 30 s before ischemia. In the 2nd set of experiments (2nd Exp), i.p. or i.d. administration was conducted at 15 min before ischemia. In the 3rd set of experiments (3rd Exp), continuous administration of ST-6, lidocaine, sematilide, or diltiazem was performed from 1 min after the onset of ischemia to the end of reperfusion. Arrhythmias were assessed throughout the experiment. At the end of reperfusion, ischemic areas were determined as described in the Methods section.

sematilide, and diltiazem that are well recognized to exert anti-arrhythmic effects in animals and humans (9 – 11). ST-6 at the rate of 0.2 mg/kg per min, lidocaine at the rate of 0.2 mg/kg per min, sematilide at the rate of 0.3 mg/kg per min, diltiazem at the rate of 0.2 mg/kg per min, or saline was infused into the femoral vein from 1 min after coronary artery occlusion to 4 min after reperfusion and their antiarrhythmic effects were examined. The doses of agents used were determined on the basis of those of bolus injection that proved to be effective in suppressing reperfusion arrhythmias in this model in a preliminary study. The total doses infused for 7 min in the third set of the experiments were similar to those of the bolus administration. These agents were dissolved in saline. The order of treatments was randomized using a table of random numbers.

Measurement of ischemic area

After the experiment, a 500 IU/kg heparin was injected into the femoral vein. The heart was removed and perfused in a Langendorff manner with 10 ml of the Krebs-Henseleit solution at a constant perfusion pressure of 100 cmH₂O through the aortic cannula. The left coronary artery was occluded again by the ligature that remained around this artery. A 2-ml aliquot of 1% Evans blue was injected into the heart from a side arm of the cannula inserted into the aorta for 1 min under a perfusion pressure of 100 mmH₂O. The heart was cut into 1.5-mm-thick transverse sections and these sections were blotted on filter paper. Each section was divided into two: one was the ischemic region that was not colored by Evans blue and the other, the non-ischemic region that was stained. The wet weights of ischemic and non-ischemic areas were expressed as percentages of the total heart weight.

Selection of animals based on the ischemic area

In the rat heart, the severity of reperfusion-induced arrhythmias is highly dependent on the size of the ischemic area (12, 15). Thus, for the analysis of data, 70 rats that had 40 – 55% ischemic area were used, whereas 16 rats that had less than 40% ischemic area were not. This elimination criterion has been used for the effects of anti-arrhythmic agents on ischemia/reperfusion-induced arrhythmias in a previous study (12).

Criteria of arrhythmias and death

The classification of arrhythmias was carried out according to the Lambeth Conventions (16) with a slight modification (17). That is, ventricular fibrillation is defined as a signal from which individual QRS deflections vary in amplitude and coupling interval on a cycle-to-cycle basis. When ventricular fibrillation-induced hypotension (below 50 mmHg) remained for longer than 2 min, animals were considered to be terminal. Rats that were deemed to be terminal never recovered normal cardiac rhythm during the experiment. Irreversible ventricular fibrillation was the only cause of death.

Statistics

The results are expressed as the means $\pm$ S.E.M. Statistical significance was compared between untreated (control) and agent-treated groups. One-way ANOVA followed by Bonferroni's multiple comparison test was used to compare the ischemic area and hemodynamic parameters among all groups. Fisher's exact test was used to compare the incidence of ventricular fibrillation and mortality between untreated (control) and agent-treated groups. A probability of less than 5% was considered significant.

Results

Effects of bolus injection on reperfusion-induced arrhythmias

Four minutes of ischemia and 4 min of reperfusion always induced ventricular fibrillation and death in control animals in the present study. ECGs of ischemic/reperfused rats are shown in Fig. 2. Coronary

Control

a

Ischemia

b

c

d

Reperfusion

e

f

1 s 2 mV

Fig. 2. ECGs (lead II) of coronary artery-ligated rats. a) ECG of a pre-ischemic rat. b) ECG at the onset of coronary ligation. c) ECG at 16 s after the coronary ligation (ischemia). A rise in the ST segment was seen. d) ECG at the end of ischemia. e) ECG at 12 s after the release of the coronary ligation (reperfusion). Ventricular tachycardia occurred. f) ECG at 36 s after reperfusion. Ventricular fibrillation occurred in this animal.

artery-ligated rats (controls) elicited ventricular arrhythmias including ventricular tachycardia and ventricular fibrillation during ischemia/reperfusion, which did not recover to a control rhythm at the end of 4-min reperfusion. The rats were injected intravenously with a bolus of 0.1 to 2 mg/kg of ST-6 at 1 min prior to coronary occlusion (Table 1). Treatment with saline (control group) did not prevent reperfusion-induced arrhythmias at all. In rats given the intravenous injection of ST-6, a dose-dependent suppression of the reperfusion-induced ventricular fibrillation was observed. Complete abolishment of the arrhythmias was seen in rats treated with 1 mg/kg of ST-6. The rats that were intravenously injected with 2.0 mg/kg of ST-6 showed no significant alterations in SBP, but revealed decreases in HR at 1 min after administration of the agent and at 4 min after occlusion as compared with controls. Ischemic areas in the treated animals did not differ from those of controls.

Effects of intraperitoneal and intraduodenal injection on reperfusion arrhythmias

In the second set of experiments, the rats were intraperitoneally injected with different doses of ST-6 ranging from 2 to 10 mg/kg (Table 2). A dose-dependent suppression of the reperfusion-induced ventricular fibrillation was also observed. ST-6 at a dose of 10.0 mg/kg completely and significantly abolished the reperfusion-induced ventricular fibrillation. Intraduodenal injection of 10 mg/kg of ST-6 also resulted in significant suppression of the reperfusion-induced

Table 1. Systemic blood pressure, heart rate, ischemic area, and incidence of ventricular fibrillation of coronary artery-ligated rats treated with intravenous administration of ST-6 1 min prior to coronary ligation

	Saline	ST-6			
		0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	2.0 mg/kg
SBP (mmHg)					
Before	92.5 ± 6.0	98.3 ± 8.3	100.0 ± 2.4	98.8 ± 5.5	97.5 ± 5.8
0 min	92.5 ± 6.0	98.3 ± 8.3	100.0 ± 2.9	96.3 ± 5.2	95.0 ± 5.9
4 min	86.3 ± 5.5	71.7 ± 10.7	95.0 ± 10.0	81.3 ± 3.8	80.0 ± 6.0
HR (beats/min)					
Before	375 ± 17	379 ± 10	389 ± 13	400 ± 11	366 ± 12
0 min	375 ± 17	373 ± 11	372 ± 14	358 ± 8	320 ± 10*
4 min	378 ± 15	356 ± 3	385 ± 36	357 ± 9	296 ± 11*
Incidence of VF	4/4	2/3	1/3	0/4*	0/3*
Ischemic area (% total heart)	49.7 ± 0.6	49.2 ± 1.2	49.4 ± 0.8	50.4 ± 0.9	48.9 ± 1.0

Systolic blood pressure (SBP) and heart rate (HR) of rats under open chest conditions were measured before the administration of ST-6 (before), at 1 min after the administration (0 min), and at 4 min after coronary artery occlusion (4 min). ST-6 was injected through the femoral vein 1 min before coronary artery occlusion. The incidence of ventricular fibrillation (VF) is expressed as incidence/number of animals. Values represent the means ± S.E.M. of 3 or 4 experiments. *Significantly different from controls ($P < 0.05$).

arrhythmias.

There were no significant decreases in SBP and HR after intraperitoneal or intraduodenal administration of ST-6 as compared with controls. Also, there was no significant difference in the ischemic areas produced between control and treated animals.

Effects of various anti-arrhythmic agents on reperfusion-induced ventricular fibrillation

Rats were treated with an intravenous injection of vehicle, 0.1 mg/kg per min of lidocaine, 0.3 mg/kg per min of sematilide, 0.5 mg/kg per min of diltiazem, and 0.2 mg/kg per min of ST-6 from 1 min of occlusion to the end of 4-min reperfusion (totally for 7 min), and the suppression of reperfusion-induced ventricular fibrilla-

Table 2. Systolic blood pressure, heart rate, ischemic area, and incidence of ventricular fibrillation of coronary artery-ligated rats treated with intraperitoneal (i.p.) or intraduodenal (i.d.) administration of ST-6 15 min prior to coronary occlusion

	Saline	ST-6			
		2 mg/kg, i.p.	5 mg/kg, i.p.	10 mg/kg, i.p.	10 mg/kg, i.d.
SBP (mmHg)					
Before	93.6 ± 5.0	93.3 ± 1.7	101.7 ± 10.1	112.0 ± 12.0	102.0 ± 3.4
0 min	93.7 ± 5.2	94.3 ± 11.0	99.3 ± 14.4	90.0 ± 7.4	92.0 ± 6.6
4 min	86.8 ± 5.5	75.0 ± 7.6	81.0 ± 14.5	72.0 ± 8.1	80.6 ± 5.0
HR (beats/min)					
Before	380 ± 17	387 ± 32	393 ± 21	428 ± 19	417 ± 21
0 min	381 ± 17	372 ± 53	366 ± 32	359 ± 11	384 ± 18
4 min	377 ± 15	373 ± 49	401 ± 44	384 ± 12	391 ± 12
Incidence of VF	4/4	2/3	1/3	0/4*	1/5*
Ischemic area (% total heart)	49.0 ± 2.8	48.4 ± 3.0	48.7 ± 1.8	47.5 ± 1.8	47.1 ± 2.1

Systolic blood pressure (SBP) and heart rate (HR) of rats under open chest conditions were measured before the administration of ST-6 (before), just prior to coronary occlusion (0 min), and at 4 min after coronary occlusion (4 min). ST-6 was administered intraperitoneally (i.p.) or intraduodenally (i.d.) 15 min prior to coronary occlusion. The incidence of ventricular fibrillation (VF) is expressed as incidence/number of animals. Values represent the mean ± S.E.M. of 3 – 5 experiments. *Significantly different from controls ($P < 0.05$).

Table 3. Systolic blood pressure, heart rate, and ischemic area of coronary artery-ligated rats treated with intravenous administration of lidocaine, sematilide, diltiazem, and ST-6 during and after coronary ligation

	Control	Lidocaine	Sematilide	Diltiazem	ST-6
SBP (mmHg)					
Before	106.1 ± 5.3	117.4 ± 4.1	100.2 ± 4.3	124.1 ± 5.3	105.3 ± 2.4
Occlusion					
1 min	86.6 ± 6.0	94.3 ± 4.3	77.0 ± 3.9	103.3 ± 5.2	82.0 ± 5.2
4 min	93.3 ± 6.5	104.7 ± 4.7	92.0 ± 6.0	89.3 ± 3.4	93.0 ± 5.0
HR (beats/min)					
Before	431 ± 9	411 ± 7	398 ± 10	404 ± 9	433 ± 10
Occlusion					
1 min	460 ± 9	421 ± 7	414 ± 12	403 ± 13	448 ± 12
4 min	458 ± 9	415 ± 12	407 ± 12	400 ± 13	425 ± 10
Ischemic area (% total heart)	49.3 ± 1.1	47.2 ± 0.9	49.5 ± 1.1	47.3 ± 0.9	48.1 ± 0.3

Systolic blood pressure (SBP) and heart rate (HR) of rats under open chest conditions were measured before the administration of agents (before) and at 1 min (1 min) and 4 min (4 min) after coronary artery occlusion. Lidocaine, sematilide, diltiazem, and ST-6 were injected into the femoral vein at doses of 0.1, 0.3, 0.5, and 0.2 mg/kg per min, respectively. Values represent the means ± S.E.M. of 14 experiments. There were no significant differences in these parameters for treated groups as compared with controls.

Fig. 3. The incidence of ventricular fibrillation (hatched columns) and mortality (striped columns) of saline-treated (Con) and 0.1 mg/kg per min lidocaine (Lid)-, 0.3 mg/kg per min semaltilide (Sem)-, 0.5 mg/kg per min diltiazem (Dil)-, and 0.2 mg/kg per min ST-6 (ST6)-treated rats. Values represent the incidence of ventricular fibrillation and mortality. *Significantly different from controls ($P < 0.05$).

tion was examined (Table 3 and Fig. 3). Incidence of ventricular fibrillation and the subsequent sudden death were observed in all control animals. The fibrillation and death were attenuated by treatment with an intravenous administration of the anti-arrhythmic agents employed (Fig. 3). Significant attenuations in ventricular fibrillation and mortality were seen in the animals treated with lidocaine, diltiazem, and ST-6. In some rats treated with either of the three agents, reperfusion-induced ventricular fibrillation ceased and ventricular tachycardia occurred, resulting in a survival of animals during the experiment. The most prominent reduction in mortality was seen in the animals given ST-6. In contrast, the suppression of ventricular fibrillation and mortality by semaltilide was not significant. Effects of anti-arrhythmic agents on SBP and HR were examined (Table 3). The SBP and HR of each agent-treated, occluded animals did not significantly decrease as compared with controls. This model showed an approximately 50% ischemic area. There were no significant differences in the ischemic area among the groups examined.

Discussion

The present study has demonstrated that the serious arrhythmias detected during reperfusion were mainly ventricular tachycardia and ventricular fibrillation and that ischemia/reperfusion-induced arrhythmias *in vivo* were prevented by pretreatment with an intravenous administration of a novel cyclohexane dicarboximide derivative, ST-6, in rats. This antiarrhythmic effect was associated with no significant alteration in SBP at any

doses employed and a considerable decrease in HR at the higher doses when the agent was administered intravenously, suggesting that ST-6 at high doses affects cardiac rhythm. The prevention of arrhythmias was also observed on the intraperitoneal and intraduodenal administration of this agent, suggesting that ST-6 is capable of preventing reperfusion-induced arrhythmias when administered orally. In addition, we observed a similar anti-arrhythmic action when the agent was administered intravenously from 1 min after coronary artery occlusion to 4 min after reperfusion, suggesting that post-ischemic administration is also effective in the prevention of reperfusion-induced arrhythmias and mortality. We observed relatively less antiarrhythmic effect of the continuous infusion of ST-6 as compared with that of the bolus injection of the agent. This may be due to differences in the dose of the agent applied and the method of administration. That is, the tissue concentration of ST-6 by the continuous administration at the time when reperfusion is started, might be less than that by the bolus pre-administration.

Arrhythmias associated with myocardial ischemia are classified into three types (5): arrhythmias that occur within 30 min of myocardial ischemia, delayed-phase arrhythmias occurring after 1.5 – 24 h of ischemia, and reperfusion-induced arrhythmias. The arrhythmias that occurred in the present study are of the reperfusion-induced type, the mechanism of which is considered to be different from that of the former two types (7). Arrhythmias during an early phase of ischemia and those induced by reperfusion are thought to be associated with sudden cardiac death (18). Both types of arrhythmias are considered to be due to a reentry resulting from decreased conduction velocity and increased inhomogeneity in the refractory periods of myocardial cells (19). The mechanism of action of ST-6 might be related to these properties, although further electrophysiological study is required to elucidate exactly how this agent prevents ventricular arrhythmias.

Generally, reperfusion-induced arrhythmias are believed to occur due to oxygen free radicals and ionic disturbances involving Na^+ and Ca^{2+} (20). Numerous antioxidants have been shown to prevent reperfusion-induced arrhythmias in various animal species (21 – 24). Ohoi et al. (25) demonstrated that an oxygen radical scavenger, recombinant human superoxide dismutase, prevented reperfusion-induced arrhythmias in this model. It remains unclear at present whether ST-6 might have antioxidant effects in the heart or not.

In the present study, we compared the antiarrhythmic effects of ST-6 with those of several ion channel blockers. A sodium channel blocker lidocaine at a dose similar to ST-6 appreciably attenuated reperfusion-

induced arrhythmias. Lidocaine has been shown to exert a suppressive effect on the Vmax of the action potential of the cardiac muscle (3). Similarly, we observed in a previous study that ST-6 had the suppressive effects on the Vmax of the left ventricle (2). Furthermore, there is accumulating evidence that class I type antiarrhythmic agents that are capable of suppressing Na⁺ channels prevent reperfusion-induced arrhythmias (8). We also proposed that class I type antiarrhythmic agents enhanced the post-ischemic contractile recovery associated with suppression of Na⁺ accumulation in the ischemic and ischemic/reperfused heart (3, 4). Furthermore, ST-6 has been shown to attenuate the ischemia- and ischemia/reperfusion-induced Na⁺ accumulation and K⁺ loss in the perfused heart (1, 2). These results suggest that the prevention by ST-6 of ischemia/reperfusion-induced ionic disturbances plays an important role in the improvement of reperfusion-induced injury including ventricular fibrillation.

The prevention of reperfusion-induced arrhythmias was also detected on treatment with diltiazem in the present study. As described above, Ca²⁺ may play an important role in the incidence of ventricular arrhythmias during reperfusion (10, 26–28). Osada et al. (28) have proposed that extracellular Ca²⁺ plays an important role as a promoter of reperfusion ventricular fibrillation. The exact mechanism underlying the contribution of the L-type calcium channel blocker to reperfusion-induced ventricular arrhythmias remains to be elucidated.

We found no significant effects of a class III type antiarrhythmic agent, sotalol, on reperfusion-induced ventricular arrhythmias. Class III antiarrhythmic agents are known to block K⁺ currents and prolong action potential duration and QT interval without having any effect on the impulse conduction (29), indicating relatively selective action on refractoriness of the action potential. Reperfusion-induced arrhythmias are caused by multiple mechanisms (7); that is, conduction and refractoriness abnormalities account for propagation of arrhythmias and their initiation is due to an extra-stimulus likely related to triggered activity (30). Thus, it is unlikely that a drug acting on refractoriness would affect reperfusion arrhythmia.

The present study demonstrated that ST-6 was capable of exerting antiarrhythmic effects on the reperfusion-induced ventricular arrhythmias in vivo in the rat. We previously demonstrated an amelioration of ischemia/reperfusion-induced contractile recovery by ST-6 in the perfused heart. Thus, this agent might be useful for the therapy of ischemic heart diseases.

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