**α-Adrenoceptor Stimulation With Exogenous Norepinephrine or Release of Endogenous Catecholamines Mimics Ischemic Preconditioning**

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**Background** Brief episodes of ischemia induced by proximal coronary artery occlusion can precondition the myocardium. Whether other stressful stimuli have the potential to protect the myocardium from subsequent ischemia remains controversial.

**Methods and Results** To study the hypothesis that transient α-adrenoceptor stimulation mimics preconditioning, for 5 minutes we administered 0.25 μg · kg⁻¹ · min⁻¹ norepinephrine or saline 10 minutes before a 30-minute coronary occlusion and 4 hours of reperfusion in an in vivo rabbit model. The area of necrosis (AN) and area of risk (AR) were measured. We found that norepinephrine pretreatment caused a reduction in infarct size when compared with controls (AN/AR, 0.17±0.04 versus 0.31±0.04; *P*<.02). Ischemic preconditioning also reduced infarct size (AN/AR, 0.22±0.03). The protection observed with norepinephrine treatment was entirely eliminated by pretreatment with α-adrenergic blockade using prazosin (AN/AR, 0.42±0.06). Tyramine, an agent that causes release of endogenous catecholamines, was administered (1.5 mg/kg IV) 10 minutes before coronary occlusion in another group of rabbits. Tyramine pretreatment resulted in a smaller infarct size than in untreated controls (AN/AR, 0.16±0.04 versus 0.41±0.07; *P*<.01). Both norepinephrine and tyramine caused an increase in systemic arterial pressure during infusion; tyramine also increased heart rate. In rabbits pretreated with prazosin, heart rate and systemic pressure during the norepinephrine infusion were similar to baseline values. During coronary occlusion, the degree of ischemia was similar in all groups.

**Conclusions** Exposure of the heart to either transient exogenous norepinephrine or endogenous release of norepinephrine and/or other catecholamines by tyramine can mimic the effects of ischemic preconditioning in rabbits. *(Circulation, 1994;90:1023-1028.)*

**Key Words** • norepinephrine • tyramine • myocardium • α₁-adrenergic agonists

brief episodes of ischemia before a sustained coronary artery occlusion precondition the heart, leading to a marked reduction in myocardial infarct size. The mechanism(s) of preconditioning are under study. Whether preconditioning requires the stress of coronary artery occlusion or stenosis to protect the heart or whether other forms of stressful stimuli before a sustained ischemic episode can protect the heart is not known.

High concentrations of catecholamines can damage the myocardium. Pathological changes include leukocyte infiltration, myofibrillar degeneration, and myofibrillar necrosis. Norepinephrine has complex effects on the heart, which are mediated by both α and β receptors. Briefly, norepinephrine can cause coronary vasoconstriction (α effect), which appears to be mediated ultimately by an increased concentration of calcium in coronary vascular smooth muscle. Intravenous administration of norepinephrine induces a brief fall, followed by a sustained rise, in coronary vascular resistance, accompanied by a fall in coronary sinus PO₂. In addition, both mean and systolic blood pressures rise, coronary flow and flow velocity increase slightly, and the heart rate remains constant. Tyramine, when administered intravenously, has been shown to release endogenous catecholamines, including norepinephrine.

We hypothesized that either transient exogenous administration of catecholamines or endogenous release of catecholamines might provide sufficient stress to precondition the heart to a subsequent sustained period of ischemia. In an attempt to mimic the effects of ischemic preconditioning we studied whether catecholamine stimulation, by administering either an infusion of norepinephrine or an injection of tyramine, could reduce infarct size induced by a subsequent coronary artery occlusion in the in vivo rabbit model. In addition, we tested whether α-adrenergic blockade would block the beneficial effects of norepinephrine treatment. Previous studies by both our group and others have demonstrated that ischemic preconditioning reliably reduces infarct size in this model. This was confirmed in the present study.

**Methods**

All experiments were conducted at the Heart Institute Research Laboratory, an AALAC-accredited laboratory. All animals were treated in accordance with the American Physiological Society’s recommendation on the humane care of animals.

**Protocol**

Male New Zealand White rabbits weighing 2.5 to 4.0 kg were anesthetized with a ketamine-xylazine mixture. The
animals were intubated and resired with room air. The respirator was set to deliver 30 to 35 breaths per minute with a tidal volume of 8 to 10 mL/kg. A cutdown was made in the neck. The left or right internal jugular and common carotid vessels were dissected free, and fluid-filled catheters were placed into them for delivery of drug and for blood flow, heart rate, and blood pressure measurements. A left thoracotomy was performed in the fourth intercostal space, and the pericardium was opened. A silk suture was placed around a large marginal branch of the left circumflex coronary artery, which supplies much of the anterolateral and apical walls of the left ventricle in the rabbit; the ends of the suture were passed through a short length of vinyl tubing, forming a snare. A 23-gauge butterfly needle was inserted into the left atrium and secured in place by a clip. The animals were then randomly assigned to receive a 5-minute infusion of norepinephrine (0.25 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) or saline. A 10-minute period of stabilization followed. The coronary artery was occluded for 30 minutes by clamping the vinyl tubing. Evidence of ischemia was assessed by the presence of cyanosis and visible wall motion abnormalities in the region of the occlusion. Regional myocardial blood flow (RMBF) and hemodynamics were measured during the occlusion. RMBF was measured by injecting approximately 500,000 radioactive microspheres labeled with \(^{111}\text{In}, \text{Ir}, \text{Ru}, \text{or} \text{Nb}, \text{while blood was withdrawn at a fixed rate (2.06 mL/min) from the carotid artery. After 30 minutes of occlusion, the snare was released, and the myocardium was allowed to reperfuse for 3 hours. After the first four experiments, the reperfusion period was extended to 4 hours, and all rabbits subsequently studied underwent 4 hours of reperfusion. RMBF measurements were performed during norepinephrine or saline infusion, during occlusion, and 30 minutes after reperfusion. Heart rate and blood pressure were measured using fluid-filled catheters connected to a monitor with recording capability (Gould Instruments). Heart rates and blood pressures were obtained at baseline, during drug infusion, just before occlusion, during occlusion, and at 30, 60, 120, 180, and 240 minutes after reperfusion. At the end of 4 hours of reperfusion, hemodynamics were obtained; then the coronary artery was clamped briefly, and 4 mL of a 50% solution of merynsephine blue dye was injected into the left atrium to stain the area that was perfused. The ischemic area at risk (AR) thus appeared as a pale nonstaining region. While under deep anesthesia, the rabbits were euthanized by giving intravenous KCl, and the hearts were removed. After slicing the left ventricle into six to eight slices, we photographed the hearts and then placed them into triphenyltetrazolium chloride for 10 minutes to stain the noninfarcted zone. This causes viable myocardium to stain brick-red, while the infarcted area appears pale.\(^{15}\) The hearts were then rephotographed, and the projected areas of necrosis as well as AR were planimetered.

**Protocol 2**

In a second series of experiments, rabbits were prepared as described above and then were randomized to receive either 1.5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) tyramine (Sigma Chemical Co) or saline. Intravenous treatment was administered 10 minutes before the 30-minute occlusion, which was followed by 4 hours of reperfusion. RMBF was measured during occlusion and reperfusion in all animals. In one animal, it was also measured just after tyramine was injected. We also measured RMBF in two additional nonoccluded animals at baseline and after tyramine.

**Protocol 3**

To determine if the \( \alpha \)-adrenergic effects of norepinephrine contribute to the infarct size reduction observed with treatment by this drug and to confirm the ability of ischemic preconditioning to reduce necrosis, we performed an additional series of studies. Rabbits were prepared as described above and then randomized to receive either \( \alpha \)-blockade by prazosin, given before the norepinephrine infusion, or ischemic preconditioning. Rabbits assigned to the \( \alpha \)-blockade group received prazosin (Sigma Chemical Co), 200 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), for a total of 10 minutes. Beginning at 5 minutes, a 5-minute infusion of norepinephrine (0.25 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) was given simultaneously. The dose of prazosin was chosen because of its ability to block the pressor effect of the norepinephrine dose tested in protocol 1. Rabbits assigned to the ischemic preconditioning group received two 5-minute coronary artery occlusions separated by two 5-minute reperfusions. Both groups then received 30 minutes of occlusion and 4 hours of reperfusion as in the first two protocols. RMBF was measured during the norepinephrine infusion in the \( \alpha \)-blockade group and during occlusion and 30 minutes of reperfusion in all animals.

Exclusion criteria for all protocols included RMBF > 0.4 mL min\(^{-1} \cdot \text{g}^{-1} \) in the ischemic zone during occlusion: AR < 10% of the left ventricle; and failure to reperfuse, as determined by blood flow of < 0.4 mL min\(^{-1} \cdot \text{g}^{-1} \) at 30 minutes of reperfusion.

**Statistical Analysis**

Statistical analyses were performed using SAS (Version 1.1). Because protocols were performed sequentially, not simultaneously, Student’s \( t \) test was used to analyze differences in infarct size data between groups within each individual protocol. Linear regression analysis was performed to determine if there was a relation between area of necrosis (AN) and AR. Analysis of covariance was used to determine whether group was a significant covariate of this relation. All values are reported as mean ± SEM.

**Results**

**Protocol 1**

**Mortality and Exclusions**

A total of 52 experiments were performed in this arm of the study. Of these, 25 animals were excluded from analysis for the following reasons. Fifteen had anesthetic, surgical, or respirator problems. One died as a result of a possible Twice reaction. One animal was excluded because the RMBF during occlusion was > 0.4 mL min\(^{-1} \cdot \text{g}^{-1} \), and two animals were excluded because the AR was < 10% of the left ventricular mass. Five animals were excluded because of failure to reperfuse. Finally, one animal was excluded because a photographic problem made it impossible for us to adequately assess the AN. Thus, analysis was performed on 27 animals.

**Development of Necrosis**

Fourteen rabbits were successfully randomized to receive norepinephrine, and 13 received saline infusion. There were no significant differences in left ventricular weight or AR between the two groups. However, mean infarct size was reduced in norepinephrine-treated rabbits. The average AN was 0.50 ± 0.1 g in the controls and 0.27 ± 0.08 g in the norepinephrine-treated group (\( P = .08 \)). Similarly, the AN divided by the AR (AN/AR) was much smaller in the treated (0.17 ± 0.04) than in the control group (0.31 ± 0.04, \( P < .02 \); Fig 1). This suggests that a brief infusion of norepinephrine before a coronary artery occlusion can reduce infarct size in this model.

**RMBF**

RMBF was measured during infusion of drug, during occlusion, and 30 minutes after reperfusion. Blood flow...
rose significantly during infusion of norepinephrine compared with during saline infusion (Table 1). During occlusion, the groups were equally ischemic, and during reperfusion, RMBF was similar in the treated and control groups.

**Hemodynamics**

Norepinephrine infusion caused a marked but transient rise in blood pressure (Fig 2), which returned to baseline by the time of occlusion. The heart rate was not different at the time of drug infusion (Fig 3). The remainder of the blood pressure and heart rate measurements did not differ between groups.

**Protocol 2**

**Mortality and Exclusions**

Eighteen animals were studied in this group. Three died as a result of hypotension during occlusion; 1 had a surgical mishap before randomization; and 1 died as a result of ventricular fibrillation at the time of reperfusion. Thus, 13 animals were used in the analysis.

**Development of Necrosis**

Seven animals were randomized to receive tyramine, and six received saline. The left ventricular weight and

**TABLE 1. Regional Myocardial Blood Flow for Norepinephrine Protocol**

<table>
<thead>
<tr>
<th>Time</th>
<th>Area</th>
<th>Norepinephrine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion</td>
<td>AR</td>
<td>3.65±0.33</td>
<td>2.05±0.19*</td>
</tr>
<tr>
<td></td>
<td>Non-AR</td>
<td>4.02±0.32</td>
<td>2.23±0.21*</td>
</tr>
<tr>
<td>Occlusion</td>
<td>AR</td>
<td>0.03±0.02</td>
<td>0.04±0.02</td>
</tr>
<tr>
<td></td>
<td>Non-AR</td>
<td>1.49±0.14</td>
<td>1.33±0.06</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>AR</td>
<td>1.35±0.10</td>
<td>1.29±0.15</td>
</tr>
<tr>
<td></td>
<td>Non-AR</td>
<td>1.10±0.10</td>
<td>1.17±0.10</td>
</tr>
</tbody>
</table>

AR indicates zone of ischemia during occlusion; non-AR, zone of normal perfusion during occlusion.

Note that drug infusion caused a marked rise in blood flow in the treated animals and that both treated and control animals were subjected to a similar degree of ischemia. *P<.001, control vs norepinephrine.

AR were similar in both groups. However, the average AN was 0.24±0.05 g in the tyramine-treated rabbits and 0.58±0.17 g in the controls. When the AN was expressed as a percent of the AR, infarct size was significantly reduced in the tyramine-treated group compared with the control group (0.16±0.04 versus 0.41±0.07, P<.01) (Fig 4).

**RMBF**

During occlusion and during reperfusion, RMBF was similar in the groups (Table 2). Blood flow was also measured immediately after tyramine injection in one animal, and there was a marked rise in flow to 6.07 mL·min⁻¹·g⁻¹. We measured blood flow at baseline and after tyramine injection in two additional nonocluded rabbits and observed an average increase in RMBF from 2.6 mL·min⁻¹·g⁻¹ at baseline to 8.3 mL·min⁻¹·g⁻¹ immediately after the tyramine injection. This pronounced increase in RMBF may have been due to coronary artery dilation caused by β-adrenergic-stimulating effects, since the release of catecholamines by tyramine is not specific for α sympathomimetic stimulation.

**Hemodynamics**

Tyramine injection caused a marked transient rise in heart rate and blood pressure (Figs 2 and 3). This
response was short-lived, and values had essentially returned to baseline by the onset of coronary occlusion. Measurements performed at baseline, during occlusion, and during reperfusion were similar in the groups.

Protocol 3

Mortality and Exclusions

Sixteen animals were studied in this arm. Four rabbits (all in the preconditioned group) died as a result of ventricular fibrillation before completion of the protocol—three during preconditioning occlusions, and one during the 30-minute occlusion. Thus, 12 hearts—6 with a-blockade plus norepinephrine and 6 preconditioned—were used in this analysis.

Development of Necrosis

Left ventricular weight and AR were not statistically different between groups. As expected, ischemic preconditioning resulted in a small extent of necrosis (0.24±0.02 g, or 0.22±0.03 of the risk zone), comparable to that observed in both the norepinephrine- (0.17±0.044) and tyramine- (0.16±0.044) treated groups (Table 3). In contrast, pretreatment with a-adrenergic blocker negated the protective effect of norepinephrine. Infarct size (0.61±0.13 g) as a fraction of the risk zone was 0.42±0.06 in this group (P=.015 versus the preconditioned group) and was similar to control values in protocols 1 and 2. This suggests that infarct size reduction resulting from preischemic norepinephrine treatment is due to an a-adrenergic mechanism.

**Table 2. Regional Myocardial Blood Flow for Tyramine Protocol**

<table>
<thead>
<tr>
<th>Time</th>
<th>Area</th>
<th>Tyramine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusion</td>
<td>AR</td>
<td>0.02±0.01</td>
<td>0.09±0.04</td>
</tr>
<tr>
<td></td>
<td>Non-AR</td>
<td>1.54±0.13</td>
<td>1.75±0.20</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>AR</td>
<td>1.54±0.29</td>
<td>2.26±0.53</td>
</tr>
<tr>
<td></td>
<td>Non-AR</td>
<td>1.63±0.35</td>
<td>1.75±0.35</td>
</tr>
</tbody>
</table>

*AR indicates zone of ischemia during occlusion; non-AR, zone of normal perfusion during occlusion.*

**Table 3. Infarct Size Data for Protocol 3**

<table>
<thead>
<tr>
<th></th>
<th>Prazosin Plus Norepinephrine</th>
<th>Ischemic Preconditioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR/LV</td>
<td>0.33±0.03</td>
<td>0.26±0.03</td>
</tr>
<tr>
<td>AN/LV</td>
<td>0.14±0.03</td>
<td>0.05±0.00*</td>
</tr>
<tr>
<td>AN/AR</td>
<td>0.42±0.06</td>
<td>0.22±0.03*</td>
</tr>
</tbody>
</table>

AR/LV indicates area of risk as a fraction of left ventricle; AN/LV, area of necrosis as a fraction of left ventricle; and AN/AR, area of necrosis as a fraction of risk region. *P<.03.

**RMBF**

RMBF was measured during infusion of norepinephrine in the hearts treated with a-adrenergic blocker (Table 4). In contrast with rabbits receiving norepinephrine alone, in which myocardial blood flow rose significantly during infusion of norepinephrine, pretreatment with prazosin prevented this increase. For example, in the nonischemic region, myocardial blood flow was 2.11±0.38 mL·min⁻¹·g⁻¹ in the group receiving a-adrenergic blocker plus norepinephrine compared with 4.02±0.32 in the group given norepinephrine alone. Both groups were severely ischemic during the coronary occlusion, and there were no significant differences between groups at reperfusion.

**Hemodynamics**

Preceded by a-blockade with prazosin, norepinephrine administration did not increase systemic pressure (Figs 2 and 3). Mean arterial pressure was 83±6 mm Hg at baseline and 76±5 mm Hg at the end of the norepinephrine infusion. Heart rate averaged 160±8 beats per minute at baseline and 172±11 beats per minute at the end of the norepinephrine infusion.

**Discussion**

Our study shows that transiently exposing the myocardium to norepinephrine or tyramine before a prolonged coronary artery occlusion causes a reduction in infarct size compared with controls. For any amount of risk zone, there was less necrosis in animals transiently exposed to either exogenous norepinephrine or tyramine (Fig 5). When the a-adrenergic effects of

**Table 4. Regional Myocardial Blood Flow for Prazosin Plus Norepinephrine and Ischemic Preconditioning Protocol**

<table>
<thead>
<tr>
<th>Time</th>
<th>Area</th>
<th>Prazosin Plus Norepinephrine</th>
<th>Ischemic Preconditioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion</td>
<td>AR</td>
<td>2.10±0.47</td>
<td>2.81±0.48</td>
</tr>
<tr>
<td></td>
<td>Non-AR</td>
<td>2.11±0.38</td>
<td>2.21±0.19</td>
</tr>
<tr>
<td>Occlusion</td>
<td>AR</td>
<td>0.02±0.00</td>
<td>0.13±0.06</td>
</tr>
<tr>
<td></td>
<td>Non-AR</td>
<td>1.99±0.22</td>
<td>1.97±0.35</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>AR</td>
<td>1.77±0.40</td>
<td>2.56±0.52</td>
</tr>
<tr>
<td></td>
<td>Non-AR</td>
<td>1.98±0.44</td>
<td>1.82±0.39</td>
</tr>
</tbody>
</table>

AR indicates zone of ischemia during occlusion; non-AR, zone of normal perfusion during occlusion. There were no significant differences between groups.
norepinephrine were blocked by pretreatment with the α-adrenergic-blocking agent prazosin, the protective effect of norepinephrine on infarct size was lost.

In animals pretreated with prazosin, the infusion of norepinephrine failed to create a pressor effect, but in animals treated with either norepinephrine alone or tyramine, blood pressure rose transiently; in addition to a higher rise in blood pressure, heart rate increased in the tyramine-treated group. It is possible that this rise in heart rate and blood pressure, and consequently in myocardial oxygen demand, caused a stress to the heart sufficient to mimic the preconditioning phenomenon. It is unlikely that either of these agents produced severe ischemia during administration. RMBF increased during infusion, presumably as a response to increased oxygen demand and greater driving pressure in the coronary artery. However, we cannot rule out the possibility that the increase in oxygen demand outweighed the increase in oxygen supply. These results suggest that the stress of transient exposure to catecholamines makes the heart more resistant to the subsequent stress of a coronary occlusion. Thus, maneuvers other than transient coronary artery occlusion may be capable of causing a preconditioning-like phenomenon.

In the present study, we reconfirmed the effectiveness of ischemic preconditioning in reducing myocardial injury as was shown in a previous study in rabbits from our laboratory.12 Preconditioning has been observed in several models, including the dog,13 pig,14 rabbit,12,14 rat,18 and probably humans. Deutsch et al19 found less angina, less ST-segment shift, and lower mean pulmonary artery pressure during the second inflation in 12 patients undergoing elective percutaneous transluminal coronary angioplasty (PTCA) of the left anterior descending coronary artery. They also noted lower coronary vein blood flow and lactate production during the second inflation and concluded from this that ischemic preconditioning causes the myocardium to adapt to ischemia, perhaps by downregulating its metabolic activity. A similar study by Cribier et al20 with elective PTCA of the left anterior descending coronary artery confirmed these results.

Although the exact mechanism of preconditioning is not known, theories include activation of the adenosine A₁ receptor,23 glycojen depletion,4 opening of ATP-dependent potassium channels,7,8 preservation of high-energy phosphate stores,6 limitation of catabolite accumulation during ischemia leading to reduced osmolar load or acidosis, and downregulation of metabolic demand.5

Myocardial ischemia has been shown to induce the release of endogenous catecholamines. Schomig et al21 noted that there was release of norepinephrine after 10 minutes of ischemia in isolated, perfused rat hearts. It is possible during brief periods of preconditioning ischemia that catecholamine release may occur and that this might contribute to the beneficial effects of preconditioning.

One potential mechanism by which stimulation of α-adrenoreceptors could reduce ischemic injury in a manner similar to ischemic preconditioning is the release of adenosine. Ischemia caused an increase in adenosine release,22 but this response was markedly attenuated in the presence of the α₁-adrenoceptor antagonists phenolamine and prazosin. In another series of experiments, Kitakaze et al23 found that treatment with the α₁-adrenoceptor agonists methoxamine and norepinephrine improved contractile dysfunction after 15 minutes of ischemia and increased release of adenosine both when given alone and in the presence of α₁- and β-blockers. They also noted that administration of 8-phenylthephyloline, an adenosine antagonist, abolished the beneficial effects of α₁-adrenoceptor stimulation on stunning. They concluded from these experiments that α₁-adrenoceptor activation can reduce stunning and that this is enabled, at least in part, by the action of adenosine. However, the investigators in these studies were evaluating the effects of α₁-adrenoceptor activation on stunning, using brief periods of occlusion, and this may not translate to a beneficial effect with more prolonged ischemia. In another study,24 however, transient ischemia was shown to increase the release of norepinephrine, whereas reserpine (which depletes catecholamines) appeared to block the beneficial effects of preconditioning when administered before the period of transient ischemia.

An adrenergic mechanism may play a role in the improvement of myocardial dysfunction that is observed in isolated rat hearts after ischemic preconditioning. In a study by Banerjee and coworkers,25 adrenergic blockade by reserpine pretreatment blocked the beneficial effects of preconditioning on recovery of left ventricular function after 20 minutes of global ischemia, and pretreatment with exogenous norepinephrine or phenylephrine mimicked the effects of transient preconditioning. These investigators concluded that the beneficial effects of ischemic preconditioning are mediated by release of neurotransmitters and stimulation of α₁-adrenergic receptors.

We have recently shown in our laboratory that phenylephrine, an adrenergic agonist with primarily α₁ effects at therapeutic doses, can reduce myocardial necrosis if given before coronary occlusion in rabbits.26 This suggests that activation of α₁ receptors by norepinephrine produces the cardioprotection rather than α₁ or β receptors.

Thornton et al27 recently showed that infusion of tyramine, an agent that causes release of endogenous catecholamines, reduces infarct size when given shortly before coronary artery occlusion in rabbits. This protective effect was eliminated by α₁-receptor blockade.
using BE 2254 but not by β-receptor blockade. The authors concluded that α-adrenergic activation reduces ischemic damage; however, it is not the mechanism of ischemic preconditioning. Our results would agree with the concept that it is the α₁ action of catecholamines that may be important for the preconditioning-like effect associated with brief exposure of the heart to catecholamines. In addition, we have shown that administration of exogenous norepinephrine can either induce or mimic ischemic preconditioning.

In conclusion, we observed that either exogenous norepinephrine or tyramine (which causes release of catecholamines) reduced myocardial infarct size. One potential explanation for this is that the transient increase in oxygen demand was greater than the increase in oxygen supply resulting in relative ischemia that caused preconditioning. Another potential mechanism is that the catecholamine surge stimulated adenosine release and adenosine-A₁ receptors were then stimulated with a subsequent preconditioning-mimetic effect. Finally, catecholamine depletion within the ischemic myocardium may have resulted in the protective effect.

When the α-adrenergic effects of norepinephrine were blocked by prazosin treatment, no beneficial reduction in infarct size was observed. Although the exact mechanism remains to be determined, it appears that when administered before a prolonged coronary occlusion, either α-adrenoceptor stimulation with exogenous norepinephrine or release of endogenous catecholamines with tyramine can confer a protective effect. Thus, forms of stimuli other than coronary artery occlusion are capable of producing a preconditioning-like effect.

References

Alpha-adrenoceptor stimulation with exogenous norepinephrine or release of endogenous catecholamines mimics ischemic preconditioning.

Z Bankwala, S L Hale and R A Kloner

Circulation. 1994;90:1023-1028
doi: 10.1161/01.CIR.90.2.1023

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