Effect of Preconditioning Ischemia on Reperfusion Arrhythmias After Coronary Artery Occlusion and Reperfusion in the Rat

James M. Hagar, Sharon L. Hale, and Robert A. Kloner

Severe arrhythmias occur predictably on reperfusion after 5 minutes of coronary occlusion in the rat. There is little data available on whether ischemic preconditioning (PC) of hearts can reduce the incidence of such arrhythmias. The effect of PC (three cycles of 2 minutes of coronary occlusion and 5 minutes of reperfusion) on development of arrhythmias after a subsequent 5-minute coronary artery occlusion and reperfusion was studied. Rats (n=16 each group) underwent 5-minute occlusion and reperfusion alone or preceded by PC; arrhythmias were monitored during ischemia and for 10 minutes of reperfusion, and biopsies were taken for creatine phosphate and adenosine triphosphate in ischemic and nonischemic zones of the left ventricle. PC reduced the incidence of ventricular tachycardia (VT) during occlusion (81% control versus 13% PC, p<0.001). On subsequent reperfusion, ventricular fibrillation (VF) developed in zero PC animals versus 13 (81%) of controls (p<0.001) and irreversible VF in zero of PC versus seven (44%) of controls (p=0.007). VT occurred in four (25%) of PC versus all (100%) of controls (p<0.001). PC reduced mean duration of VT plus VF from 320±54 to 5±1 seconds (p<0.001) and delayed arrhythmia onset from 8±2 to 85±35 seconds after reperfusion. There was no difference in creatine phosphate levels in the ischemic zone at the end of reperfusion in PC animals compared with controls without irreversible VF (16.2±4.1 versus 15.5±3.9 nmol/mg protein, p=NS). There was no relation between creatine phosphate levels and occurrence of VT or VF (14.0±5.6 nmol/mg protein VF versus 16.7±3.3 no VF; 16.4±3.5 VT versus 15.4±4.5 no VT; p=NS). Adenosine triphosphate levels in the ischemic zone were unaffected by PC (15.5±2.1 versus 14.5±1.9 nmol/mg protein, PC versus control). When a coronary occlusion of 5 minutes duration is preceded by PC, the usually severe reperfusion arrhythmias are markedly attenuated. This protective effect of PC is not likely to be related to alterations in high-energy phosphate compounds. (Circulation Research 1991;68:61–68)

Life-threatening ventricular arrhythmias, ventricular tachycardia (VT) and ventricular fibrillation (VF), are known to occur on restoration of coronary flow after a period of myocardial ischemia. This is believed to be the mechanism underlying many cases of sudden cardiac death in humans. These reperfusion arrhythmias can be predictably produced in experimental animals, and their occurrence is time dependent. In the rat, for example, a 5–7-minute coronary artery occlusion followed by reperfusion produces VT in virtually all cases and VF in 70–80%; both shorter and longer occlusions produce less severe arrhythmias. Such arrhythmias seem to be distinct from ischemia-related arrhythmias in their pathogenesis. Many factors have been implicated in the genesis of reperfusion arrhythmias, including oxygen-derived free radicals, catecholamines, and other ischemia- or reperfusion-derived metabolites.

An episode or episodes of brief ischemia alter the myocardium’s response to a subsequent coronary occlusion, a phenomenon termed preconditioning. Preconditioning has been shown to delay the onset of necrosis and preserve levels of high-energy phosphate intermediates compared with a continuous occlusion of similar duration, with rebound of creatine phosphate levels on reperfusion. Multiple brief occlusions can, however, lead to necrosis in some cases. The preconditioning phenomenon has potential clinical relevance in light of evidence that human myocardial infarction often is preceded by progressively increasing numbers of such brief ischemic

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Supported in part by National Institutes of Health Specialized Center of Research grant HL-26215.

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Received December 30, 1989; accepted August 15, 1990.
episodes, as documented on ambulatory electrocardiographic monitoring.8

The effect of such patterns of ischemia on reperfusion arrhythmias has not been studied extensively. One study showed that reperfusion arrhythmias in the rat after 5 minutes of ischemia decreased in proportion to the duration of preconditioning ischemia, and that this protective effect of preconditioning was attenuated as the period between the two ischemic periods was increased.9 This study used a single preconditioning occlusion and defibrillated animals having VF during preconditioning. Because of the design of this study, it cannot be differentiated whether preconditioning prevents arrhythmias altogether or simply causes them to occur during the preconditioning period instead of later. Therefore, we examined the effects of multiple episodes of brief preconditioning ischemia on the development of reperfusion arrhythmias in the rat to document whether preceding ischemia attenuates reperfusion arrhythmias and whether alterations in high-energy phosphate levels are implicated in this process.

Materials and Methods

Female Sprague-Dawley rats (n=35) were anesthetized with pentobarbital (50 mg/kg i.p.) and remained fully anesthetized for the duration of the protocol (approximately 45 minutes). The rats then were intubated and ventilated with room air. The chest was opened by left thoracotomy through the fourth intercostal space. After pericardiotomy, the left main coronary artery was isolated near its origin beneath the left atrial appendage by an intramural stitch with 6-0 silk. Coronary artery occlusions were performed by passing a short length of tubing over the ends of the suture and clamping it firmly against the heart. Reperfusion was achieved by removing the clamp.

In protocol 1, depicted in Figure 1, rats were randomized to receive either a period of preconditioning followed by a 5-minute period of ischemia and 10 minutes of reperfusion, or a control period of comparable length without preconditioning followed by the same 5 minutes of ischemia and 10 minutes of reperfusion. Preconditioning consisted of three occlusions of 2-minute duration, each followed by a 5-minute period of reperfusion. Two leads of the surface electrocardiogram (ECG) were monitored for heart rate and rhythm disturbances at baseline and throughout the occlusion and reperfusion periods. Monoastral blue pigment was injected at the termination of the protocol to verify coronary artery reperfusion. Two experiments were replaced because of lack of ischemic ECG changes (QRS and ST) during occlusion, and one because of incomplete reperfusion; 16 experiments remained in each of the two treatment groups. Typical ECG tracings from experiments with and without preconditioning are shown in Figure 2.

An in vivo biopsy for biochemical analysis was obtained at the end of the 10-minute reperfusion period. Three-millimeter core biopsies from the ischemic zone of the anterior wall10 and from the nonischemic posterior free wall or septum of the left ventricle were flash frozen in liquid nitrogen and stored at −80°C until analysis. Samples were homogenized in 0.4N perchloric acid, neutralized with phosphate buffer, and centrifuged. The pellet was resuspended in 1N NaOH, and protein was measured by the method of Lowry et al.11 An aliquot of the supernatant was used for enzymatic measurement of ATP and creatine phosphate (CP) by the method of Lowry and Passaneau.12 Biopsies were obtained successfully in 14 control and 10 treated rats; all values are expressed in units of nanomoles per milligram of cardiac protein.

The occurrence and duration of ventricular ectopic beats, VT, VF, irreversible VF, or atrioventricular block during the periods of ischemia and reperfusion were compared between groups. VT was defined as four or more consecutive ectopic beats, and criteria for VF conforming to commonly used guidelines.13 Values are expressed as mean±SEM. Discrete variables were analyzed using χ2 tests. T tests were used for normally distributed variables (heart rate, CP,
and ATP), and Mann-Whitney U tests for nonnormal variables (arrhythmia duration).

In protocol 2, using identical methods, rats \(n=6\) underwent a continuous 11-minute coronary occlusion followed by 10 minutes of reperfusion. This was done to confirm that any reduction in arrhythmia incidence in the first protocol was not simply a result of the total duration (11 minutes) of preconditioning and ischemic episodes.

**Results**

**Protocol 1**

The incidence of reperfusion arrhythmias during the preconditioning period was low, occurring with the approximate frequency that would have been expected from a single 2-minute occlusion followed by reperfusion.\(^1\) VF occurred briefly in one case, runs of VT in three (19%), isolated ventricular ectopics alone in one, and no arrhythmias in 75%. During the subsequent 5-minute occlusion period, VT occurred in 13 (81%) of nonpreconditioned and two (13%) of preconditioned experiments \(p<0.001\). Any ventricular ectopic activity developed in 15 (94%) non preconditioned versus seven (44%) preconditioned animals \(p=0.006\).

During the final 10-minute reperfusion period, arrhythmias were markedly decreased in the preconditioned group compared with controls, as shown in Figure 3 and Table 1. VF occurred in 13 of 16 (81%) nonpreconditioned animals and was irreversible in seven (44%). In contrast, no VF occurred in preconditioned animals \(p<0.001\). VT incidence, which was 100% in nonpreconditioned animals, was 25% in the preconditioned group, and its mean duration was less: 98.8±18.0 seconds in nonpreconditioned versus 4.9±3.1 seconds in the preconditioned rats \(p<0.001\). Total duration of arrhythmias (VT plus VF) was markedly less in the preconditioned group: 4.9±1.1 versus 320.4±54.2 seconds in the nonpreconditioned group \(p<0.001\). The time to onset of the first VT after reperfusion was significantly delayed (from 7.7±2.1 seconds after reperfusion in the

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**Figure 2.** Panel A: Tracing from nonpreconditioned experiment. Onset of ventricular fibrillation 8 seconds after reperfusion. Panel B: Tracing from preconditioned experiment. No arrhythmias occur after reperfusion; ischemic electrocardiographic changes resolve.

**Figure 3.** Incidence of reperfusion arrhythmias (% incidence±SEM); ventricular fibrillation (VF), irreversible ventricular fibrillation (IR-REV VF), ventricular tachycardia (VT), ventricular ectopics (VEs), and atrioventricular block (AVB): preconditioned vs. nonpreconditioned (control). *\(p<0.001\); **\(p<0.01\).
Arrhythmia duration is total seconds of each arrhythmia; onset is time of onset of first ventricular tachycardia (VT) or ventricular fibrillation (VF) following reperfusion; average duration is number of VT episodes per total duration of VT; number of VT episodes is total per experiment.

TABLE 1. Duration of Arrhythmias During Reperfusion

<table>
<thead>
<tr>
<th></th>
<th>Nonpreconditioned</th>
<th>SEM</th>
<th>Preconditioned</th>
<th>SEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>410.6</td>
<td>7.9</td>
<td>387.5</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td>Duration VT (sec)</td>
<td>98.8</td>
<td>18.0</td>
<td>4.9</td>
<td>3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration VF (sec)</td>
<td>222.2</td>
<td>63.1</td>
<td>0.0</td>
<td>0.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration VT+VF (sec)</td>
<td>320.4</td>
<td>54.2</td>
<td>4.9</td>
<td>1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arrhythmia onset (sec)</td>
<td>7.7</td>
<td>2.1</td>
<td>85.3</td>
<td>35.1</td>
<td></td>
</tr>
<tr>
<td>Average duration VT episodes (sec)</td>
<td>6.0</td>
<td>0.9</td>
<td>0.4</td>
<td>0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. VT episodes</td>
<td>21.7</td>
<td>4.3</td>
<td>2.3</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TABLE 2. High-energy Phosphates

<table>
<thead>
<tr>
<th></th>
<th>Nonpreconditioned (mean±SEM)</th>
<th>Preconditioned (mean±SEM)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP (no irreversible VF)</td>
<td>15.5 3.9</td>
<td>16.2 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>CP (all experiments)</td>
<td>11.1 2.7</td>
<td>16.2 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>ATP</td>
<td>14.5 1.9</td>
<td>15.5 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Nonischemic zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td>9.1 1.8</td>
<td>9.9 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>ATP</td>
<td>15.9 1.8</td>
<td>17.9 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic/nonischemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td>1.47 0.3</td>
<td>2.59 0.7</td>
<td>0.12</td>
</tr>
<tr>
<td>ATP</td>
<td>0.92 0.1</td>
<td>0.92 0.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

ATP and creatine phosphate (CP) expressed as nmol/mg protein. CP values in ischemic zone given for all experiments and for experiments without irreversible ventricular fibrillation (VF); all other values are for all experiments.
14.0±5.6 nmol/mg protein in animals having VF versus 16.7±3.3 nmol/mg protein in those without VF, and 16.4±3.5 nmol/mg protein in animals having VT versus 15.4±4.5 nmol/mg protein in those without VT (p>0.6 for each).

Protocol 2

In the group that underwent 11-minute occlusion followed by reperfusion, reperfusion VT developed in all, VF in 50%, and atrioventricular block in one (17%). The mean duration of VT plus VF was 36.2±11 seconds.

Discussion

This study demonstrates that preconditioning markedly reduces arrhythmias occurring at reperfusion, completely eliminates VF, and also reduces arrhythmias associated with ischemia before reperfusion. The degree of reduction of arrhythmia by preconditioning in this model is quite striking but has been the subject of little investigation.

In the study of Shiki and Hearse,9 rats underwent 5 minutes of ischemia followed by reperfusion, were defibrillated if necessary, then had a second 5-minute occlusion at intervals varying from 10 minutes to 3 days later. The duration of the preconditioning occlusion was then varied from 0.5 to 5 minutes. It was shown that reperfusion arrhythmias after the second occlusion—reperfusion decreased in proportion to the duration of preconditioning ischemia; those animals with brief preconditioning, which had few arrhythmias after the first occlusion, had more arrhythmias after the second occlusion—reperfusion and vice versa, suggesting a “quota” of reperfusion arrhythmias that is distributed variably between the two periods. It also was demonstrated that this protective effect of preconditioning began to abate 30 minutes after reperfusion but did not completely resolve until 3 days. Although this data defines the phenomenon and its temporal features, the study used a single preconditioning occlusion. It cannot be differentiated from their study whether preconditioning prevents arrhythmias altogether or simply causes them to occur (be “used up”) during the preconditioning period instead of later, as the authors suggest. In addition, animals were defibrillated during preconditioning, with unknown metabolic and hemodynamic effects. Our protocol was designed to further elucidate the preconditioning phenomenon and to avoid some of the difficulties in interpreting this data. A series of 2-minute occlusions was chosen as a preconditioning regimen. Ischemic periods of this duration will produce few arrhythmias by themselves and are very unlikely to produce necrosis even after multiple repetitions. The regimen is analogous to one shown to delay the onset of cell necrosis in a dog model.5 That the decrease in arrhythmias is not due to a cumulative effect of the multiple ischemic periods is evident from a separate experiment in which 11 minutes of continuous ischemia followed by reperfusion is associated with the high incidence of arrhythmias that would be expected based on other studies.1

It is clear from the data that preconditioning in this manner does in fact prevent arrhythmias, and its action is not due to a simple “using up” of a quota of arrhythmias that might occur during a given time period.

The effects of preconditioning on high-energy phosphates, myocardial function, ultrastructure, and infarct size have been fairly well characterized. Lange and coworkers14,15 first described that progressive functional deterioration and loss of high-energy phosphates did not occur with repeated occlusions. A series of experiments by Reimer et al16 and Basuk et al17 using a dog model has shown that repeated brief occlusions of 5–10 minutes produce no cumulative effect; depletion of high-energy phosphates, necrosis,16 and ultrastructural and cell volume changes17 are not greater than after a single occlusion and are much less than after a continuous occlusion of identical total duration. Furthermore, preconditioning delays the onset of necrosis, limiting infarct size resulting from a subsequent 40-minute, but not 3-hour, occlusion.5 The rate of ATP depletion during subsequent ischemia is decreased because of decreased ATP utilization, and accumulation of glycolytic intermediates is reduced.18 Although cumulative deterioration of wall motion does not occur with three successive occlusions,15 others have found that previous brief ischemia leads to an exaggerated decrease in wall motion with a subsequent occlusion, probably a subtle form of stunning.19 That myocardial stunning is not responsible for preservation of ATP and limitation of infarct size with preconditioning is suggested by an experiment in which 120 minutes of reperfusion after preconditioning eliminated the preconditioning effect on infarct size, although stunning persisted.20 The preconditioning effect now has been demonstrated using a variety of preconditioning regimens and in several species,21,22 including the rat.23

The mechanism by which preconditioning acts on cellular injury and arrhythmogenesis is as yet unknown. Washout or diminished production of hydrogen ion,24 lactate,18,25 or other glycolytic products has been proposed as a mechanism of the preconditioning effect. Regional autonomic denervation, known to occur after ischemia, is prevented by preconditioning.26 Oxygen free radical formation by xanthine oxidase could be decreased if preconditioning allowed washout of adenosine and hypoxanthine. Both reperfusion arrhythmias and the preconditioning effect have been demonstrated in xanthine oxidase-deficient species, however, making this mechanism unlikely.22 Preconditioning with low-flow ischemia followed by total occlusion reduces ischemia-related arrhythmias by hastening the rise of extracellular potassium and onset of activation block.27 It is also possible that preconditioning stimulates production of endogenous substances, such as prostacyclin, that are antiarrhythmic.28 None of these mechanisms has
yet been directly linked to preconditioning of reperfusion arrhythmias.

Levels of CP, which fall to very low values during ischemia then quickly return to normal early in reperfusion, rise progressively to supranormal levels with successive cycles of ischemia and reperfusion.\textsuperscript{5,29–32} Impaired use of ATP brought on by preconditioning might act to preserve energy stores during later ischemia\textsuperscript{18}; overshoot of CP levels during repetitive occlusions and during reperfusion could be either a manifestation of this abnormal use\textsuperscript{33} or the mechanism by which the preconditioning effect is mediated. This last mechanism is particularly attractive, because CP infusion has been shown to markedly attenuate reperfusion arrhythmias in the isolated perfused rat heart\textsuperscript{34} and after cardiopulmonary bypass.\textsuperscript{35} However, our findings that there is no correlation between levels of CP and arrhythmias, nor in ATP between preconditioned and nonpreconditioned animals, would tend to argue that CP overshoot is not the means by which preconditioning mediates its protective effect.

Preconditioning in this study reduced both ischemia-related and reperfusion-related arrhythmias, even though reperfusion arrhythmias appear to have a pathogenesis distinct from arrhythmias occurring during ischemia or after completed myocardial infarction.\textsuperscript{2} Heterogeneity of refractoriness between ischemic and nonischemic tissues is postulated to establish an electrophysiological substrate capable of supporting sustained arrhythmias, and uneven recovery after reperfusion may provoke arrhythmias by exacerbating this inhomogeneity.\textsuperscript{36} Cellular events at the moment of reperfusion, involving shifts of calcium, potassium ions, and oxygen,\textsuperscript{1} are believed to act as a trigger to initiate arrhythmias, possibly by enhancing automaticity or perhaps by producing afterpotentials. These reperfusion arrhythmias are not suppressed by most antiarrhythmic agents\textsuperscript{37} but are affected by interventions aimed at metabolic intermediates such as prostanoids,\textsuperscript{28} oxygen-derived free radicals,\textsuperscript{38} and catecholamines.\textsuperscript{4} That both are reduced by preconditioning indicates that they also share common pathogenic features. 

Limitations

Some inherent limitations in the analysis of high-energy phosphates in this model must be recognized. Unlike the canine model, biopsies cannot be taken without the death of the animal, and even if possible, would cause arrhythmias, interfering with the study end point. Knowing what effect preconditioning has on CP and ATP in this model, which could be obtained by earlier sampling, does not bear on the issue of whether those changes have any relation to subsequent arrhythmias. Thus, sampling at the end of the reperfusion period is the only strategy for obtaining biopsies that can be used to test the hypothesis in this model. Given the rapid recovery of CP at reperfusion, levels of CP measured after 10 minutes of reperfusion are likely to be similar to (or higher than) levels at the end of preconditioning, but this cannot be verified directly. Levels of CP would be expected to be higher in preconditioned than in nonpreconditioned animals, and in fact a nonsignificant trend in this direction was seen. Although significant overshoot was not demonstrated in this study, it is evident that preservation of CP did not predict the occurrence of serious arrhythmias.

In experiments in which irreversible VF occurred, the heart was exposed to several minutes of global ischemia before samples could be taken, and CP values in both ischemic and nonischemic samples were lower as a result in these animals. These values do not, therefore, contribute meaningfully to the analysis, and we cannot rule out the possibility that lower CP levels might be present in these animals before onset of irreversible VF.

Differences between species cannot be ruled out in considering studies of the preconditioning phenomenon. The ability of preconditioning to delay or reduce infarction now has been demonstrated in multiple species, including the rat, and with a variety of preconditioning regimens.\textsuperscript{5,21–23} However, whether preconditioning reduces reperfusion arrhythmias in species other than the rat has yet to be determined. Preconditioning studies in the dog have not specifically analyzed reperfusion arrhythmias. This is because protocols that maximize reperfusion arrhythmias do not produce significant infarction or ultrastructural changes, and vice versa. Although the effect of preconditioning on cellular metabolism and its effect on arrhythmias may be two aspects of the same phenomenon, the two effects have not been precisely correlated in the same model. We have not determined that protection from the metabolic consequences of ischemia or reduction of infarct size occur with the exact preconditioning regimen used in our study.

The data in this study were obtained with a single 5-minute duration of ischemia. It is known that the incidence of reperfusion arrhythmias is highly dependent on the duration of preceding ischemia and follows a bell-shaped curve; that is, durations of ischemia shorter or longer than 5 minutes in this model produce fewer reperfusion arrhythmias.\textsuperscript{1} The effect of preconditioning on reperfusion arrhythmias after other durations of ischemia has not been determined. It is not known whether preconditioning reduces the height of the bell curve (reducing reperfusion arrhythmias at all durations of ischemia) or shifts the curve to the right or left (causing reperfusion arrhythmias to occur maximally after a different duration of ischemia). This possibility awaits further study.

The optimum preconditioning regimen is not known. Li et al\textsuperscript{39,40} found that one 5-minute occlusion in the dog was as effective as a series of six or 12 preconditioning occlusions. On the other hand, Shiki and Hearse\textsuperscript{4} found that a single 2-minute occlusion in the rat would not be expected to produce as great a preconditioning effect as a longer occlusion.
Implications

Reperfusion arrhythmias occur after a critical duration of ischemia when there is a large ischemic zone with poor collateral blood flow. They are less frequent if reperfusion is gradual or if coronary flow during reperfusion is restricted by a coronary stenosis. We have shown that the presence of antecedent periods of ischemia (preconditioning) is another such modifying factor. The mechanism by which the antiarrhythmic effect of preconditioning is mediated remains to be elucidated.

Reperfusion arrhythmias are more difficult to study in humans compared with experimental animals. Differentiation of reperfusion arrhythmias from ischemia-related arrhythmias often is impossible. Such arrhythmias sometimes occur after coronary thrombolysis. They also are reported in variant angina, during discontinuation of cardiopulmonary bypass, and may underlie some cases of sudden arrhythmic death, associated pathologically with nonocclusive coronary thrombosis and contraction-band necrosis. The infrequency of human reperfusion arrhythmias could be partly explained by a preconditioning effect, because human infarction often is preceded by multiple brief periods of ischemia. However, the clinical consequences of repeated ischemia and reperfusion on human infarction and arrhythmias are still unknown.

Conclusion

When coronary occlusion is preceded by reperfusion with repeated, very brief coronary occlusions, the severe reperfusion arrhythmias that normally occur are dramatically reduced, and VF is completely prevented. Arrhythmias during ischemia also are reduced. Although these data apply to the 5-minute occlusion used in this study, they may not apply to occlusions of shorter or longer duration. The protective effect of preconditioning is unlikely to be related to alterations in levels of the high-energy phosphates ATP and CP. The phenomenon described may be relevant to human ischemia and reperfusion arrhythmias. The mechanism by which preconditioning acts to prevent reperfusion arrhythmias requires further investigation and could contribute to our understanding of these arrhythmias.

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Key Words: arrhythmia · myocardial reperfusion · ischemia · preconditioning · phosphocreatine
Effect of preconditioning ischemia on reperfusion arrhythmias after coronary artery occlusion and reperfusion in the rat.
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Circ Res. 1991;68:61-68
doi: 10.1161/01.RES.68.1.61

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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