Effects of a Beta Adrenergic Antagonist Combined with Vasodilators on Cardiac Arrhythmia in Ischemic-induced Rat Hearts

Promporn Raksaseri 1  Wuthichai Klomkleaw 1  Suwanakiet Sawangkoon 2*

Abstract

Sixty male Spraque-Dawley rats were used in this study. The hearts were isolated and placed on a constant-pressure Langendorff apparatus, and perfused with only Krebs-Henseleit buffer (control), atenolol, atenolol plus prazosin, and atenolol plus salbutamol. After that the left anterior descending artery was occluded for 8 minutes and reperfused for 30 minutes to induce cardiac arrhythmias. The left ventricular pressure and coronary flow rate were monitored, and ECGs were recorded to evaluate cardiac arrhythmias. The administration of atenolol ($\beta_1$-adrenergic antagonist) combined with prazosin ($\alpha_1$-adrenergic antagonist) prolonged RR intervals whereas that of atenolol combined with salbutamol ($\beta_2$-adrenergic antagonist) did not prolong RR intervals during the ischemic period. Moreover, reperfusion induced sustained ventricular fibrillation in all groups except the atenolol plus prazosin treated group. The decline of coronary flow rate after reperfusion in atenolol and atenolol plus salbutamol treated groups were lower than the atenolol plus prazosin group. Our results support the theory that $\alpha_1$-adrenergic receptors play an important role on reperfusion arrhythmia whereas coronary vasodilation is mediated through $\beta_2$-adrenergic receptors. Furthermore, the combination of $\beta_1$-adrenergic antagonist and $\alpha_1$-adrenergic antagonist could have a more beneficial effect for anti-arrhythmia in cardiac ischemia.

Keywords: Adrenergic, arrhythmias, beta blocker, ischemia, rat, vasodilator

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Introduction

Cardiac disease, which affects many millions of people around the world, is a leading cause of death as a result of contractile dysfunction, or sudden cardiac death caused by ventricular arrhythmia (Packer, 1985). About 40% of sudden death victims experience cardiac arrest at the first manifestation of coronary artery diseases (Zipes and Wellens, 2000).

Disturbances of cardiac rhythm, including lethal ventricular arrhythmia and post-ischemic contractile dysfunction are a consequence of reperfusion following myocardial ischemia. Many possible mechanisms contribute to contractile dysfunctions. The first one is an increase in sympathetic activity during myocardial ischemia leading to cardiac arrhythmia (Du et al., 1999). Oxidative stress is also a cause of contractile dysfunction (Aiello et al., 1995; Bolli, 1998). In addition, the fall in intracoronary pressure downstream from an occlusion is itself a significant cause of an immediate decline in pump function (Katz, 2001).

Many studies both in human and animal models have produced somewhat inconsistent results with respect to the functional level of β-adrenergic mediating signaling in ischemic heart disease. A general feature of the failing human heart is a decrease in the density of β₁-adrenergic receptor (AR) leading to shifts in β₁ and β₂-ARs ratio towards β₂-ARs (Bristow, 1993). It has been reported that β₂-ARs are not down-regulated but...
their sensitivity may be increased (Altschuld et al., 1995).

The α₁-adrenergic receptors in the heart can initiate an inotropic response under physiological conditions while they also play an important role in reperfusion arrhythmia, where extensive norepinephrine release has been documented (Sheridan, 1986; Schomig, 1990). In addition, reperfusion of ischemically damaged myocardium is associated with large Ca²⁺ accumulations, which can be inhibited by α₁-adrenergic receptor blockade. These studies suggest a link between α₁-adrenergic receptor stimulation and arrhythmia produced by myocardial ischemia and reperfusion.

β-adrenergic antagonists are commonly used for the treatment of ischemic heart disease (Erdmann, 1998). Possible mechanisms contributing to their effects include cardiac protection from the toxic catecholamine effect inducing apoptosis but also a reduction in heart rate leading to lower myocardial energy expenditure (Reiter and Reiffel, 1998), prolong diastolic filling, and protection from cardiac arrhythmia (Kennedy et al., 1994). Nevertheless, acute administration of first generation adrenergic antagonists, such as propanolol, causes a decrease in the contractile state (Haber et al., 1993), increased systemic vascular resistance (Armstrong et al., 1977; Bristow et al., 1998), and leads to a decrease in cardiac output, which results in a drug intolerance rate of more than 20% (Talwar et al., 1996). On the other hand, the second generation, β₁-selective blockers have less reflex vasoconstriction because unblocked peripheral vascular β₂-adrenergic receptors may respond and cause vasodilation. The overall effect is that cardiac output and organ perfusion are reduced to a lesser degree than the first-generation β-blockers (Bristow et al., 1998). Nowadays, it seems that a third-generation β-blocker, carvedilol, a non-selective β-blocker with vasodilating properties, is an effective β-blocker for the treatment of myocardial ischemia. It has the advantage of afterload reduction to counteract the negative inotropic properties of adrenergic withdrawal (Bristow, 2000). Compared to β₁-selective blocker, carvedilol produces more beneficial effects on the left ventricular function (Gilbert et al., 1996; Bristow et al., 1997). However, some data also demonstrated no difference between them (Kulkin et al., 1999). Furthermore, the high price of newly developed drugs may limit drug availability especially in developing countries.

It is interesting that the combination of vasodilating drugs mediated through α₁-adrenergic antagonist or β₂-adrenergic stimulation with a beta blocker can have beneficial effects on patients with ischemic heart diseases. However, the effects of these combined drugs on cardiac arrhythmia in ischemic hearts are still unclear. Therefore, the present study was designed to observe the effects of drug combinations on cardiac arrhythmia in ischemic rat hearts.

Materials and Methods

Isolated heart preparations (Langendorff apparatus)

Sixty male Spraque-dawley rats weighing between 250-350 grams were used in this study. The animals were anesthetized with pentobarbital sodium (60 mg/kg) intraperitonially. After the intravenous administration of heparin (500 IU/kg), the chest was opened and the heart was rapidly excised before cannulated on a non-recirculating Langendorff apparatus (Maulik et al., 1997). Retrograde perfusion was established at a constant pressure of 80 mmHg with an oxygenated (95% O₂/5% CO₂) normothermic (37°C) Krebs-Henseleit bicarbonate (KHB) buffer at pH 7.4.

Experimental protocol

To monitor the isometric tension developed by the left ventricle, a latex balloon tipped catheter connected to a pressure transducer was inserted into the left ventricle via a small incision made in the left atrium. The pressure transducer was connected to a physiograph (Grass Model 79, Grass instruments Co., MA, USA), and the data was transferred to a computer by an A/D converter (Powerlab ADInstruments, CO, USA). Two electrodes were placed on the cardiac epicardium to monitor electrograms (epicardial ECG). To obtain a stable cardiac function, all hearts perfused with KHB were placed for a period of 10 minutes before baseline recording. After that, the isolated hearts were then perfused with Krebs-Henseleit buffer (KHB) in group 1 (control), 10 µM atenolol (a β₁-selective antagonist, Sigma-Aldrich, MO, USA) in group 2 (ATEN), 10 µM atenolol + 0.01 µM salbutamol (a β₂-selective agonist, Ventolin, OH, USA) in group 3 (ATEN/SALBU), and 10 µM atenolol + 5 µM prazosin (an α₁-selective antagonist, Sigma-Aldrich, MO, USA) in group 4 (ATEN/PRAZ).
antagonist, Sigma-Aldrich, MO, USA) in group 4 (ATEN/PRAZ) for 10 minutes, and the data was recorded as a perfusion period. After that, the left anterior descending artery was ligated for 8 minutes and then reperfused for 30 minutes.

**Data analysis**

Left ventricular developed pressure was defined as the pressure difference between systolic pressure and diastolic pressure (Tosaki et al., 1998), and the maximal first derivative of left ventricular developed pressure (LV dp/dt max) was made at each wave of LVDP at the period of isovolumic contraction and relaxation (Tosaki et al., 1998). Coronary flow rate was measured by a time collection of the coronary effluent that dripped from the heart (Tosaki et al., 1998).

The ECG signals were recorded continuously for 5 minutes in the baseline condition followed by 5 minutes at each period of drug perfusion, ischemic conditions and reperfusion conditions. The RR, QT, and QTc calculated by Bazett’s method were determined. The heart rate was calculated by the apparent QRS complex in a minute.

For arrhythmia analysis, the acquired single-lead ECG tracings were displayed and analyzed. After coronary reperfusion, ECG was recorded for 30 minutes to evaluate cardiac arrhythmia. Ventricular premature beats (VPB) classified as singlet, couplet, triplet, non-sustained ventricular tachycardia (VT), sustained VT, and ventricular fibrillation (VF) were determined according to the Lembeth convention criteria (Walker et al., 1988) with more stringent modifications. The ranking scores are arbitrary numerical grades of different sorts of ventricular arrhythmias. The scaling was applied as follows: 0 = no arrhythmias, 1 = single VPB, 2 = couple or salvos of VPB, 3 = VT, 4 = sustained VT, 5 = VF. When multiple forms of arrhythmias occurred in one heart, only the highest single score was used (Di Napoli et al., 1998). The incidence of ventricular arrhythmia was also present according to the experiment of Du et al. (1999).

All data is presented as mean ± SD. Changes in indices of left ventricular function were compared using repeating-measure analysis of variance with appropriate statistical contrasts employed to make all pair-wise between-group and within-group followed by Student-Newman Keuls. The non-parametric method was used if the data had failed normality, and a one way analysis of variance with repeated measures on ranks was used instead. Arrhythmia scores were compared using the unpaired t-test when results passed the normal distribution test, or otherwise, the Mann-Whitney rank sum test when the normality failed. The Chi-square test was used for a comparison of the incidences of arrhythmia. p<0.05 was considered for statistical significance.

**Results**

**Effects of adrenergic drugs on left ventricular developed pressure (LVDP)**

At baselines, LVDP in the control, atenolol (ATEN), atenolol combined with salbutamol (ATEN/SALBU), and atenolol combined with prazosin (ATEN/PRAZ) treated groups were 102.2±10.9, 104.5±9.2, 101.4±11.0, and 103.6±18.2 mmHg, respectively (Fig.1). Although slight decreases in LVDP following drug perfusion period were observed in A TEN, A TEN/SALBU, and A TEN/PRAZ treated groups, a marked decrease in LVDP could be seen in all groups during coronary occlusion which were 55.9±13.3, 52.7±13.1, 53.2±13.8, and 54.2±9.4 mmHg respectively (p<0.05). However, LVDP quickly increased upon reperfusion to 60.7±9.9, 70.1±11.5, and 81.3±21.9 mmHg in A TEN, A TEN/SALBU, and A TEN/PRAZ, respectively, whereas LVDP in the control group did not recover from the occlusion period. Interestingly, LVDP in the A TEN/PRAZ treated group was the highest compared to other groups during reperfusion.

**Effects of adrenergic drugs on dp/dt max**

At baselines, dp/dt max in the control, ATEN, ATEN/SALBU, and ATEN/PRAZ groups were 3221±268, 3235±490, 3311±432, and 3350±470 mmHg/s respectively and slightly decreased after drug perfusion (Fig.2). During cardiac ischemia, the dp/dt max in all groups dropped to 2077±351, 1933±635, 2041±636, and 1887±414 mmHg/s, respectively (p<0.05). After coronary reperfusion, increases in dp/dt max were observed only in the ATEN/SALBU and ATEN/PRAZ groups which were 2543±709 and 2554±658 mmHg/s, respectively (p<0.05). However, there was no significant difference in dp/dt max between these two groups.

**Effects of adrenergic drugs on dp/dt min**

As shown in Fig. 3, the dp/dt min at baselines in the control, ATEN, ATEN/SALBU and ATEN/PRAZ
treated group were 2601±705, 2235±294, 2434±410, and 2394±655 mmHg/s, respectively. The dP/dt min slightly declined in all groups nevertheless statistical significances were detected only in the control and the ATEN/PRAZ treated groups during drug perfusion. The dP/dt min markedly decreased to 1179±403, 1080±405, 1251±432, and 1111±435 mmHg/s following coronary occlusion. This data had demonstrated that coronary occlusion caused the decrease in cardiac relaxation. During reperfusion, the dP/dt min in ATEN/SALBU and ATEN/PRAZ increased to 1522±472 and 1393±390 mmHg/s, respectively (p<0.05).

**Effects of adrenergic drugs on heart rates**

In this model, heart rates did not significantly change during drug perfusion and coronary occlusion whereas a decrease in heart rate was observed in the control group during reperfusion. The ATEN/PRAZ treated group showed a significant decrease in heart rate during drug perfusion (p<0.05), but not in the coronary occlusion and reperfusion periods. In contrast, the ATEN/SALBU treated group did not have alterations of heart rates at any period. Interestingly, heart rates in the ATEN/SALBU treated group were higher than the ATEN/PRAZ treated group as shown in Fig. 4.

**Effects of adrenergic drugs on coronary flow rate (ml/min)**

The coronary flow rates of all groups are shown in Table 1. At baselines, coronary flow rates in the control, ATEN, ATEN/SALBU, and ATEN/PRAZ treated groups were not different. After drug perfusion, declines in coronary flow were detected in the control and ATEN/PRAZ treated groups compared to their baselines (p<0.05), whereas coronary flows in ATEN and ATEN/SALBU treated groups were slightly decreased compared to the baselines. Coronary flow rates dropped in all groups during the coronary occlusion period and increased after perfusion (p<0.05). Only the control group showed that coronary flow rate during the reperfusion period was not different from the drug perfusion period. There was no significant difference of coronary flow rate among groups at the same period.

**Effects of adrenergic drugs on electrograms**

As shown in Table 2, there were no significant differences in RR and QT intervals among experimental groups at the baselines. During the drug perfusion period, only ATEN/PRAZ prolonged RR intervals and shortened...
Figure 2 Comparison of the effect of perfusion with a Krebs-Henseleit buffer (control; n=9), 10 µM atenolol (ATEN; n=12), 10 µM atenolol combined with 0.01 µM salbutamol (ATEN/SALBU; n=12), or 10 µM atenolol combined with 5 µM prazosin (ATEN/PRAZ; n=13) on the rate of rise (dP/dt\text{max}) during the baseline, drug perfusion, occlusion, and reperfusion of isolated rat hearts. The dP/dt\text{max} decreased significantly after drug perfusion, and then abruptly decreased during occlusion period in all groups (p<0.05). After coronary reperfusion, increases in dP/dt\text{max} were observed in the ATEN/SALBU and ATEN/PRAZ treated groups although there was no significant difference between these two groups. The data is presented as mean ± SD. a, b, c, and d represent significant differences (p<0.05) among periods in the same treated group.

Figure 3 Comparison of the effects of perfusion with a Krebs-Henseleit buffer (control; n=9), 10 µM atenolol (ATEN; n=12), 10 µM atenolol combined with 0.01 µM salbutamol (ATEN/SALBU; n=12), and 10 µM atenolol combined with 5 µM prazosin (ATEN/PRAZ; n=13) on the rate of fall (dP/dt\text{min}) during the baseline, drug perfusion, ischemia, and reperfusion of isolated rat hearts. The dP/dt\text{min} decreased significantly after drug perfusion, and then abruptly decreased during coronary occlusion period in all groups (p<0.05). After coronary reperfusion, increases in dP/dt\text{min} were observed in the ATEN/SALBU and ATEN/PRAZ treated groups although there was no significant difference between these two groups. The data is presented as mean ± SD. a, b, and c represent significant differences (p<0.05) among periods in the same treated group.

QT intervals (p<0.05). RR intervals of ATEN/PRAZ treated group was much wider than that of ATEN/SALBU treated group during reperfusion (p<0.05). Prolonged RR intervals during coronary occlusion were observed in all groups nevertheless there was a significant difference only in the ATEN/PRAZ treated group (p<0.05). Interestingly, ATEN/PRAZ increased RR intervals at all periods.

QT intervals were prolonged in all groups during reperfusion, and it should be noted that QT intervals in
the ATEN/PRAZ treated group were wider than other groups (p<0.05). However, QTc intervals in all groups were not different at any period. This data demonstrated that no drugs used in this experiment altered QTc intervals.

**Effects of adrenergic drugs on cardiac arrhythmias**

The 30 minutes reperfusion following coronary occlusion produced ventricular arrhythmia in all experimental groups. As shown in Table 3, singlet, couplet, and triplet ventricular premature beats (VPB) appeared in all groups during coronary reperfusion. Non-sustained VT was present in all groups nevertheless sustained ventricular tachycardia was present only in the control and the ATEN/SALBU treated group. However, there was no significant difference in the incidence of singlet, couplet, and triplet, non-sustained, and sustained VT among groups. The incidence of VF was highest in the ATEN/SALBU treated group as shown in Table 3 and Fig. 5 although there was no statistically significant difference compared to other groups. ATEN slightly reduced the occurrence of VF compared to the control. Notably, there was no incidence of VF in the ATEN/PRAZ treated group after reperfusion as shown in Table 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Drug perfusion</th>
<th>Occlusion</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=9)</td>
<td>21.0±3.6⁶</td>
<td>19.7±3.5⁶</td>
<td>15.0±3.9⁶</td>
<td>18.2±3.3⁶</td>
</tr>
<tr>
<td>ATEN (n=12)</td>
<td>20.4±3.0⁶</td>
<td>19.8±3.9⁶</td>
<td>14.7±3.4⁶</td>
<td>17.3±4.0⁶</td>
</tr>
<tr>
<td>ATEN/SALBU (n=12)</td>
<td>21.5±3.4⁶</td>
<td>21.4±3.0⁶</td>
<td>15.5±5.6⁶</td>
<td>17.8±5.5⁶</td>
</tr>
<tr>
<td>ATEN/PRAZ (n=13)</td>
<td>22.9±4.7⁶</td>
<td>22.0±5.8⁶</td>
<td>12.1±4.5⁶</td>
<td>15.6±4.6⁶</td>
</tr>
</tbody>
</table>

The data is presented as mean ± SD. ATEN, atenolol; ATEN/SALBU, atenolol combined with salbutamol; ATEN/PRAZ, atenolol combined with prazosin.

⁶, ⁷, and ⁸ represent significant differences (p<0.05) among periods in the same treated group.
Table 2  Effects of adrenergic drugs on R-R, Q-T, and Q-Tc intervals

<table>
<thead>
<tr>
<th>Group/Period</th>
<th>ECG interval</th>
<th>Baseline</th>
<th>Drug</th>
<th>Occlusion</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (msec)</td>
<td>QT (msec)</td>
<td>QTc  (msec)</td>
<td>RR (msec)</td>
<td>QT (msec)</td>
</tr>
<tr>
<td>Control (n=9)</td>
<td>194±11</td>
<td>83±12</td>
<td>190±27</td>
<td>188±19</td>
<td>86±7</td>
</tr>
<tr>
<td>ATEN (n=12)</td>
<td>195±15</td>
<td>83±10</td>
<td>188±24</td>
<td>193±22</td>
<td>83±4.7</td>
</tr>
<tr>
<td>ATEN/SALBU (n=12)</td>
<td>188±28</td>
<td>84±3</td>
<td>195±15</td>
<td>187±33</td>
<td>84±6</td>
</tr>
<tr>
<td>ATEN/PRAZ (n=13)</td>
<td>187±26a</td>
<td>85±3a</td>
<td>200±13</td>
<td>219±33ab</td>
<td>84±24a</td>
</tr>
</tbody>
</table>

The data is presented as mean ± SD. ATEN, atenolol; ATEN/SALBU, atenolol combined with salbutamol; ATEN/PRAZ, atenolol combined with prazosin.

* and † represent significant differences (p<0.05) among periods in the same treated group.

‘ represents the significant difference of the ATEN/PRAZ treated group from the control group (p<0.05) in the same period.

# represents significant difference of the ATEN/PRAZ treated group from the ATEN/SALBU treated group (p<0.05) in the same period.

Table 3 Incidences of ventricular arrhythmia after reperfusion in control and drug treated groups

<table>
<thead>
<tr>
<th>Group</th>
<th>% VPB (singlet)</th>
<th>% VPB (couplet)</th>
<th>% VPB (triplet)</th>
<th>% Non-sustained VT</th>
<th>% Sustained VT</th>
<th>% VF</th>
<th>Arrhythmia score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>83.8</td>
<td>66.7</td>
<td>33.3</td>
<td>58.3</td>
<td>8.3</td>
<td>66.7</td>
<td>4.2±1.4</td>
</tr>
<tr>
<td>(n=12)</td>
<td>(10/12)</td>
<td>(7/12)</td>
<td>(8/12)</td>
<td>(4/12)</td>
<td>(1/12)</td>
<td>(1/12)</td>
<td>(1/12)</td>
</tr>
<tr>
<td>ATEN</td>
<td>92.8</td>
<td>78.6</td>
<td>57.1</td>
<td>64.3</td>
<td>0.0</td>
<td>50.0</td>
<td>3.6±1.5</td>
</tr>
<tr>
<td>(n=14)</td>
<td>(13/14)</td>
<td>(11/14)</td>
<td>(8/14)</td>
<td>(9/14)</td>
<td>(0/14)</td>
<td>(1/14)</td>
<td>(1/14)</td>
</tr>
<tr>
<td>ATEN/SALBU</td>
<td>94.7</td>
<td>73.7</td>
<td>31.631.6</td>
<td>63.2</td>
<td>5.3</td>
<td>68.4</td>
<td>4.1±1.4</td>
</tr>
<tr>
<td>(n=19)</td>
<td>(18/19)</td>
<td>(14/19)</td>
<td>(6/19)</td>
<td>(12/19)</td>
<td>(1/19)</td>
<td>(13/19)</td>
<td>(13/19)</td>
</tr>
<tr>
<td>ATEN/PRAZ</td>
<td>100</td>
<td>40.0</td>
<td>40.0</td>
<td>33.3</td>
<td>0.0</td>
<td>0.0</td>
<td>1.8±0.9</td>
</tr>
<tr>
<td>(n=15)</td>
<td>(15/15)</td>
<td>(6/15)</td>
<td>(6/15)</td>
<td>(5/15)</td>
<td>(0/15)</td>
<td>(0/15)</td>
<td>(0/15)</td>
</tr>
</tbody>
</table>

Incidences of ventricular arrhythmia were present as percentage and its proportion, and arrhythmia scores were present as mean±SD. VPB, ventricular premature beat; VT, ventricular tachycardia; VF, ventricular fibrillation; ATEN, atenolol; ATEN/SALBU, atenolol combined with salbutamol; ATEN/PRAZ, atenolol combined with prazosin.

* and † represent significant differences in the types of arrhythmia within the same treated group.

‘ represents significant differences of arrhythmia score in the ATEN/PRAZ treated group from other groups (p<0.05)

# represents significant differences of arrhythmia incidences among treated groups (p<0.05).
Discussion

In the present study, atenolol, a selective $\beta_1$-adrenergic antagonist combined with a selective $\alpha_1$-adrenergic antagonist, prazosin, showed the highest potential antiarrhythmic effects whereas atenolol alone does not have significant antiarrhythmic effects. These results indicate that $\alpha_1$-AR plays an important role on reperfusion arrhythmias. Firstly, it is possible that $\alpha_1$-AR stimulation may induce delayed afterdepolarization in reperfused myocardium, the same as an investigation in Purkinje fibers isolated from cat hearts in the presence of an elevated Ca$^{2+}$ concentration (Kimura et al., 1984).

Moreover, the $\alpha_1$-adrenergic stimulation of canine hypoxic cardiac myocytes with norepinephrine resulted in the appearance of delayed afterdepolarizations which may be a response to an increase in intracellular Ca$^{2+}$ (Kurz et al., 1991). Secondly, $\alpha_1$-AR antagonist may prevent a fall in the ventricular fibrillation threshold. As previously described, prazosin prevented an $\alpha_1$-adrenergic agonist, metoxamine, induced a fall in the ventricular fibrillation threshold in normoxic rat myocardium (Thandroyen et al., 1987), and the enhanced vulnerability ventricular fibrillation induced by $\alpha_1$-adrenergic agonist could be demonstrated only at supraphysiological extracellular calcium concentrations, but not at physiological calcium concentrations (Thandroyen et al., 1987). Prazosin also blocked the metoxamine-induced increases in Ica (L) in chick and human single cardiac cells (Bkaily et al., 2003). Furthermore, the arrhythmogenic effects of $\alpha_1$-adrenergic agonists may be prevented by blocking L-type calcium channel. Likewise, in the present study, ischemic-reperfusion which causes Ca$^{2+}$ ion influx through the sarcolemma and induces ventricular arrhythmia has been described (Lu et al., 1999), and reperfusion arrhythmias could be prevented by the blockade of $\alpha_1$-adrenergic receptors with prazosin. Moreover, prazosin not only has $\alpha_1$-adrenergic blocking

and Fig. 6, and the decreased incidence of VF in ATEN/PRAZ treated group was significantly lower compared to other groups ($p<0.001$). Moreover, ATEN/PRAZ also appeared to decrease incidences of sustained VT. In concurrence with arrhythmia incidences, the arrhythmia score was the lowest in the ATEN/PRAZ treated group ($p<0.001$) while there were no significant difference of the scores among control, ATEN, and ATEN/SALBU treated groups. However, ATEN did not decrease the incidences of ventricular arrhythmia compared to the control whereas ATEN/SALBU did not enhance the incidence of ventricular arrhythmia in reperfusion hearts.

Figure 5 Tracing shows electrocardiogram (ECG), left ventricular developed pressure (LVDP), and the rate of rise and fall (dP/dt) during reperfusion in isolated rat hearts perfused with 10 $\mu$M atenolol combined with 0.01 $\mu$M salbutamol (ATEN/SALBU). A few seconds after reperfusion, the normal ECG changed to ventricular tachycardia (VT) and finally ventricular fibrillation (VF). LVDP and dP/dt also decreased suddenly during reperfusion.

Moreover, the $\alpha_1$-adrenergic stimulation of canine hypoxic cardiac myocytes with norepinephrine resulted in the appearance of delayed afterdepolarizations which may be a response to an increase in intracellular Ca$^{2+}$ (Kurz et al., 1991). Secondly, $\alpha_1$-AR antagonist may prevent a fall in the ventricular fibrillation threshold. As previously described, prazosin prevented an $\alpha_1$-adrenergic agonist, metoxamine, induced a fall in the ventricular fibrillation threshold in normoxic rat myocardium (Thandroyen et al., 1987), and the enhanced vulnerability ventricular fibrillation induced by $\alpha_1$-adrenergic agonist could be demonstrated only at supraphysiological extracellular calcium concentrations, but not at physiological calcium concentrations (Thandroyen et al., 1987). Prazosin also blocked the metoxamine-induced increases in Ica (L) in chick and human single cardiac cells (Bkaily et al., 2003). Furthermore, the arrhythmogenic effects of $\alpha_1$-adrenergic agonists may be prevented by blocking L-type calcium channel. Likewise, in the present study, ischemic-reperfusion which causes Ca$^{2+}$ ion influx through the sarcolemma and induces ventricular arrhythmia has been described (Lu et al., 1999), and reperfusion arrhythmias could be prevented by the blockade of $\alpha_1$-adrenergic receptors with prazosin. Moreover, prazosin not only has $\alpha_1$-adrenergic blocking
Figure 6 Tracing shows electrocardiogram (ECG), left ventricular developed pressure (LVDP), and rate of rise and fall (dP/dt) during reperfusion in isolated rat hearts perfused with 10 \( \mu \)M atenolol combined with 5 \( \mu \)M prazosin (ATEN/PRAZ). No evidence of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) was seen during reperfusion in this group.

However, there was an experiment demonstrating that prazosin (5.2 \( \mu \)M) alone could not prevent reperfusion arrhythmias in the isolated rat heart (Bralet et al., 1985). In this study, the left main coronary artery was ligated for 10 minutes and followed by reperfusion. This data demonstrates that 5.2 \( \mu \)M prazosin alone was not antiarrhythmic. Therefore, the combination of a \( \beta \)-adrenergic antagonist and an \( \alpha \)-adrenergic antagonist in our study may produce stronger antiarrhythmic effects compared to \( \alpha \)- or \( \beta \)-adrenergic antagonist alone.

In our study, the coronary flow rate in the ATEN/SALBU treated group tended to be the highest during ischemia. This implies that \( \beta \)-adrenergic receptors may play an important role on coronary vasodilation. In agreement with our study, a study shows that administration of \( 10^{-5} \) mol/L of propanolol or \( 10^{-6} \) mol/L of butoxamine in isolated human coronary arterioles completely eliminated norepinephrine (NE)-induced dilation whereas \( 10^{-6} \) mol/L of prazosin inhibited NE induced constriction only 2 of 39 vessels. This data indicated that isolated coronary arterioles from patients with dilated cardiomyopathy may mediate vasodilation via \( \beta \)-ARs (Sun et al., 2002).

In conclusion, the combination of \( \beta \)-adrenergic antagonist and \( \beta \)-adrenergic antagonist has the most potential antiarrhythmic effects compared to the
β₁-β₂-adrenergic antagonist alone or β₁-β₂-adrenergic antagonist plus β₂-adrenergic agonist. Our results support that α₁-ARs play an important role on reperfusion arrhythmia whereas coronary vasodilation mediates through β₂-ARs in ischemia/reperfusion isolated rat hearts.

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References


