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Attenuation of conduction delay by ischemic preconditioning reduces ischemia-induced ventricular arrhythmias.

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Abstract

Ischemic preconditioning has been acknowledged as a powerful method of decreasing ischemic injury. However, the antiarrhythmic mechanism of ischemic preconditioning during ischemia is unclear. We studied the effects of ischemic preconditioning on arrhythmias and cardiac electrophysiology during ischemia in Langendorff rat hearts (n = 44). In the non-preconditioned group (PC(-); n = 24), the hearts underwent 5-min zero-flow global ischemia without any prior ischemic preconditioning. In the preconditioned group (PC(+); n = 20), the hearts were preconditioned by three cycles of 3-min zero-flow global ischemia and 5-min reperfusion before undergoing 5-min global ischemia. Ischemic preconditioning reduced the incidence of ischemia-induced arrhythmias (PC(-); 38.9%, PC(+): 8.3%, $p < 0.05$), shortened monophasic action potential duration (MAPD, $P < 0.05$), attenuated conduction delay (conduction time; PC(-): 234.2%, PC(+): 173.4%, $P < 0.05$) and increased the ventricular fibrillation threshold. Although the shortening of MAPD in PC(-) hearts was not influenced by the presence or absence of arrhythmias, conduction time prolongation at 3-min was more obvious in PC(-) hearts with arrhythmia than in PC(-) hearts without arrhythmia (PC(-) with arrhythmia: 220.2%, PC(-) without arrhythmia: 190.7%, $P < 0.05$). We concluded that ischemic preconditioning could protect the rat hearts from ischemia-induced arrhythmias and postulated that attenuation of conduction delay during ischemia might be an important factor in the antiarrhythmic action of ischemic preconditioning.

Attenuation of Conduction Delay by Ischemic Preconditioning Reduces Ischemia-Induced Ventricular Arrhythmias

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Ischemic preconditioning has been acknowledged as a powerful method of decreasing ischemic injury. However, the antiarrhythmic mechanism of ischemic preconditioning during ischemia is unclear. We studied the effects of ischemic preconditioning on arrhythmias and cardiac electrophysiology during ischemia in Langendorff rat hearts (n = 44). In the non-preconditioned group (PC$_{(-)}$; n = 24), the hearts underwent 5-min zero-flow global ischemia without any prior ischemic preconditioning. In the preconditioned group (PC$_{(+)}$; n = 20), the hearts were preconditioned by three cycles of 3-min zero-flow global ischemia and 5-min reperfusion before undergoing 5-min global ischemia. Ischemic preconditioning reduced the incidence of ischemia-induced arrhythmias (PC$_{(-)}$: 38.9%, PC$_{(+)}$: 8.3%, p < 0.05), shortened monophasic action potential duration (MAPD, P < 0.05), attenuated conduction delay (conduction time; PC$_{(-)}$: 234.2%, PC$_{(+)}$: 173.4%, P < 0.05) and increased the ventricular fibrillation threshold. Although the shortening of MAPD in PC$_{(-)}$ hearts was not influenced by the presence or absence of arrhythmias, conduction time prolongation at 3-min was more obvious in PC$_{(-)}$ hearts with arrhythmia than in PC$_{(-)}$ hearts without arrhythmia (PC$_{(-)}$ with arrhythmia: 220.2%, PC$_{(-)}$ without arrhythmia: 190.7%, P < 0.05). We concluded that ischemic preconditioning could protect the rat hearts from ischemia-induced arrhythmias and postulated that attenuation of conduction delay during ischemia might be an important factor in the antiarrhythmic action of ischemic preconditioning.

Key words: preconditioning, ischemia, arrhythmia

I schemic preconditioning is a phenomenon in which a brief episode of ischemia reduces the ischemic injury during subsequent prolonged ischemia (1). It is becoming apparent that ischemic preconditioning can offer a wide range protection against ischemia/reperfusion-induced malignant arrhythmias in many animal species (2-5). From the electrophysiological view point, it is well known that the development of malignant arrhythmia is closely related to action potential duration and conduction delay. It has been reported that one of the antiarrhythmic mechanisms associated with ischemic preconditioning is related to a more obvious shortening of action potential. However, little attention has been paid to the electrophysiological mechanism of the effects of ischemic preconditioning on ischemia-induced arrhythmias. In particular, the data on conduction delay during ischemia is lacking. Therefore, the purpose of this study was to determine whether ischemic preconditioning might reduce ischemia-induced arrhythmias and to clarify the electrophysiological mechanisms of the effects of ischemic preconditioning on ischemia-induced arrhythmias in a global ischemia model.

Materials and Methods

Animals and experimental protocol. All experiments were conducted according to the 'Guiding Principles in the Care and Use of Laboratory Animals of the Okayama University Medical School and the American Physiological Society'.

Male rats weighting 190-250 g were used in all studies. The experiments were carried out on a total of 44 isolated rat hearts that were divided into two groups (as shown in Fig. 1). In the non-preconditioned group (PC$_{(-)}$), the 24 rats were subjected to a 5-min global

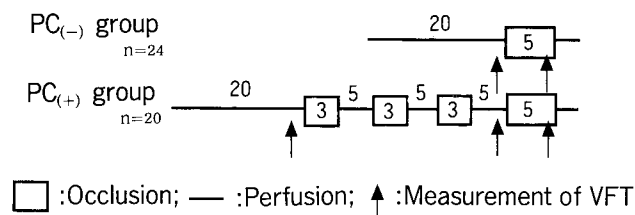* To whom correspondence should be addressed.

PC(-) group
n=24

PC(+) group
n=20

□ :Occlusion; —— :Perfusion; ↑ :Measurement of VFT

Fig. I   Experimental protocol: 24 hearts were subjected to 5-min global ischemia (PC(-)). Preconditioned hearts were subjected to three cycles of 3-min zero-flow global ischemia followed by 5-min reperfusion and then subjected to 5-min global ischemia (PC(+)). Monophasic action potentials and conduction time were recorded at baseline, preischemia, I-min, 2-min, 3-min, 4-min and 5-min, respectively, and ventricular fibrillation threshold (VFT) was measured at baseline, preischemia and 3-min of ischemia (arrow).

ischemia (zero flow). In the preconditioned group (PC(+)), the other 20 rats were preconditioned by three cycles of 3-min brief global ischemia with a 5-min reperfusion interval followed by a 5-min global ischemia. The incidence of premature ventricular capture, ventricular tachycardia and ventricular fibrillation were analyzed, and monophasic action potential duration at 75 % repolarization (MAPD$_{75}$) and conduction time (CT) were measured in both the PC(-) (n = 18) and the PC(+) (n = 12) groups. Ventricular fibrillation threshold (VFT) was measured in both the PC(-) (n = 6) and the PC(+) (n = 8) groups.

Preparation of the heart.   All animals were anesthetized with sodium pentobarbital (30 mg/kg) after heparin (1,000 U/kg) was given intraperitoneally. The chests were opened via the diaphragm and then the hearts were immediately arrested from beating by ice-cold 0.9 % saline. After the aorta was cannulated, the hearts were quickly removed. Coronary perfusion through the aortic cannula was begun immediately. The hearts were perfused at a constant pressure of 80 cm H$_2$O (8 kPa), with a modified Krebs Henseleit buffer (pH = 7.4) containing (mmol): NaCl 122.3, NaHCO$_3$ 27.0, KCl 3.7, CaCl$_2$ 1.3, MgSO$_4$ 0.6, KH$_2$PO$_4$ 1.3, glucose 5.0 and sodium puruvate 2.0, which was prewarmed to 37 °C and equilibrated with 95 % O$_2$ and 5 % CO$_2$. The hearts were supported vertically in an organ bath of 37 °C in order to avoid temperature changes. Experiments were started after a 20-min equilibration period. The arrhythmias were continuously displayed on oscilloscope (Siemens E 167 E, Sweden) at 100 mm s^{-1} sweep speed and permanent chart recordings at 100 mm s^{-1} speed were taken during for the duration of the arrhythmias. Monophasic action potential

duration (MAPD) and conduction time (CT) recordings were connected to an oscilloscope and an 8-channel recorder (Grapheteic Corp. Japan) at a paper speed of 250 mm s^{-1}.

Analysis of arrhythmia.   The incidence of ventricular arrhythmias occurring during the 5-min episode of ischemia was determined. Diagnosis and quantification on arrhythmias were made following the Lambeth Conventions (6). Ventricular tachycardia was defined as four or more consecutive ventricular premature beats and ventricular fibrillation as a signal in which individual QRS complexes could not be distinguished from one another and for which a rate could not be determined.

Measurement of MAPD$_{75}$ and CT. MAPDs from the left ventricular (LV) epicardium were recorded with bipolar Ag-AgCl contact electrodes with interelectrode distances of 2 mm. They were measured from the steepest upstroke of the monophasic action potential (MAP) to the level of 75 % at repolarization (MAPD$_{75}$). CT was measured from the stimulus of the right ventricular apex to the upstroke of MAP at the LV epicardial recording site. Right ventricular apex pacing at 330 beats/min was performed throughout the experiment.

VFT measurement (7).   The right ventricular apex was stimulated at 330 beats/min (S$_1$) throughout the experiment via a unipolar needle electrode, the effective refractory period (ERP) of the LV was firstly determined before VFT of the LV was measured. Extra stimulus (S$_2$) with a duration of 2 ms at twice the pacing threshold was applied to every 8 beats of S$_1$. The interval between the S$_1$ and S$_2$ was progressively increased in steps of 5 ms from S$_1$ until it successfully captured the ventricle (ERP). The VFT was determined by measuring the minimal voltage (V) needed to produce ventricular fibrillation. A current (2 ms pulse) was applied after the 8th heart beat during the vulnerable period at an ERP-5 ms interval and was increased in 0.1 V increments from twice the pacing threshold until ventricular fibrillation was initiated.

Statistical analysis.   Data are presented as either percent incidence or mean ± standard deviation (SD). Arrhythmia incidence was analyzed using the χ^2 test. Time-dependent changes or the differences among the values of PC(-) and PC(+) groups were statistically analyzed by the analysis of variance test (ANOVA). The t-test was used to compare the electrophysiological parameters (MAPD, CT and VFT) between groups. A proba-

bility of < 0.05 was considered statistically significant.

Results

Incidence of Arrhythmias, MAPD$_{75}$, CT and VFT in PC$_{(+)}$ and PC$_{(-)}$. In this report, "ventricular arrhythmias" refers to the presence of premature ventricular capture, ventricular tachycardia and ventricular fibrillation. In preparations exhibiting ischemia-induced arrhythmias (Fig. 2), 38.9% (7/18) of arrhythmias were total incidence, 27.8% (5/18) of arrhythmias were premature ventricular capture and ventricular tachycardia, and 11.1% (2/18) of arrhythmias were ventricular fibrillation. Ischemic preconditioning significantly reduced the incidence of ischemia-induced arrhythmias (PC$_{(-)}$: 38.9%, PC$_{(+)}$: 8.3%, $P < 0.05$). Fig. 3 shows a representative case in MAPD and CT during ischemia. During the 5-min ischemia, MAPD was shortened, and CT was prolonged. The shortening of MAPD was more dramatic in PC$_{(+)}$ than in PC$_{(-)}$ during the 5-min ischemia (MAPD$_{75}$; PC$_{(-)}$: 81.6 ± 2.0%, PC$_{(+)}$: 72.6 ± 3.4 %, $P < 0.05$, Fig. 4). The time course of CT during ischemia is illustrated in Fig. 5. CT increased gradually from 100% of baseline to 234.2 ± 53.0% during the 5-min ischemia, and ischemic preconditioning attenuated CT prolongation from 100% of baseline to 173.4 ± 22.7% during the 5-min ischemia (PC$_{(+)}$ vs PC$_{(-)}$, $P < 0.05$). In PC$_{(-)}$ hearts, VFT at 3

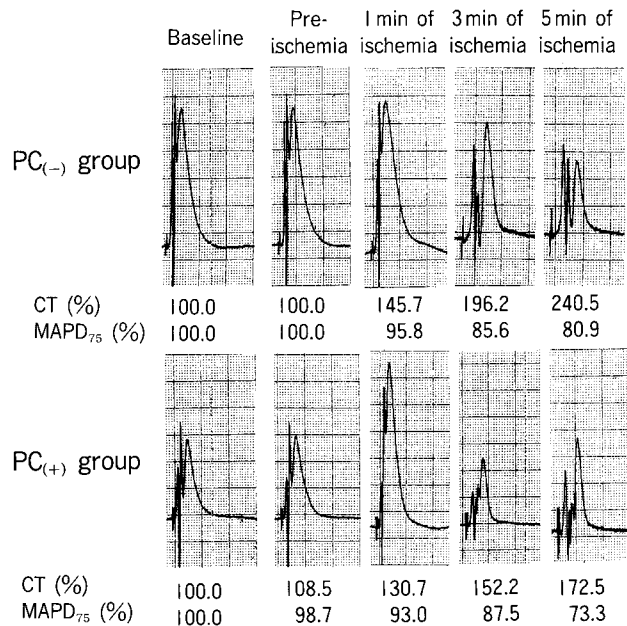|	Baseline	Pre-ischemia	1 min of ischemia	3 min of ischemia	5 min of ischemia
PC$_{(-)}$ group					
CT (%)	100.0	100.0	145.7	196.2	240.5
MAPD$_{75}$ (%)	100.0	100.0	95.8	85.6	80.9
PC$_{(+)}$ group					
CT (%)	100.0	108.5	130.7	152.2	172.5
MAPD$_{75}$ (%)	100.0	98.7	93.0	87.5	73.3

Fig. 3 Representative recordings show the electrophysiological changes during 5-min ischemia of zero flow. A reduction in monophasic action potential duration (MAPD) was less in PC$_{(-)}$ group compared PC$_{(+)}$ group but a prolongation in conduction time (CT) was greater in PC$_{(-)}$ compared to PC$_{(+)}$ group. PC$_{(-)}$: Non-preconditioned group; PC$_{(+)}$: Preconditioned group.
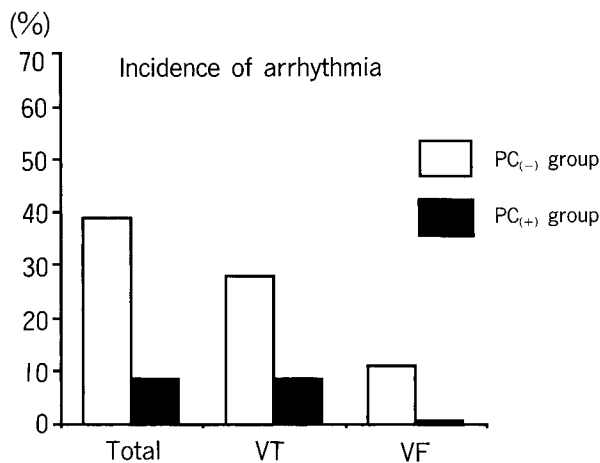

Fig. 2 Incidence (%) of ventricular arrhythmias during 5-min global ischemia: Ischemic preconditioning reduced the incidence of ventricular arrhythmia. PC$_{(-)}$: Non-preconditioned group (n = 18); PC$_{(+)}$: Preconditioned group (n = 12); VT: Ventricular tachycardia; VF: Ventricular fibrillation.
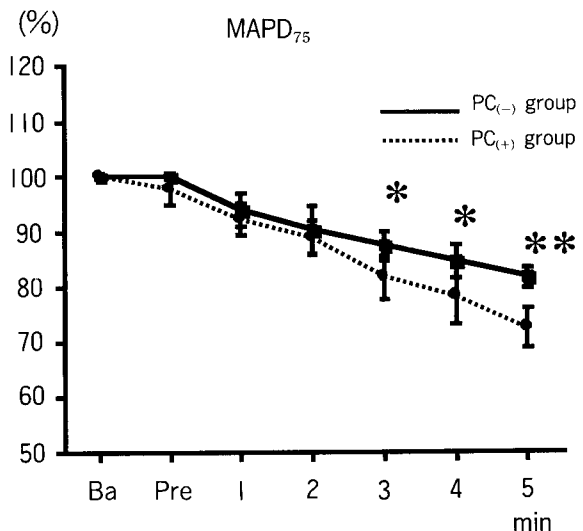

Fig. 4 Time course of monophasic action potential duration (MAPD) at 75% repolarization (MAPD$_{75}$) expressed as percentage of change during 5-min global ischemia. MAPD was gradually shortened which was greater in PC$_{(+)}$ group than PC$_{(-)}$ group, especially from 3-min ischemia on. Ba: Baseline; Pre: Preischemia; PC$_{(-)}$: Non-preconditioned group (n = 18); PC$_{(+)}$: Preconditioned group (n = 12. *$P < 0.05$, **$P < 0.01$ vs PC$_{(-)}$).
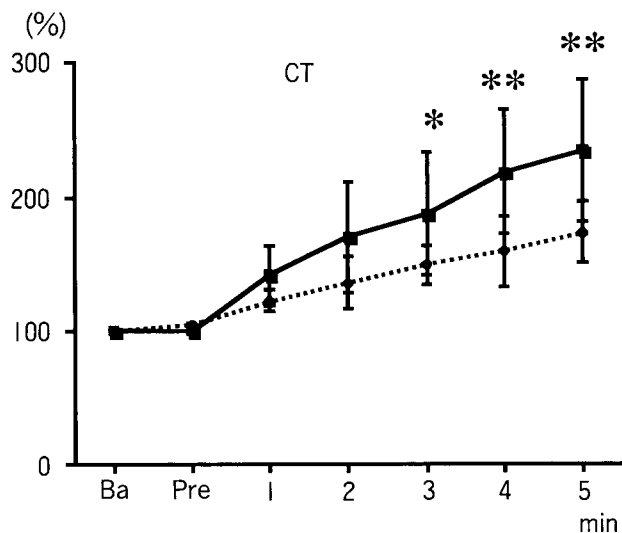
Fig. 5   Time course of conduction time (CT) expressed as percentage of change during 5-min global ischemia. CT was gradually prolonged which was greater in PC$_{(-)}$ group than PC$_{(+)}$ group. Ba: Baseline; Pre: Preischemia; PC$_{(-)}$: Non-preconditioned group (n = 18); PC$_{(+)}$: Preconditioned group (n = 12). *$P < 0.05$, **$P < 0.01$ vs PC$_{(-)}$ group.

Table I   Effect of ischemic preconditioning (IPC) on ventricular fibrillation threshold (VFT) in rat hearts

	Baseline	Pre-ischemia	3 min of ischemia
PC$_{(-)}$	6.9 ± 0.5	6.9 ± 0.5	$2.1 \pm 0.4\#$
PC$_{(+)}$	6.7 ± 0.4	6.6 ± 0.5	$3.9 \pm 0.3^*\#$

All values are mean ± SD. VFT of the isolated rat heart at baseline, pre-ischemia and at 3 min of ischemia in PC$_{(-)}$ and PC$_{(+)}$ groups are presented. The table shows that IPC can increase the VFT during ischemia.
PC$_{(-)}$: Non-preconditioned   group; PC$_{(+)}$: Ischemic   preconditioned group.
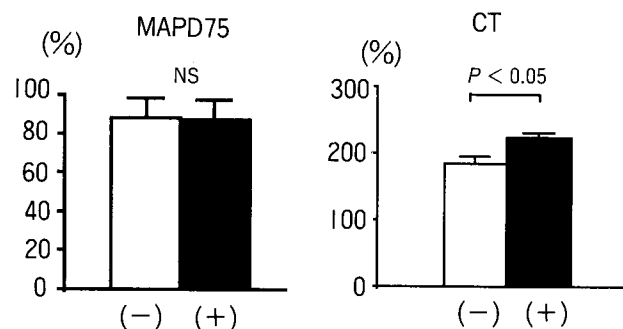*$P < 0.05$ vs PC$_{(-)}$; #$P < 0.05$ vs baseline.

Fig. 6   Comparison of monophasic action potential duration at 75% repolarization (MAPD$_{75}$) and conduction time (CT) between arrhythmia$_{(+)}$ and arrhythmia$_{(-)}$ in PC$_{(-)}$ rats. Because arrhythmia almost occurred during 4-5 min ischemia, MAPD$_{75}$ and the CT was selected to record only at 3-min ischemia.

min of ischemia was significantly reduced compared with that of the baseline (from 6.9 ± 0.5 V to 2.1 ± 0.4 V), but in PC$_{(+)}$ hearts the reduction in VFT at 3 min of ischemia was significantly less as compared with PC$_{(-)}$ hearts   (PC$_{(-)}$: 2.1 ± 0.4 V, PC$_{(+)}$: 3.9 ± 0.3 V, $P <$ 0.05) (Table 1).

MAPD$_{75}$ and CT changes during ischemia in PC$_{(-)}$ hearts with arrhythmia and without arrhythmia.   To analyze the electrophysiological mechanism of ischemia-induced arrhythmia, PC$_{(-)}$ hearts were divided into two groups: hearts with arrhythmia (arrhythmia$_{(+)}$) and hearts without arrhythmia (arrhythmia$_{(-)}$). MAPD$_{75}$ and CT of arrhythmia$_{(+)}$ were compared with those of arrhythmia$_{(-)}$. There were no significant differences in MAPD$_{75}$ at 3 min of ischemia between arrhythmia$_{(+)}$ and arrhythmia$_{(-)}$ (arrhythmia$_{(+)}$: $86.6 \pm$ 11.5%, arrhythmia$_{(-)}$: $85.6 \pm 8.5\%$, $P =$ NS), but CT at 3 min of ischemia was significantly prolonged in arrhythmia$_{(+)}$ compared with arrhythmia$_{(-)}$ (arrhythmia$_{(+)}$: 220.2 ± 7.6 %, arrhythmia$_{(-)}$: 190.7 ± 10.5 %, $P <$ 0.05; Fig. 6).

Discussion

Choice of the model.   There are several animal models which can be used for the study of arrhythmias caused by myocardial ischemia. In our global model, the effects of ischemia were more homogeneously distributed compared with models of regional ischemia (8). The incidence and mechanisms of arrhythmia in hearts with homogeneous ischemia versus those with regional ischemia might be very different, since the presence of boundaries between ischemic and nonischemic regions are probably important for generation of arrhythmias. Some studies suggest that, in the occurrence of ventricular fibrillation in the global ischemia group, a second (injury current independent) arrhythmogenic mechanism (i.e., reentry or abnormal automaticity) may function during ischemia (9). However, the low incidence of ventricular fibrillation indicates that the importance of this second mechanism is minor compared with the injury current-dependent mechanism. An obvious advantage of the present model is that zero-flow global ischemia precludes

all possibility of any antiarrhythmic effect being mediated by increments of collateral flow. In view of this factor, we applied the zero flow model to the study of the electrophysiological mechanism of the antiarrhythmic action of ischemic preconditioning.

Arrhythmias during ischemia. Our results demonstrated that the total incidence of ventricular arrhythmias was 38.9% and the vulnerability of the hearts towards ventricular fibrillation was increased during global ischemia. It is known that various electrophysiological mechanisms may be responsible for the genesis of ischemia-induced arrhythmias. Some researchers have reported that the most apparent change in the electrophysiological parameters during ischemia is a pronounced decrease in action potential duration (APD) in many animals (7, 10–12). In our model, a similar reduction in MAPD was observed as illustrated in Figs. 3 and 4. The shortening of MAPD could be explained by a number of mechanisms including blockage of an inward current (*i.e.*, Na^+ or Ca^{2+}), or opening of a potassium outward current (*i.e.*, Ikr, Iks, Ito, Ik1, or IK_{ATP}) (10). However, the shortening of MAPD has not been proven to be the cause of ischemia-induced arrhythmias by other studies and our results.

As is well known, the reentrant mechanism is responsible for arrhythmias following ischemic myocardium. Slow conduction is a prerequisite for reentry. Our results show that CT was prolonged during ischemia in $PC_{(-)}$ hearts (Fig. 5) and CT prolongation was more obvious in $PC_{(-)}$ with arrhythmia than that without arrhythmia as illustrated in Fig. 6. Our results also show that the shortening of MAPD in $PC_{(-)}$ hearts was not influenced by the presence or absence of arrhythmias as illustrated in Fig. 6. Thus, CT prolongation seems to be more important in ischemia-induced arrhythmias and this abnormal conduction supports the notion that global ischemia-induced arrhythmias are initiated by electrophysiological abnormalities. Conduction delay in the ischemic myocardium has been demonstrated previously (9). Factors that may contribute to conduction delay in the ischemic myocardium are a decrease in cell-to-cell coupling due to an increase in the concentration of Ca^{2+} and H^+ in cardiac cells (10) or a decrease in the velocity of membrane depolarization due to extracellular potassium accumulation (13). These ions affect the conductivity of the gap junctions that facilitated coupling between adjacent cells.

Preconditioning and arrhythmias. In the present study, the VFT during ischemia in the hearts subjected to ischemic preconditioning ($PC_{(+)}$) was higher than the corresponding values in $PC_{(-)}$, indicating a reduction in vulnerability of the ischemic ventricle to fibrillation. In addition, the significant reduction in the incidence of ventricular arrhythmias following ischemic preconditioning found in this study indicates that ischemic preconditioning can protect against ischemia-induced arrhythmias. However, the mechanism underlying these findings is not completely clear. Some investigators have shown that a correlation exists between APD shortening and cardioprotection during ischemia, but little attention has been paid to the electrophysiological mechanism of the effects of ischemic preconditioning on conduction delay. Our observations suggest that the antiarrhythmic effect of preconditioning might also act by altering conduction time and the attenuation of conduction delay played a major role in antiarrhythmic effect in $PC_{(-)}$ in this study. The common mechanism involved in ischemic preconditining are myocardial, neural and endothelial factors. These include activation of A_1 adenosine receptors, activation of protein-kinase C, activation of antioxidant enzymes, activation of prostaglandin pathways, preservation of ATP, production of heat shock protein and release of noradrenaline. However, adenosine and bradykinin have been proven to be unimportant for ischemic preconditioning in rat hearts. A more recent study using rat hearts has indicated that ischemic preconditioning also leads to a reduction in sodium and calcium loading, possibly because of limitation of Na^+-H^+ and Na^+-Ca^{2+} exchange during ischemia (14, 15). According to Tosaki *et al.* (15), ischemic preconditioning can modify deleterious ischemia-induced ion shifts and limit the electrophysiological disturbances that appear during ischemia.

Clinical implications. The possibility that an innate mechanism of myocardial protection might be inducible in the human hearts has generated considerable interest in the medical community. Several methods have been tried to research this phenomenon, including cross clamping of the aorta during cardiac surgery, balloon inflation during coronary angioplasty, warm up angina and pre-infarction angina (16–18). The results of the present experiment indicate that the attenuation of conduction delay after ischemic preconditioning may be crucial to the beneficial effect of ischemic preconditioning in guarding against ischemia-induced arrhythmia. In view of the fact that malignant arrhythmias are the major cause of mortality in victims of acute myocardial infarction, the antiarrhythmic effect of ischemic preconditioning may be

of use in future cardiac medicine.

Ischemic preconditioning can protect rat hearts from ischemia-induced arrhythmias. Moreover, the attenuation of conduction delay might play an important role in the antiarrhythmic effect of ischemic preconditioning.

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