α2-Adrenergic stimulation is protective against ischemia-reperfusion-induced ventricular arrhythmias in vivo

JOHN J. CAI, DONALD A. MORGAN, WILLIAM G. HAYNES, JAMES B. MARTINS, AND HON-CHI LEE

1Department of Internal Medicine, University of Iowa College of Medicine, and Veterans Administration Medical Center, Iowa City, Iowa 52242; and
2Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota 55905

Received 4 March 2002; accepted in final form 1 August 2002


Until recently, postjunctional α2-adrenergic receptors (ARs) were thought not to be present in the heart. We found that postjunctional α2-ARs are present in canine cardiac Purkinje fibers but not in working myocardium (18, 26). α2-AR stimulation prolongs the action potential duration and suppresses the β-adrenergic stimulation-induced delayed afterdepolarizations and sustained triggered activities. We examined the effects of α2-AR stimulation on reperfusion-induced ventricular arrhythmias [ventricular tachycardia/ventricular fibrillation (VT/VF)] in vivo. Arterial blood pressure, heart rate, surface electrocardiogram, and renal sympathetic nerve activities were recorded simultaneously in Sprague-Dawley rats. The incidence of VT/VF was 87.5% for controls, 50% for the β-blocker group, 72% for the α1-blocker group, and 12.5% for the α1 + β-blockers group (unopposed α2-adrenergic activation). Direct α2-AR stimulation with UK-14304 also prevented VT/VF. These effects were reversed by the α2-adrenergic antagonist yohimbine. Increases in renal sympathetic nerve activity were associated with left anterior descending coronary artery ligation and reperfusion (33 ± 1.5 and 62 ± 1.7% over baseline, respectively) in controls. Similar patterns were observed among all experimental groups irrespective of the incidence of VT/VF on reperfusion. We conclude that α2-AR stimulation has a potent antiarrhythmic effect on ischemia-reperfusion-induced VT/VF in vivo and that this effect is not centrally mediated.

sympathetic nerve activities; ventricular tachycardia; ventricular fibrillation; Purkinje fibers

SUDEN CARDIAC DEATH due to ventricular arrhythmias accounts for ~300,000–400,000 deaths each year in this country (24, 33). In the adult population, ischemic heart disease represents the most common substrate underlying such devastating events (11, 33). During the early hours of acute coronary occlusion, intense adrenergic activation of the ischemic myocardium may contribute to the evolution of abnormal cellular electrical behavior and, ultimately, result in lethal ventricular arrhythmias, ventricular tachycardia (VT) or ventricular fibrillation (VF) (9, 16).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
ventilated, and the arterial pH was maintained between 7.35 and 7.45 with $P_{O_2} > 80$ mmHg. Surface electrocardiogram was obtained through minigrip leads on shaved skin. A rectal thermistor was inserted for monitoring core temperature, which was maintained at 37.5°C with a heating pad.

Renal sympathetic nerve activity recordings. Renal sympathetic nerve activity (RSNA) recording is an established method for measuring sympathetic discharge during physiological and pathological conditions (12, 23) and was performed as previously described (12). Specifically, the left renal sympathetic nerve was exposed retroperitoneally through a left flank incision. Under a dissection microscope, a nerve branch of the left kidney was carefully dissected free of surrounding tissue, and a bipolar platinum-iridium electrode (Cooner Wire, Chatsworth, CA) was applied to the nerve. In all studies, the nerve was transected distally to exclude renal afferent signals. Nerve recording electrodes were connected to a high-impedance probe (model HIP-511, Grass Instrument, Quincy, MA), amplified by 10³, and filtered at low- and high-frequency cutoffs of 100 and 1,000 Hz with a nerve traffic analysis system (model 662-C, Department of Bioengineering, University of Iowa). The filtered and amplified nerve signal was displayed on an oscilloscope, acquired through a MacLab analog-to-digital converter (AD Instruments, Grand Junction, CO) for permanent recording of the neurogram on a Macintosh 9500 computer, and processed by a nerve traffic analyzer (model 706, Department of Bioengineering, University of Iowa), which counts the number of spikes exceeding a threshold cursor set just above background. RSNA was recorded throughout the experiment.

Left anterior descending coronary artery ligation and reperfusion. Animals were allowed to stabilize for 45–60 min after the recording system was established. A midsternotomy was performed, and the heart was exposed. A 6-0 silk suture was passed through the myocardium under the proximal portion of the left anterior descending coronary artery (LAD) ~1.5 mm distal to the ostium of the vessel. Temporary LAD occlusion was achieved by tightening the suture over the PE-50 tubing for 10 min. Discoloration of the ischemic area compared with the rest of the myocardium indicated successful LAD occlusion (21). Reperfusion was achieved by releasing the suture after a 10-min ligation. Diluted Evans blue dye was injected to determine whether there was permanent myocardial damage at the end of the experiment. No permanent necrosis of the myocardium was found from the 10-min LAD ligation.

Evaluation of rhythm disturbances. The incidence of ventricular extrasystole (VES), VT, and VF was continuously characterized by a loss of synchronicity of electrocardiogram plus decreased amplitude and a precipitous fall in blood pressure (BP) for $>1$ s.

Study protocols. All drugs were infused through the femoral vein ~5 min before LAD ligation. Protocol 1 consisted of five experimental groups: 1) the control group was studied with normal saline injection, 2) the β-blocker group was treated with the nonselective β-blocker propranolol (1 mg/kg), 3) the α₁-blocker group was treated with prazosin (0.2 mg/kg), 4) the β + α₁-blockers group (unopposed endogenous α₂-adrenergic stimulation) was established by using propranolol (1 mg/kg) and prazosin (0.2 mg/kg), and 5) the β + α₁ + α₂-blockers group (establishing the reversibility of the endogenous α₂-adrenergic stimulation) was treated with propranolol (1 mg/kg), prazosin (0.2 mg/kg), and the α₂-adrenergic-specific blocker yohimbine (0.03 mg/kg).

Protocol 2 was carried out by directly stimulating α₂-AR with UK-14304 (0.03 mg/kg), and the α₂-AR specificity was established by reversing the effect with addition of yohimbine. After the drug treatments, animals were subjected to 10 min of LAD ligation followed by reperfusion.

Statistical analysis. Eight determinations were obtained for each experimental protocol. Group data are expressed as means ± SE. Comparisons between the different hemodynamic measurements and the incidence of ischemia-reperfusion-induced VT/VF among the groups were performed by one-way analysis of variance and a mixed-model analysis for repeated measures. Pairwise comparisons among the groups were performed using post hoc tests, and the P values were adjusted using Bonferroni’s method to account for the multiple tests performed. Bonferroni-adjusted $P < 0.05$ was considered statistically significant.

RESULTS

Hemodynamic parameters. Table 1 summarizes the hemodynamic data of all study groups at baseline and during LAD ligation. There were no statistical differences in heart rate (HR) and mean arterial blood pressure (MBP) among the groups at baseline. HR decreased significantly during ischemia only in the β-blocker (propranolol) group compared with its baseline (341 ± 11.4 vs. 308 ± 7.6, $n = 8$, $P = 0.027$). During LAD ligation, significant decreases in MBP from baseline were found in controls ($P = 0.007$) and in the β + α₁-blockers group (propranolol + prazosin, $P = 0.011$) but not in the other groups. However, there were no statistical differences in MBP among all treatment groups ($P > 0.7$).

Effects of unopposed endogenous α₂-adrenergic stimulation on the incidence of reperfusion-induced ventricular arrhythmias and RSNA. Figure 1 shows representative recordings from the experiments. During a control experiment (Fig. 1A), there was a decrease in BP associated with LAD ligation. On reperfusion, the heart developed polymorphic VT and rapidly deteriorated into sustained VF with loss of BP. There was an increase in RSNA during LAD ligation and an additional increase during reperfusion. In the presence of

Table 1. Hemodynamic effects of drug interventions

<table>
<thead>
<tr>
<th>Heart Rate, beats/min</th>
<th>Baseline</th>
<th>LAD Ligation</th>
<th>Control</th>
<th>β-Blocker</th>
<th>α₁-Blocker</th>
<th>β + α₁-Blockers</th>
<th>+ YO</th>
<th>UK</th>
<th>UK + YO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>361 ± 11.3</td>
<td>341 ± 11.4</td>
<td>399 ± 12.0</td>
<td>371 ± 16.6</td>
<td>354 ± 11.6</td>
<td>402 ± 18.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>388 ± 18.6</td>
<td>308 ± 7.6†</td>
<td>424 ± 12.0</td>
<td>373 ± 11.3</td>
<td>374 ± 14.6</td>
<td>411 ± 21.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>388 ± 18.6</td>
<td>308 ± 7.6†</td>
<td>402 ± 19.2</td>
<td>373 ± 11.3</td>
<td>374 ± 14.6</td>
<td>411 ± 21.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>110 ± 6.9</td>
<td>99.3 ± 3.9</td>
<td>113 ± 5.2</td>
<td>116.0 ± 7.8</td>
<td>105.6 ± 7.4</td>
<td>98.8 ± 6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85.4 ± 3.8*</td>
<td>87.5 ± 5.2</td>
<td>95.9 ± 4.3</td>
<td>92.9 ± 5.7*</td>
<td>87.8 ± 2.8</td>
<td>96.8 ± 6.3</td>
</tr>
</tbody>
</table>

Values are means ± SE; $n = 8$. MBP, mean arterial blood pressure; LAD, left anterior descending coronary artery; UK, UK-14304 (α₂-receptor agonist); YO, yohimbine (α₂-receptor blocker). Propranolol was the β-blocker, prazosin was the α₁-blocker, *$P < 0.03$ compared with baseline; †$P < 0.008$ compared with control, α₁-blocker, UK, and UK + YO.
RSNA during LAD ligation and during reperfusion in both groups. Effects of direct \( \alpha_2 \)-adrenergic stimulation on ischemia-reperfusion-induced VT/VF. Pretreatment with the \( \alpha_2 \)-adrenergic agonist UK-14304 resulted in a slight increase in HR but not in MBP, and these changes were not altered by the addition of yohimbine. Also, after treatment with UK-14304, alone or with yohimbine, there was no significant decrease in BP during LAD ligation. Rather dramatically, after treatment with UK-14304, reperfusion could no longer induce VT/VF in these animals. Furthermore, the protec-

\[\text{RSNA} \text{ at baseline, during LAD ligation, and during reperfusion for protocol 1. All groups showed an increase in RSNA during LAD ligation, with further increase in activity on reperfusion. Although not statistically significant, the} \beta\text{-blocker group and the} \beta + \alpha_1\text{-blockers group (unopposed} \alpha_2\text{-adrenergic effect) appeared to have blunted RSNA during LAD ligation and during reperfusion compared with the other treatment groups. These two groups also had the lowest incidence of ischemia-reperfusion-induced VT/VF. The incidence of VT/VF, however, was significantly reduced in the} \beta + \alpha_1\text{-blockers group but not in the} \beta\text{-blocker group, suggesting that unopposed} \alpha_2\text{-adrenergic stimulation is protective. On the basis of these experiments, we were still unable to determine whether this} \alpha_2\text{-adrenergic effect is centrally or locally mediated. Hence, we performed the experiments in protocol 2 using direct} \alpha_2\text{-adrenergic stimulation and blockade.}

**Effects of direct \( \alpha_2 \)-adrenergic stimulation on ischemia-reperfusion-induced VT/VF.** The incidence of VT/VF was 87.5% for controls, 50% for \( \beta \)-blocker group, 72% for \( \alpha_1\)-blocker group, and 12.5% for \( \beta + \alpha_1\)-blockers (unopposed \( \alpha_2 \)-adrenergic receptor (AR) stimulation) group. The \( \beta + \alpha_1\)-blockade effect was completely reversed by addition of the \( \alpha_2 \)-adrenergic receptor (AR) antagonist yohimbine and \( \beta + \alpha_1\)-blockers (\( n = 8 \) for all groups). \( \#P < 0.05 \text{ vs. control.} \)**

Figure 2 summarizes the RSNA at baseline, during LAD ligation, and during reperfusion in both groups. There was no reperfusion-induced VT/VF with \( \beta + \alpha_1\)-adrenergic stimulation (treatment with \( \beta + \alpha_1\)-blockers; \( B \)). There were similar increases in RSNA during LAD ligation and during reperfusion in both groups.

\[\beta + \alpha_1\]-blockers (Fig. 1B) was a similar decrease in BP during LAD ligation, as in controls. However, VT/VF did not occur on reperfusion, suggesting that endogenous \( \alpha_2 \)-adrenergic stimulation is protective against ischemia-reperfusion-induced VT/VF. The RSNA changes in the \( \beta + \alpha_1\)-blockers group were also similar to the control, with an increase in activity during LAD ligation and a further increase during reperfusion.

Figure 2 shows the incidence of ischemia-reperfusion-induced VT/VF. The incidence of VT/VF was 87.5% for controls, indicating that, under control conditions, short periods of LAD occlusion with reperfusion resulted in a high incidence of lethal ventricular arrhythmias in these animals. The incidence of VT/VF was 50% for the \( \beta \)-blocker group, suggesting that \( \beta \)-adrenergic blockade may have antiarrhythmic effects, but the difference did not reach statistical significance. \( \alpha_1\)-Adrenergic blockers had no apparent protective effect, with 72% incidence of VT/VF. However, there was only 12.5% VT/VF in the \( \beta + \alpha_1\)-blockers group (\( P < 0.05 \text{ vs. control.} \)** This effect was completely reversed by addition of the \( \alpha_2 \)-adrenergic-specific antagonist yohimbine, suggesting a specific \( \alpha_2 \)-adrenergic-mediated effect.

Fig. 2. Incidence of reperfusion-induced ventricular arrhythmias (VT/VF) in protocol 1: 87.5% for controls, 50% for \( \beta \)-blocker group, 72% for \( \alpha_1\)-blocker group, and 12.5% for \( \beta + \alpha_1\)-blockers (unopposed \( \alpha_2 \)-adrenergic receptor (AR) stimulation) group. The \( \beta + \alpha_1\)- blockade effect was completely reversed by addition of the \( \alpha_2 \)-adrenergic receptor (AR) antagonist yohimbine and \( \beta + \alpha_1\)-blockers (\( n = 8 \) for all groups). \( \text{***P} < 0.05 \text{ vs. control.} \text{**P} < 0.05 \text{ vs.} \beta + \alpha_1\)-blockers.

\[\text{AJP-Heart Circ Physiol} \cdot \text{VOL 283} \cdot \text{DECEMBER 2002} \cdot \text{www.ajpheart.org}

---

AJP-Heart Circ Physiol • VOL 283 • DECEMBER 2002 • www.ajpheart.org
tive effects of UK-14304 were reversed by the addition of yohimbine (0% incidence of VT/VF for UK-14304 vs. 87.5% for UK-14304 + yohimbine, n = 8, P < 0.05; Fig. 4). The RSNA patterns, however, were similar between UK-14304 (114 ± 4.2% over baseline during LAD ligation and 129 ± 11% during reperfusion) and UK-14304 + yohimbine (112 ± 3% during LAD ligation and 134 ± 8% during reperfusion, n = 8; Fig. 5). Similar to the treatments with unopposed endogenous α2-AR effects (β + α1-blockers, Fig. 3), UK-14304 appeared to have blunted the RSNA during LAD ligation and during reperfusion, but these changes were not statistically significant. In addition, when the results of reperfusion-induced VT/VF (Fig. 4) were compared with the corresponding RSNA (Fig. 5), there was no correlation between the centrally mediated sympathetic activity and the incidence of VT/VF. These results suggest that the antiarrhythmic effect of α2-adrenergic stimulation is not centrally mediated.

**DISCUSSION**

We have made the following novel observations. First, we found that α2-adrenergic stimulation was protective against ischemia-reperfusion-induced VT/VF in open-chest anesthetized rats induced with 10 min of LAD ligation followed by reperfusion. This protective α2-adrenergic effect was blocked by the α2-AR-specific antagonist yohimbine. Second, we found that the antiarrhythmic effect of α2-adrenergic stimulation was independent of sympathetic discharge measured by RSNA, suggesting that the α2-adrenergic effects were not centrally mediated. We also found that sympathetic activities increased with coronary ligation, and we observed an additional increase during reperfusion. This pattern of sympathetic activity changes was observed in all treatment groups with various adrenergic blockades. Only the groups with α2-adrenergic stimulation, both endogenously with β + α1-blockade and exogenously through direct infusion of UK-14304, showed significant reduction in ischemia-reperfusion-induced VT/VF.

The results of this study are consistent with our previously published in vitro studies suggesting that α2-adrenergic stimulation has potent antiarrhythmic effects (8, 18, 26, 28). Increased intracellular cAMP has been implied to cause arrhythmias under ischemia and reperfusion (20). In isolated canine Purkinje fibers in vitro, we have demonstrated that the α2-adrenergic effects on Purkinje action potential were mediated through a PTX-sensitive G protein, G, which is known to inhibit adenylate cyclase activity, thereby counteracting the β-adrenergic stimulation on cAMP production. Electrophysiologically, α2-adrenergic stimulation prolongs the action potential duration and suppresses the β-adrenergic stimulation-induced delayed afterdepolarizations and sustained triggered activities in canine Purkinje fibers (26). The present study not only corroborated the in vitro findings but also brought new insight to our understanding of the ischemia-reperfusion-induced ventricular arrhythmia mechanism in vivo. This study is unique, in that we incorporated RSNA recordings in the study of ischemia-reperfusion-induced arrhythmias.

The relationship between sympathetic activities and VT/VF has long been debated (27). Ischemia-reperfusion is known to cause sympathetic activation, resulting in elevated systemic catecholamine levels (22, 31), and is associated with a decrease in the VF threshold (19). Catecholamine levels are frequently measured during ischemia in arrhythmia-related studies (19, 22, 31). Some of the animal studies dismissed the effect of central nervous system activation as the main culprit for reperfusion-induced arrhythmia (20), and the important role of sympathetic activation in VF was strongly implicated in other studies (19, 27, 31). Our study showed that the β-blocker and the β + α1-blockers (unopposed α2-AR stimulation) groups had the lowest incidence of reperfusion-induced VT/VF, and both also had blunted RSNA compared with the controls and the other experimental groups (Figs. 2 and 3). This observation suggests that sympathetic activation may well be a determinant in ischemia-reperfusion-induced arrhythmias.
VT/VF. Although there are ample clinical data suggesting a protective role of β-adrenergic blockade on sudden cardiac death in patients with ischemic heart disease (13, 14), this study was not adequately powered to detect a significant effect of these agents on ischemia-reperfusion arrhythmias. β-Adrenergic blockade may serve to blunt the sympathetic activity in the development of VT/VF. Hence, β-adrenergic blockade plus unopposed α2-adrenergic stimulation could have an even more significant antiarrhythmic effect, because the generation of cAMP would be reduced through reduced stimulation at the receptor level and the inhibition of adenylate cyclase at the intracellular level. However, the results of protocol 2 indicated that direct α2-adrenergic stimulation alone, without simultaneous β-blockade, not only is adequate and effective but is also significantly more potent than β-blocker alone in preventing the development of ischemia-reperfusion-induced VT/VF (Fig. 4). More importantly, our data also indicated that the protective α2-adrenergic effects were independent of sympathetic nerve activities as measured by RSNA profiles (Figs. 3 and 5). These important findings prompted us to speculate that the α2-adrenergic protective effect might be mediated through the α2-ARs in the Purkinje fibers in the heart. Our findings have significant clinical implications, inasmuch as α2-adrenergic agonists are not used for the treatment of ischemia-related cardiac arrhythmias. This should be further explored in the clinical arena.

Research and clinical data have supported and confirmed unequivocally the beneficial effects of β-blocker in patients with ischemic heart disease and in the prevention of sudden cardiac death (13, 14). In contrast, the effects of α1-adrenergic blockade on the development of ventricular arrhythmias are unclear. The predominant effect of α1-adrenergic blockade is vasodilatation, which may result in reflex tachycardia and may further activate the sympathetic system (17). However, recent studies suggested that stimulation of the α1-AR activates the second messenger inositol triphosphate, which appears to be arrhythmogenic during ischemia-reperfusion, suggesting that α1-adrenergic blockade could be beneficial for control of arrhythmia (32). Our data did not substantiate such an effect in vivo, because there was no statistically significant effect of prazosin on ischemia-reperfusion-induced VT/VF (72% vs. 87.5% in controls). There are only limited data on α2-adrenergic effects on ischemia-reperfusion-induced arrhythmia in vivo (3). In intact dogs, stimulation of α2-ARs prolongs the Purkinje relative refractory period (7) and selectively prevents ischemia- and pacing-induced VT of focal Purkinje fiber (3).

The primary limitation of this study is that we were unable to delineate that the antiarrhythmic α2-adrenergic effects are dependent on the α2-AR in cardiac Purkinje fibers. We were not able to directly assess the origin of the ventricular arrhythmias in our model. However, the Purkinje system has long been suspected to be the site of origin of ventricular arrhythmias during acute ischemia (2, 3, 15), and our previously published canine in vitro data showed that α2-ARs are present only in Purkinje fibers (18, 26, 28). We would speculate that the noncentrally mediated α2-adrenergic antiarrhythmic effect could well be a result of the action on the cardiac Purkinje fibers.

We have not been able to establish the presence of α2-ARs in human Purkinje fibers because of limited tissue availability, inasmuch as the only source for human Purkinje fibers is explanted hearts from cardiac transplantation. Further studies are needed to demonstrate the presence of α2-ARs and to identify the α2-AR subtypes in human Purkinje fibers, and these results may help us determine whether the proposed mechanism is relevant to human ischemia-reperfusion-induced arrhythmia. Interestingly, clinical trials have shown that carvedilol, a third-generation β-blocker that also has an α1-AR blockade effect, provides significant additional benefits for prevention of cardiac sudden death in patients with heart failure and ischemic heart disease (1, 4, 10, 25). A recent animal study by Takusagawa et al. (29) also showed clear beneficial effects of carvedilol on ischemia-reperfusion-induced ventricular arrhythmia over the β-blocker alone. Our study may provide an alternative explanation that the beneficial effects of carvedilol could be from its unopposed α2-adrenergic stimulation effects.

In conclusion, the results of our study suggest that α2-adrenergic stimulation has a potent antiarrhythmic effect on ischemia-reperfusion-induced VT/VF in vivo and that this effect is not mediated through the α2-adrenergic effects at presynaptic sites.

Statistical analysis was performed by Dr. Bridget Zimmerman (Biostatistics Consulting Center, Department of Biostatistics, College of Public Health, University of Iowa). J. J. Cai is a recipient of the 2000 North American Society Pacing and Electrophysiology Fellowship Award. This work was supported in part by National Heart, Lung, and Blood Institute Grant R01 HL63754, a Merit Award from the Department of Veterans Affairs, and American Heart Association Grant-in-Aid 0051311Z.

REFERENCES

7. Cable DG, Rath TE, Dreyer ER, and Martins JB. Refractory period response of cardiac Purkinje tissue to α1- and α2-adrenergic stimulation alone, without simultaneous β-blockade, not only is adequate and effective but is also significantly more potent than β-blocker alone in preventing the development of ischemia-reperfusion-induced VT/VF (Fig. 4). More importantly, our data also indicated that the protective α2-adrenergic effects were independent of sympathetic nerve activities as measured by RSNA profiles (Figs. 3 and 5). These important findings prompted us to speculate that the α2-adrenergic protective effect might be mediated through the α2-ARs in the Purkinje fibers in the heart. Our findings have significant clinical implications, inasmuch as α2-adrenergic agonists are not used for the treatment of ischemia-related cardiac arrhythmias. This should be further explored in the clinical arena.

Research and clinical data have supported and confirmed unequivocally the beneficial effects of β-blocker in patients with ischemic heart disease and in the prevention of sudden cardiac death (13, 14). In contrast, the effects of α1-adrenergic blockade on the development of ventricular arrhythmias are unclear. The predominant effect of α1-adrenergic blockade is vasodilatation, which may result in reflex tachycardia and may further activate the sympathetic system (17). However, recent studies suggested that stimulation of the α1-AR activates the second messenger inositol triphosphate, which appears to be arrhythmogenic during ischemia-reperfusion, suggesting that α1-adrenergic blockade could be beneficial for control of arrhythmia (32). Our data did not substantiate such an effect in vivo, because there was no statistically significant effect of prazosin on ischemia-reperfusion-induced VT/VF (72% vs. 87.5% in controls). There are only limited data on α2-adrenergic effects on ischemia-reperfusion-induced arrhythmia in vivo (3). In intact dogs, stimulation of α2-ARs prolongs the Purkinje relative refractory period (7) and selectively prevents ischemia- and pacing-induced VT of focal Purkinje fiber (3).

The primary limitation of this study is that we were unable to delineate that the antiarrhythmic α2-adrenergic effects are dependent on the α2-AR in cardiac Purkinje fibers. We were not able to directly assess the origin of the ventricular arrhythmias in our model. However, the Purkinje system has long been suspected to be the site of origin of ventricular arrhythmias during acute ischemia (2, 3, 15), and our previously published canine in vitro data showed that α2-ARs are present only in Purkinje fibers (18, 26, 28). We would speculate that the noncentrally mediated α2-adrenergic antiarrhythmic effect could well be a result of the action on the cardiac Purkinje fibers.

We have not been able to establish the presence of α2-ARs in human Purkinje fibers because of limited tissue availability, inasmuch as the only source for human Purkinje fibers is explanted hearts from cardiac transplantation. Further studies are needed to demonstrate the presence of α2-ARs and to identify the α2-AR subtypes in human Purkinje fibers, and these results may help us determine whether the proposed mechanism is relevant to human ischemia-reperfusion-induced arrhythmia. Interestingly, clinical trials have shown that carvedilol, a third-generation β-blocker that also has an α1-AR blockade effect, provides significant additional benefits for prevention of cardiac sudden death in patients with heart failure and ischemic heart disease (1, 4, 10, 25). A recent animal study by Takusagawa et al. (29) also showed clear beneficial effects of carvedilol on ischemia-reperfusion-induced ventricular arrhythmia over the β-blocker alone. Our study may provide an alternative explanation that the beneficial effects of carvedilol could be from its unopposed α2-adrenergic stimulation effects.

In conclusion, the results of our study suggest that α2-adrenergic stimulation has a potent antiarrhythmic effect on ischemia-reperfusion-induced VT/VF in vivo and that this effect is not mediated through the α2-adrenergic effects at presynaptic sites.

Statistical analysis was performed by Dr. Bridget Zimmerman (Biostatistics Consulting Center, Department of Biostatistics, College of Public Health, University of Iowa). J. J. Cai is a recipient of the 2000 North American Society Pacing and Electrophysiology Fellowship Award. This work was supported in part by National Heart, Lung, and Blood Institute Grant R01 HL63754, a Merit Award from the Department of Veterans Affairs, and American Heart Association Grant-in-Aid 0051311Z.
19. Lombardi F, Verrier RL, and Lown B.