Noradrenaline Reduces Ischemia-Induced Arrhythmia in Anesthetized Rats: Involvement of $\alpha_1$-Adrenoceptors and Mitochondrial K\textsubscript{ATP} Channels

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Noradrenaline Reduces Ischemia-Induced Arrhythmia. Introduction: We have evaluated the part played by the mitochondrial ATP-sensitive potassium (mK\textsubscript{ATP}) channels on effect of $\alpha_1$-adrenoceptor activation by noradrenaline in ischemia-induced ventricular arrhythmia.

Methods and Results: Anesthetized rats were subjected to 25 minutes of regional ischemia, and infarct size (IS) and ischemia-induced ventricular arrhythmia were measured. Group I served as saline control with ischemia ($n=9$). In group II ($n=9$), the ischemic period was preceded by three short episodes of ischemia, followed by reperfusion. In group III, noradrenaline (2 $\mu$g/kg, IV, $n=9$) was injected prior to ischemia. In group IV, an $\alpha_1$-adrenoceptor blocker (prazosin, 0.5 mg/kg, IV, $n=6$) was administrated prior to noradrenaline injection. In Groups V and VI, rats received a specific mitochondrial K\textsubscript{ATP} channel inhibitor [5-hydroxydecanoic acid (5-HD), 10 mg/kg, IV, $n=6$] prior to or after noradrenaline injection. Ischemic preconditioning (IPC) and noradrenaline markedly reduced incidences of ventricular fibrillation (VF) (0%, 0% vs. 55.5% in control, $P<0.05$) and ventricular tachycardia (VT) (11%, 44.5% vs. 100% in control, $P<0.001$ and $P<0.05$), duration of VF + VT (3 $\pm$ 1 seconds, 4.7 $\pm$ 2.1 seconds vs. 52.9 $\pm$ 6 seconds in control, $P<0.001$), number of VF + VT episodes (1.7 $\pm$ 2.4 vs. 60.5 $\pm$ 8 in control, $P<0.001$), severity of arrhythmias (0.3 $\pm$ 0.3, 1.7 $\pm$ 0.5 vs. 3.9 $\pm$ 0.3 in control rats, $P<0.001$ and $P<0.01$), and IS (13.6 $\pm$ 1.8%, 18.2 $\pm$ 1.5% vs. 49.6 $\pm$ 2.4% in control, $P<0.001$). Administration of prazosin or 5-HD prior to or after noradrenaline injection intensified incidences of VF (66.6%, 66.6% and 50%, $P<0.05$) and VT (100%, 100%, and 100%, $P<0.05$), duration of VF + VT episodes (70.2 $\pm$ 10.5 seconds, 69.8 $\pm$ 6.75 seconds, and 60.8 $\pm$ 14.9 seconds, $P<0.001$), number of VF + VT episodes (56 $\pm$ 16.4, 67 $\pm$ 11, and 45 $\pm$ 3.5, $P<0.01$, $P<0.001$, and $P<0.05$), severity of arrhythmias (3.8 $\pm$ 0.3, 4 $\pm$ 0.5, and 3.7 $\pm$ 0.2, $P<0.01$, $P<0.05$, and $P<0.01$), and IS (45.5 $\pm$ 3%, 46.8 $\pm$ 3.4%, and 43 $\pm$ 2.5%, respectively, $P<0.001$) compared with the noradrenaline-treated group.


ischemia, ventricular arrhythmias, mitochondrial K\textsubscript{ATP} channels, noradrenaline, $\alpha_1$-adrenoceptors

Introduction

Myocardial ischemic damage is still a major health problem in the world, and new approaches are required to decrease cardiomyocyte dysfunction in patients with acute myocardial infarction. A brief episode of nonlethal ischemia enhances myocardial tolerance against a subsequent prolonged ischemic injury. This phenomenon, known as ischemic preconditioning (IPC), offers one of the most powerful mechanisms for reducing the speed and extent of cardiomyocyte damage. The purpose of many investigations has been to find therapeutic approaches to mimic IPC using pharmacological agents.

Whereas preconditioning reduces infarct size and improves postischemic contractile recovery, its effect on arrhythmias is not yet clear, with contradictory reports ranging from inhibition of arrhythmias to its worsening.

A choice approach to obtain cardioprotection is the pharmacological stimulation of $\alpha_1$-adrenoceptors by catecholamines. In this approach, controversial results have been reported from the effect of $\alpha_1$-adrenoceptor stimulation on arrhythmias during sustained myocardial ischemia in the isolated rat heart. It has been shown that stimulation of this receptor promotes arrhythmias whereas another study has indicated that short-term stimulation of $\alpha_1$ adrenergic receptors is involved in the preconditioning-induced antiarrhythmic protection.

It is suggested that the mitochondrial ATP-sensitive potassium (K\textsubscript{ATP}) channels in cardiomyocytes have a physiological role in modulating cardiac function and protect myocardial tissue under hypoxic and ischemic conditions. However, this channel can serve as a mediator or trigger of IPC or pharmacological preconditioning. There is some controversy about the action of mitochondrial K\textsubscript{ATP} as a trigger or a mediator that may be related to the model used (in vitro versus in vivo) or species differences. Other factors, which are absent...
in the isolated heart but present in vivo (e.g., hormonal and/or autonomic neuronal effects and loading of the right ventricle) may also add to this controversy. Therefore, the present study was designed to analyze the preconditioning effect of \( \alpha_1 \)-adrenoceptors activation by exogenous administration of noradrenaline on ventricular arrhythmias and infarct size in open chest rats, and elucidate the part played by the mitochondrial \( K_{\text{ATP}} \) channels and their role as a trigger or a mediator on the protection conferred by noradrenaline.

**Methods**

**Surgical Preparation**

Male Wistar rats weighing 250–350 grams were housed under standard conditions (21–23°C, 12-hour light–dark cycle) with free access to food and water. The animal care was conducted in accordance with the institutional guidelines of Medical Sciences University of Tehran (I.R.) and the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals. Anesthesia was achieved by intraperitoneal administration of pentobarbital sodium (50 mg/kg body weight) and maintained with supplementary doses (25 mg/kg, i.p.) every 60–90 minutes, as needed. After a tracheotomy in the middle of the neck and tracheal intubation, all animals were ventilated with room air by Parvalux rodent respirator (15 mL/kg stroke volume and 60–70 breaths/minute). Body temperature was measured with a rectal thermometer and kept at 37 ± 1°C with a lamp. The right carotid artery and tail vein were cannulated to measure mean arterial blood pressure (MBP) and to administrate saline or drugs, respectively. Lead-II electrocardiogram (ECG) was monitored with subcutaneous stainless steel electrodes. A Power Lab monitoring system (ML750 PowerLab/4sp) was used for recording of MBP, heart rate (HR), and ECG. Rats were given heparin (200 IU/kg, I.V.), and then the chest was opened by a left thoracotomy in the fifth intercostal space to expose the heart. After incision of the pericardium, a 6–0 silk suture was placed around the left anterior descending coronary artery (LAD) close to its origin. Both ends of the silk thread were passed through a polyethylene tube. Applying tension to the suture caused regional ischemia following coronary artery occlusion, and reperfusion was achieved by releasing the tension on the ligature. Ischemia was confirmed by ST elevation and increase in R-wave amplitude in ECG, or cardiac cyanosis. At the end of the surgical procedure, any rat with a constant fall in MBP to less than 80 mmHg or ventricular fibrillation lasting for more than 5 minutes was discarded from the study. The end points used in this study were the number of episodes, duration and severity of ventricular arrhythmias, and infarct size.

**Determination of Infarct Size and Area at Risk**

At the end of the experiments, the coronary artery was reoccluded and Evans Blue dye (3mL of 2% solution) was injected into the tail vein to identify the nonperfused, known as area at risk (AAR), from perfused area. The rats were then killed and their hearts were excised and frozen overnight. The atria and right ventricle were removed and the left ventricle (LV) was cut into transverse slices of 2 mm thickness from the apex to base. The anatomic uncolored AAR (pink) was separated from the colored nonischemic area (blue) and then incubated with a 1% solution of 2, 3, 5-triphenyltetrazolium chloride (TTC, in 0/1 M phosphate buffer, pH 7.4) stain for 20 minutes at 37°C and fixed for several days in 10% phosphate-buffered formalin. Viable myocardium is stained red by TTC, whereas necrotic myocardium appears as pale yellow. In each slice, the infarct size (IS) and AAR were determined by using an image processing software program (PhotoShop, version 7.0, Adobe system). IS was expressed as a percentage of the AAR (%IS/AAR).

**Assessment of Ventricular Arrhythmias**

Ischemia-induced ventricular arrhythmias were determined in accordance with the Lambeth Conventions. Ventricular ectopic beats (VEBs) were defined as identifiable premature QRS complexes. Ventricular tachycardia (VT) was defined as the occurrence of four or more consecutive VEBs at a rate faster than the resting sinus rate. Ventricular fibrillation (VF) was defined as unidentifiable and low voltage QRS complexes. In the case of other multipart forms of VEBs such as bigeminy, couplet (two consecutive VEBs) and salvos (three consecutive VEBs), they were counted at separate episodes (Fig. 1).

Ventricular fibrillation may be sustained or may revert spontaneously to a normal sinus rhythm. VF lasting for more than 5 minutes was considered as irreversible.

The severity of arrhythmias was quantified by the following scoring system:

1. Only 50–500 VEBs, or one episode of spontaneously reversible VT or VF,
2. More than 500 VEBs, or one episode of spontaneously reversible VT and/or VF,
3. 2–30 episodes of spontaneously reversible VT and/or VF,
4. More than 30 episodes of spontaneously reversible VT and/or VF,
5. Irreversible VF.

**Evaluation of QT Interval**

The ECG tracings were analyzed visually and the following ECG parameters were examined:

1. RR interval (the interval between the apex of two consecutive adjacent R waves),
2. QT interval (the interval between beginning of Q-wave and T-wave apex), and,
3. Corrected QT interval (QTc, defined as the QT interval corrected for the heart rate by means of Bazett’s equation: corrected QTc = QT (ms)/RR (ms)^1/2).

**Materials**

Pentobarbital sodium, noradrenaline, prazosin hydrochloride (a specific \( \alpha_1 \)-adrenoceptor blocker), and 5-hydroxydecanolic acid (5-HD, a specific mitochondrial \( K_{\text{ATP}} \) channel inhibitor) were obtained from Sigma Chemical Co. Prazosin was dissolved in bidistilled water and the rest were dissolved in saline immediately before use.

**Experimental Protocols**

All animals underwent 25 minutes of coronary artery occlusion. Drugs were injected intravenously. After a
stabilization period following the surgical preparation, rats were divided into six experimental groups (Fig. 2).

**Group 1: Control** (n = 9). Saline was given 10 minutes before coronary artery occlusion.

**Group 2: Ischemic Preconditioning (IPC)** (n = 9). Three episodes of 5-minute ischemia followed by a 5-minute reperfusion were performed before coronary artery occlusion.

**Group 3: Noradrenaline (NA)** (n = 9). Noradrenaline (2 µg/kg) was administrated 10 minutes before coronary artery occlusion.

**Group 4: Prazosin (PRAZ)** (n = 6). Prazosin (0.5 mg/kg) was injected 5 minutes before noradrenaline injection.

**Group 5: 5HD-NA** (n = 6). 5-HD (10 mg/kg) was administered 10 minutes before noradrenaline injection.

**Group 6: NA-5HD** (n = 6). 5-HD (10 mg/kg) was given 5 minutes after noradrenaline injection (5 minutes before coronary artery occlusion).

**Statistical Analysis**

Data are expressed as means ± S.E.M or the percentage of incidence. Statistical comparison of means between groups was made by one-way ANOVA and a subsequent Tukey test. Within each group, differences between means in hemodynamic parameters were compared by one-way repeated measures ANOVA. Differences between means in the QTc intervals were compared by paired t-test. The arrhythmia scores were analyzed with Kruskal-Wallis test, and the incidences of VT or VF were compared using the Fisher exact test. Significant differences were determined as P < 0.05.

**Results**

**Hemodynamic**

MBP and HR were recorded continuously during the experiments and calculated throughout the 15-minute baseline, preocclusion, and 25-minute ischemia periods.

After injection of noradrenaline, MBP and HR increased instantly but returned to the baseline value after 3–4 minutes without a significant difference, compared with baseline. The hemodynamic changes are outlined in Table 1.

The results show that following injection of prazosin, MBP was not significantly decreased and HR was not significantly increased during preocclusion period, and, also, administration of 5-HD had no effect on hemodynamic parameters. No significant differences were found in HR and MBP between groups during baseline, preocclusion and 25-minute occlusion periods, but within the groups MBP was significantly reduced during the 25-minute occlusion period, compared with the baseline period.
Ventricular Arrhythmias During Ischemia

In this model of regional ischemia, severe ventricular arrhythmias peaked after 7–15 minutes of coronary artery occlusion.

Incidences of VT or VF

In the control nonpreconditioned hearts, VT was observed in 100% of rats, and 55.5% of the hearts displayed VF. Administration of three cycles of IPC or noradrenaline before ischemia attenuated VT to 11% and 44.5% and totally abolished VF, compared with the saline control rats. Administration of prazosin or 5-HD (prior to or after NA) restored the incidence of VT (100%) or VF (66.6%, 66.6%, and 50%) as shown in the control and eliminated the antiarrhythmic effect of noradrenaline on VT and VF induction (Fig. 3).

Duration of VF + VT

Compared with the saline control rats, duration of VF + VT during 25 minutes of ischemia was significantly reduced by induction of IPC or injection of noradrenaline prior to ischemia (3 ± 1 seconds, 4.7 ± 2.1 seconds vs. 52.9 ± 6 seconds in control rats). Administration of prazosin or 5-HD, prior to or after noradrenaline injection (70.2 ± 10.5 seconds, 69.8 ± 6.75 seconds and 60.8 ± 14.9 seconds), restored the duration of VF + VT, as seen in control (Fig. 4).

Number of episodes of VF + VT and VEBs/minute

The mean number of VF + VT episodes during 25 minutes of coronary artery occlusion in both IPC and noradrenaline-treated groups was markedly reduced, compared with saline-treated rats (1.7 ± 1.7, 5.75 ± 2.4 vs. 60.5 ± 8 in control rats). Treatment with prazosin (56 ± 16.4) or 5-HD, prior to or after noradrenaline injection (67 ± 11 and 45 ± 3.5), enhanced the number of VF + VT episodes, compared with the noradrenaline-treated group. Both IPC and treatment with noradrenaline significantly reduced the episodes of VEBs/minute (1 ± 0.5, 2.5 ± 0.5 vs. 9.5 ± 1.5 in control rats). Injection of prazosin or 5-HD (prior to or after noradrenaline) (7.5 ± 1.5, 10.5 ± 2, and 9 ± 2.5) increased the number of episodes of VEBs/minute, compared with the noradrenaline-treated group (Fig. 5).
Severity of arrhythmias

Compared with saline-treated rats, severity of ventricular arrhythmias significantly declined by application of three cycles of IPC or injection of noradrenaline before ischemia (0.3 ± 0.3, 1.7 ± 0.5 vs. 3.9 ± 0.3 in control rats). Administration of prazosin or 5-HD (prior to or after noradrenaline injection) intensified the severity of arrhythmias (3.8 ± 0.3, 4 ± 0.5, and 3.7 ± 0.2) and abolished the cardioprotective effect of noradrenaline on arrhythmias (Fig. 6).

Ventricular Arrhythmias During Early Reperfusion

IPC or noradrenaline preconditioning significantly reduced the incidence of VT during the first 5 minutes of reperfusion, compared with saline-treated rats (22.2% and 33.3% vs. 77.7% in control rat). Treatment with prazosin or 5-HD (prior to or after noradrenaline injection) eliminated the antiarrhythmic effect of noradrenaline on the incidence of VT (83%, 100%, and 66.6%).

VF did not occur in any rats, and no significant differences were found in duration or number of episodes of arrhythmias between the six groups.

Corrected QT (QTc) Interval

The change in QTc interval was measured between the baseline and 25-minute ischemia periods within groups (Table 2). In the saline control rats, the induction of a 25-minute ischemia period reduced the QTc interval (68.9 ± 5.3 ms vs. 79 ± 4 ms in the baseline), compared with the baseline period. Administration of noradrenaline significantly increased the QTc interval (89.5 ± 4.8 ms vs. 77.5 ± 3.5 ms in the baseline) during prolonged ischemia, compared with the baseline period. The QTc interval in prolonged periods of ischemia did not significantly change, compared with the baseline by induction of IPC (85.1 ± 3.5 ms vs. 81 ± 2.4 ms in the baseline) or the treatment with prazosin (84.7 ± 2 ms vs. 81 ± 2.4 ms in the baseline) and 5-HD prior to or after noradrenaline injection (70.7 ± 2.2 ms and 73 ± 4.5 ms vs. 74.3 ± 3.5 ms and 75 ± 2.6 ms in the baseline period).

Infarct Size

The area at risk (AAR/LV) and the infarct size (IS/AAR) expressed as percentages are shown in Figure 6. AAR/LV was not different among the six groups. Control animals had an IS/AAR of 49.6 ± 2.4%. This was significantly reduced by IPC (13.6 ± 1.8%) or pretreatment with noradrenaline (18.2 ± 1.5%). This cardioprotection induced by noradrenaline was abrogated by administration of prazosin 5 minutes prior to noradrenaline (45.5 ± 3%).

Administration of 5-HD 10 minutes prior to noradrenaline attenuated cardioprotection (46.8 ± 3.4%). In addition, when 5-HD was injected 5 minutes after noradrenaline (or 5 minutes prior to ischemia), this cardioprotection was also abolished (43 ± 2.5%).

Discussion

In this study, we have demonstrated that noradrenaline via an \(\alpha_1\)-adrenoceptor preconditioning myocardium against ventricular arrhythmias and extent of infarction in anesthetized open-chest rats, and that blockade of mitochondrial K\(_{ATP}\) channels, prior to or after administration of noradrenaline, inhibits this preconditioning responses.

We have shown that occlusion of LAD leads to a fall in MBP. Therefore, it seems that coronary flow can be affected by reduced MBP in the unoccluded myocardial area (especially since the heart rate does not change), becoming a potential trigger for additional arrhythmogenesis.

### Table 2

<table>
<thead>
<tr>
<th>Groups</th>
<th>QTc (ms) ± SEM</th>
<th>QT Interval (ms)</th>
<th>RR Interval (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>79 ± 4</td>
<td>32 ± 1.5</td>
<td>165 ± 7</td>
</tr>
<tr>
<td>IPC</td>
<td>81 ± 2.4</td>
<td>31.5 ± 0.8</td>
<td>157 ± 5.2</td>
</tr>
<tr>
<td>NA</td>
<td>77.5 ± 3.5</td>
<td>30.3 ± 1</td>
<td>155 ± 7.4</td>
</tr>
<tr>
<td>Prazosin</td>
<td>81 ± 2.4</td>
<td>35.5 ± 1.6</td>
<td>192 ± 10.9</td>
</tr>
<tr>
<td>5HD-NA</td>
<td>74.3 ± 3.5</td>
<td>32.5 ± 1.5</td>
<td>188 ± 10</td>
</tr>
<tr>
<td>NA-5HD</td>
<td>75 ± 2.6</td>
<td>30.4 ± 1.2</td>
<td>182 ± 4.3</td>
</tr>
</tbody>
</table>

5HD: 5-hydroxydecanoic acid, IPC: Ischemic Preconditioning, NA: Noradrenaline, QTc: corrected QT interval. Data are presented as mean ± SEM. \(^*P < 0.05\) compared to baseline within groups.

![Figure 6. Myocardial area at risk (AAR/LV%) and infarct size (IS/AAR%) in control (CON), Ischemic Preconditioning (IPC), noradrenaline (NA), prazosin (PRAZ), 5-HD prior to noradrenaline (5HD-NA), and 5-HD after noradrenaline (NA-5HD) groups. Data are presented as mean ± SEM. \(^{***}P < 0.001\) versus control group and \(^{##}P < 0.001\) versus noradrenaline-treated group.](image-url)
In our study, changes in infarct size correlate well with the antiaarrhythmic effects of noradrenaline and IPC. Therefore, it appears that the extent of myocardial infarction may affect directly arrhythmogenesis.

It has been suggested that in acute myocardial ischemia, $\alpha_1$-adrenergic responsivity significantly contributes to the arrhythmogenic effect of catecholamines.$^{7,8}$ On the other hand, previous studies have shown the cardioprotective effect of selective $\alpha_1$-adrenoceptor agonists against arrhythmias in isolated rat hearts.$^9,17$ Our results also indicate that the antiarrhythmic effect of noradrenaline is achieved through $\alpha_1$-adrenoceptor stimulation.

On the basis of the present study, both myocyte $\alpha_1$-adrenoceptors and noradrenaline are involved in cardioprotection. Since yohimbine, a selective blocker of presynaptic $\alpha_2$-adrenoceptor, reduces arrhythmia severity by increasing endogenous noradrenaline release via cardiac sympathetic nerves,$^{18,19}$ it isn’t apparent that exogenous noradrenaline improves cardioprotection by presynaptic inhibitory action on cardiac sympathetic noradrenaline release.$^{20}$ Therefore, activation of postsynaptic $\alpha_1$-adrenoceptors by noradrenaline may be the reason for cardioprotection.

In our experiment, we did not have any evidence to identify the direct or indirect antiarrhythmic effect of $\alpha_1$-adrenoceptor activation, although some studies have demonstrated that catecholamines indirectly can lead to cardioprotection through adenosine receptors activated by $\alpha_1$-adrenoceptors.$^{21,22}$ Moreover, others have shown that $\alpha_1$-adrenoceptor agonists can induce preconditioning by the direct activation of protein kinase C (PKC).$^{23}$

We have shown that blockade of mitochondrial K$_{ATP}$ channels by 5-HD offsets the cardioprotective effect of noradrenaline on ventricular arrhythmias and infarct size, which suggests that stimulation of $\alpha_1$-adrenoceptors by noradrenaline may open the mitochondrial K$_{ATP}$ channels. Although the mechanism of the action of noradrenaline in preconditioning responses was not explored in this study, several hypotheses are proposed to explain these effects. Stimulation of $\alpha_1$-adrenoceptors is the activating pathway for PKC$^{25}$ and nitric oxide (NO).$^{26}$ These pathways also play a major role in mediating some of the manifestations of preconditioning, such as the reduction in infarct size.$^{24,26}$ It has been proposed that activation of PKC$^{27}$ and release of NO$^{28}$ can open the mitochondrial K$_{ATP}$ channels. Therefore, noradrenaline could possibly activate mitochondrial K$_{ATP}$ channels via release of NO or activation of PKC. Opening of the mitochondrial K$_{ATP}$ channel reduces mitochondrial calcium overload$^{29}$ or ATP depletion.$^{30}$ and 5-HD by blockage of mitochondrial K$_{ATP}$ channels reverses the beneficial effect of noradrenaline.

It is not clear when or how mitochondrial K$_{ATP}$ channels open in the preconditioning phenomenon, and, for this reason, involvement of mitochondrial K$_{ATP}$ channels as a trigger or a mediator is controversial.$^{31,32}$ Pharmacological inhibition with 5-HD applied either during a preconditioning stimulus or during the long ischemia has been the principal means of examining this question.$^{12}$ Our findings suggest that the antiarrhythmic effect induced by noradrenaline as a preconditioning stimulus can be abolished when 5-HD is administered prior to noradrenaline injection or prior to 25-minute ischemia. Although we did not have any direct evidence for blockage of mitochondrial K$_{ATP}$ channels in our model of myocardial ischemia, the dose of 5-HD used in this study appears to be sufficient. The needed plasma level of 5-HD to inhibit the mitochondrial K$_{ATP}$ channels in rats is approximately 0.16 $\mu$M, and plasma half-life of 5-HD is next to 3 minutes and injection of 10 mg/kg of 5-HD could attain a peak plasma level of 200 $\mu$M.$^{33}$ Therefore, it is likely that the plasma level of 5-HD has been enough at the induction time of preconditioning by noradrenaline (with the injection of 5-HD prior to noradrenaline) and during 25 minutes of ischemia (with injection of 5-HD after noradrenaline and prior to 25 minutes of ischemia). This proposes that activation of the mitochondrial K$_{ATP}$ channels may not only be a trigger of preconditioning but also is an important downstream effector of the antiarrhythmic property of noradrenaline in the anesthetized rat heart. The present investigation is in agreement with previous reports in which the cardioprotection could be abolished when rats are treated with 5-HD prior to or after IPC$^{31}$ and administration of diazoxide.$^{34}$

It is generally believed that the QT interval is determined by the action potential duration (APD) of the ventricular myocytes.$^{35}$ The QT interval is affected by heart rate, and to assess the QT interval independently of heart rate, it is expressed as a corrected QT (QTc). In our experiment, 25 minutes of ischemia shortened the QTc interval and induced arrhythmias. Injection of noradrenaline prior to ischemia prolonged the QTc interval and reduced the incidence of ventricular arrhythmias. IPC, also by stabilizing the QTc interval during 25-minute ischemia, decreased the ischemia-induced ventricular arrhythmias. Administration of prazosin or 5-HD eliminated the prolonging effect of noradrenaline on the QTc interval and reversed the arrhythmias, as seen in control. Refractoriness may correspond to APD, and shortening of APD during ischemia will be accompanied by a corresponding shortening of refractoriness, which would be proarrhythmic.$^{36}$ APD was not measured in this study, but it is proposed that activation of $\alpha_1$-adrenoceptors prolongs the refractoriness and APD.$^{37,38}$ Therefore, it seems that noradrenaline by prolonging the QTc interval, action potential duration, and subsequent refractoriness could improve the ischemia-induced ventricular arrhythmias.

Ischemic heart disease is a common cause of mortality in the world. Therapeutic protocols aimed at protecting the myocardium from ischemic injury can significantly improve mortality. Administration of a preconditioning mimetic agent (such as $\alpha_1$-agonists or mitochondrial K$_{ATP}$ channel openers) to patients with myocardial infarction could be a helpful therapeutic choice. Prevention of $\alpha_1$-adrenoceptor blockade or inhibition of mitochondrial K$_{ATP}$ channels in patients with ischemic heart disease could therefore be useful in the improvement of cardioprotection.

It has been shown that the use of prazosin (a selective $\alpha_1$-antagonist) increases the number of chest pain episodes and ST-segment deviations in ECG from the baseline in patients with unstable angina. On the other hand, it is possible that $\beta$-blocker-induced reduction in mortality and morbidity in patients with myocardial infarction may also be mediated by induction of cardioprotection by allowing norepinephrine to activate $\alpha_1$-adrenoceptors.$^{39}$

**Conclusion**

Treatment with prazosin or 5-HD not only eliminated the beneficial effects of noradrenaline on arrhythmogenesis; it
also abolished the beneficial effects on infarct size in anesthetized open chest rat.

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