Prostaglandin-Induced Preservation of the Ischemic Myocardium

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SUMMARY The effectiveness of prostaglandin (PG) E₁, E₂, and F₂α in altering responses to acute myocardial ischemia was studied in anesthetized, open-chest cats. Following coronary artery occlusion to induce myocardial ischemia (MI) or sham operation (sham MI), a PG (or its appropriate vehicle) was infused at 1 μg/kg per minute for the 5-hour experimental period. Arterial blood pressure dropped significantly during PG infusion, whereas heart rate decreased only slightly. A pressure-rate index was significantly reduced in ischemic cats infused with either PGE₁ or PGE₂. These two groups also failed to show large elevations in S-T segment which were usually observed in ischemic cats receiving PGF₂α or 0.9% NaCl. Arterial blood samples (i.e., at 5 hours) showed significantly increased plasma creatine phosphokinase (CPK) specific activities in MI cats receiving PGF₂α or NaCl, whereas PGE₁ and PGE₂ infusions prevented significant elevations in plasma CPK during ischemia. Myocardial tissue samples from ischemic cats receiving either PGF₂α or NaCl showed significantly reduced tissue CPK in ischemic myocardial tissue. However, PGE₁ or PGE₂ prevented decreases in myocardial CPK activity. Infusion of either E-type PG was further shown to prevent labilization of myocardial lysosomes in ischemic tissue, without significantly altering free amino-nitrogen concentrations in ischemic tissue. Thus, infusion of E-type prostaglandins significantly improved the hemodynamic status and moderated the leakage of enzymes from ischemic myocardial tissue in the cat. These prostaglandins may protect ischemic myocardial tissue by reducing cardiac oxygen demand and stabilizing cardiac lysosomal membranes.

PROSTAGLANDINS are naturally occurring substances with a wide variety of biological activities. Prostaglandins may influence blood flow locally in several organs by their direct vasoactive properties or influences on capillary permeability, as well as by their ability to moderate sympathetic neural activity. Prostaglandins are synthesized de novo from membrane phospholipids or fatty acids in response to a variety of stimuli including trauma, nerve stimulation, hypoxia, and ischemia.₁⁻⁴ Recently, several investigators have demonstrated enhanced cardiac prostaglandin synthesis in response to coronary artery occlusion,⁵⁻⁸ and this has generated further interest in the role of prostaglandins in the coronary circulation and in the pathogenesis of myocardial ischemia.

Nonsteroidal anti-inflammatory drugs such as aspirin and indomethacin inhibit prostaglandin synthesis⁹⁻¹⁰ and have provided a technique for studying the consequences of prevention of prostaglandin synthesis and release. However, inhibition of prostaglandin synthesis with aspirin, indomethacin, or sodium meclofenamate did not significantly alter the hemodynamic, electrocardiographic, or biochemical response to myocardial ischemia in the cat.¹¹ One interpretation of these findings is that prostaglandin production is not directly detrimental to the ischemic myocardium. Alternatively, the diverse actions of prostaglandins may modulate the pathological conse-
S-T segment elevations were observed after induction of myocardial ischemia, but the severity of the trauma induced by coronary artery occlusion may prevent endogenous prostaglandins from exerting any significant beneficial effect.

To investigate further the significance of prostaglandin release from the ischemic myocardium and the therapeutic potential of prostaglandins in preserving the ischemic myocardium, we have examined the influence of selected prostaglandins on key hemodynamic, electrocardiographic, and biochemical responses of the open-chest cat after acute coronary artery occlusion. We also studied some prostaglandin metabolites to determine whether the native prostaglandin is necessary for a protective effect in myocardial ischemia.

Methods

Cats of either sex weighing 2.5-3.5 kg were anesthetized with sodium pentobarbital (30 mg/kg) given intravenously. The left external jugular vein and right common carotid artery were cannulated with polyethylene catheters which were positioned for measurement of central venous and aortic blood pressures. Lead III of the electrocardiogram was continuously monitored for S-T segment elevation, and heart rate was continuously recorded by use of a cardiotachometer coupler connected to a Beckman model 411 oscillographic recorder. Following tracheotomy, a mid-sternal thoracotomy was performed and positive-pressure ventilation was instituted with a Harvard small-animal respirator. The heart was then exposed through a pericardial incision and a 3-0 silk ligature was tied around the left anterior descending (LAD) branch of the left coronary artery. After a 15- to 20-minute period of hemodynamic stabilization, control measurements were recorded, and an initial 5-ml arterial blood sample was drawn and placed in a cold, polyethylene centrifuge tube containing 80 U of sodium heparin (Upjohn, beef lung). Arterial blood samples were collected hourly throughout the 5-hour experimental protocol, and lost blood volume was replaced with 0.9% NaCl maintained at 37°C.

Cats were subjected either to 5 hours of myocardial ischemia (MI) by occlusion of the LAD coronary artery or to a sham operation (sham MI) which consisted of all the same surgical procedures except occlusion of the coronary artery. Cats were further assigned to groups receiving continuous intravenous infusions of different prostaglandins (1 µg/kg per minute) or appropriate vehicles (i.e., 0.9% NaCl or Tris-buffered saline). All infusions were made via the right femoral vein at a rate of 4.58 ml/hr beginning immediately after coronary occlusion or an equivalent time (i.e., after initial blood sampling) in sham-operated control cats.

S-T Segment Quantitation

Fast tracings were made every 20 minutes from standard lead III of the electrocardiogram. Five beats were used to determine an average S-T segment change. In most cases, S-T segment elevations were observed after induction of myocardial ischemia, but in a few cases S-T segment depressions were seen. Therefore, summed S-T segment elevations and depressions were made, treating all values as absolute numbers.

Myocardial Sampling

After the 5-hour observation period, each heart was rapidly excised and washed in ice-cold 0.9% NaCl. The free left ventricular wall of each ischemic heart was divided into normal and ischemic myocardium by inspection of the epicardial surface and distribution of cyanotic areas. Ischemic myocardial tissue displayed a discrete area of dark epicardial cyanosis with a corresponding pale endocardium with occasional subendocardial hemorrhagic regions. Transmural samples of severely ischemic anterior myocardium and normal posterior left ventricular myocardium were excised from each heart, blotted, and weighed. Tissue samples anatomically equivalent to ischemic (i.e., sham-ischemic) and normal samples were excised from hearts obtained from sham-operated controls. Tissue samples were then prepared for enzyme and protein determinations, according to the method of Kjekshus and Sobel.

Biochemical Determinations

Blood samples were centrifuged at 2400 g for 15 minutes at 4°C. Plasma supernatant fluids were then analyzed for creatine phosphokinase (CPK) activity by the method of Rosalki and total protein was determined by the biuret method. Plasma CPK-specific activity was expressed as international units (IU)/mg protein x 10⁶.

Approximately 0.2 g of myocardial tissue samples was minced, suspended in a solution of cold 0.25 m sucrose, containing 1 mM EDTA and 0.1 mM mercaptoethanol (1:10, wt/vol), and homogenized with a cold Potter-Elvehjem tissue grinder. Homogenates were centrifuged at 36,000 g for 30 minutes, and supernatant fluids were analyzed for CPK and protein. Myocardial CPK-specific activity was expressed as IU of CPK/mg protein.

Portions of the myocardial tissue samples (approximately 0.4 g each) were minced, suspended in cold 0.25 m sucrose (1:10, wt/vol), and homogenized. Each homogenate was divided in two equal volumes, with one sample receiving 1% Triton X-100 (1:10, vol/vol) and the other sample receiving distilled water (1:10, vol/vol). Samples were mixed on a Vortex agitator and centrifuged at 36,000 g and 4°C for 30 minutes. Supernatant fluids were analyzed for cathepsin D activity by the method of Anson and protein by the biuret method. The percentage of membrane-bound cathepsin D specific activity was determined by the following formula:

\[
\frac{\text{Activity with Triton} - \text{activity with } H_2O}{\text{Activity with Triton}} \times 100.
\]

Supernatant extracts of samples receiving distilled water were also analyzed for myocardial amino-nitrogen by the ninhydrin method of Kabat following deproteinization with trichloroacetic acid, as described by Lefer and Barnholz. Myocardial amino-nitrogen concentrations were expressed as µmol serine per mg protein. This indicates tissue content of small compounds having free amino groups.
Drugs

Prostaglandins E₁, E₂, 13,14-dihydro, 15-keto PGE₁, and 15-keto PGF₂α (Upjohn) were dissolved in ethanol to achieve a prostaglandin concentration of 10 mg/ml. The tromethamine salt (i.e., Tris) of PGF₂α was dissolved in distilled water (1 mg/ml) and frozen. All stock solutions of prostaglandins were stored at −20°C until use. For each experiment, 1 mg of prostaglandin was diluted with an appropriate volume of 0.9% NaCl to give an infusion concentration of 1 μg/kg per minute at an infusion rate of 4.58 ml/hour. Vehicle controls for PGE₁, E₂, and PG metabolites consisted of 0.9% NaCl infusion at a rate of 4.58 ml/hr. PGF₂α required a separate vehicle control of an appropriate dilution of Tris buffer in 0.9% NaCl infused at 4.58 ml/hr.

Isolated Lysosomes of Cat Liver

Livers were rapidly removed from pentobarbital-anesthetized cats and placed into cold 0.25 M sucrose with 0.02 M Tris buffer at pH 7.3. Liver homogenates (1:5, wt/vol) were prepared in a Potter-Elvehjem homogenizer and were centrifuged at 1000 g and 4°C for 15 minutes. The supernatant extracts were washed with and resuspended in the Tris buffer. Samples (4.5 ml) of the lysosomal suspension and 0.5 ml of the test agent (i.e., 15-keto PGF₂α or 13,14 dihydro, 15-keto PGE₁) were mixed to yield a final prostaglandin concentration of 20 ng/ml. A sample of lysosomal fraction and test drug diluent served as a control. Samples were incubated at 37°C in a Dubnoff incubator for 30 minutes. Release of lysosomal enzymes was stopped by placing the flasks in an ice bath. Samples were centrifuged at 15,900 g and 4°C for 30 minutes. Supernatant extracts containing the free enzyme activity were filtered and assayed for activity of the lysosomal hydrolases, cathepsin D and β-glucuronidase, using the methods of Anson13 and Talalay et al.,16 respectively. Pellets containing the bound lysosomal enzymes were resuspended with 5 ml 0.1% Triton X-100 and homogenized. After incubation at room temperature for 15 minutes, the homogenates were centrifuged at 15,900 g and 4°C for 30 minutes. Supernatant fluids were filtered and assayed for cathepsin D and β-glucuronidase activity. This fraction constitutes the bound or intralysosomal activity of these hydrolases.

Statistics

All values described in the text, figures, and tables are means ± SEM. Significance of all results was determined, using Student’s t-test for unpaired data. P values of less than 0.05 were considered statistically significant.

Results

As shown in Figure 1, PGE₁ infusion was associated with a significantly reduced arterial blood pressure in sham-operated controls from 2 to 5 hours when compared to sham-operated cats receiving the saline infusion. During PGE₁ infusion in ischemic cats, arterial pressure did not return toward control between 2 and 5 hours. This resulted in significantly reduced pressures at 4 and 5 hours compared to saline-treated cats subjected to myocardial ischemia.

The values for effects of PGE₂ on arterial blood pressure in sham-operated controls were comparable to those observed with PGE₁ infusion. Thus the initial pressure was 163 ± 10 mm Hg (mean ± SEM) and declined to 121 ± 5 mm Hg at 3 hours and to 113 ± 3 mm Hg after 5 hours (P < 0.05 compared to sham MI ± NaCl group). PGE₂ infusion during MI resulted in changes from an initial pressure of 154 ± 12 mm Hg to 111 ± 9 mm Hg at 3 hours, and to 105 ± 12 mm Hg at 5 hours. Table 1 gives the arterial pressures at the same times for PGF₂α-treated controls. In the case of ischemic cats, PGF₂α decreased arterial blood pressure from 157 ± 7 mm Hg at 0 time to 113 ± 7 mm Hg at 3 hours, and to 112 ± 7 mm Hg at 5 hours. It can be seen that comparable pressure changes occurred in response to PGE₁, PGE₂, and PGF₂α.

As shown in Table 1, infusion of 15-keto PGF₂α, a PGF₂α metabolite, resulted in a significantly elevated mean arterial blood pressure at 20 minutes when compared to PGF₂α infusion in sham-operated cats. Infusion of this PG metabolite also prevented the hypotension which occurred from 3 to 5 hours during PGF₂α infusion. However, no other hemodynamic, electrocardiographic, or biochemical differences between PGF₂α and 15-keto PGF₂α infusions were observed in either sham-operated controls or in MI cats.

The computed product of mean arterial blood pressure and heart rate (PRI) was used as an indicator of cardiac oxygen demand. As shown in Figure 2, PGE₁ infusion resulted in significant reduction of the PRI from 20 minutes on, when compared to sham-operated controls given saline. A significantly reduced PRI was also seen in the sham MI + PGF₂α group from 1 through 5 hours. However, PGF₂α infusion did not significantly alter the PRI in cats subjected to myocardial ischemia. Nevertheless, PGE₁ infusion in ischemic cats significantly reduced

![Figure 1](image-url) Average responses of mean arterial blood pressure and heart rate in cats receiving NaCl or PGE₁ infusions. Points represent mean values for six to nine experiments and brackets indicate SEM. When compared to sham + NaCl (solid circles), sham + PGE₁ cats (open triangles) exhibited significantly reduced arterial pressure at 2, 3, 4, and 5 hours (P < 0.05). MI + PGE₁ cats (solid triangles) had significantly reduced arterial pressure at 4 and 5 hours compared to the MI + NaCl group (P < 0.05). No significant differences in heart rate were observed in comparing any two groups.
the PRI from 3 hours on, and PGE₂ infusion was associated with reduced cardiac PRI at 4 and 5 hours when compared to untreated cats subjected to myocardial ischemia. Thus, infusion of PGE₁ or PGE₂, but not of PGF₂α, resulted in significant reductions in the PRI during myocardial ischemia.

The S-T segment changes at 5 hours are summarized in the top panel of Figure 3. Cats subjected to myocardial ischemia receiving saline or PGF₂α demonstrated significant S-T elevations at 5 hours (P < 0.025 and P < 0.01, respectively), as did ischemic cats given either prostaglandin metabolite. However, PGE₁ infusion prevented these S-T segment elevations. Cats given PGE₂ during myocardial ischemia had intermediate S-T segment elevations which were not different from those of sham-operated controls. None of the groups of cats subjected to the sham operation experienced significant S-T segment changes.

The bottom panel of Figure 3 shows plasma CPK-specific activities in blood samples drawn 5 hours after the start of the experiments. Sham-operated controls exhibited relatively low circulating CPK activities. In contrast, MI animals receiving saline or PGF₂α demonstrated significantly elevated plasma CPK activities (P < 0.05). However, cats treated with PGE₁ or PGE₂ did not experience significantly elevated plasma CPK 5 hours after the onset of myocardial ischemia, when compared to sham-operated controls.

Analysis of myocardial tissue samples for CPK activity (Fig. 4) demonstrated a significant reduction of CPK activity in ischemic myocardial tissue from cats receiving saline or PGF₂α compared to the non-ischemic left ventricular myocardial tissue obtained from the same hearts. However, infusion of PGE₁ or PGE₂ prevented significant reduction of CPK activity in the ischemic myocardium. All sham-operated control cats, independently of the substance infused, exhibited comparable myocardial CPK activities. Thus, there were no significant differences

![Figure 2](http://circres.ahajournals.org/)

**Figure 2** Time course of a derived pressure-rate index (PRI) for all sham groups (left panel) and MI groups (right panel) ranging from five to nine cats per group. The ordinates represent values of the PRI calculated as mean arterial pressure × heart rate + 10⁴ for times shown on the abscissa. Standard errors are given for initial and final values. Solid symbols represent values which are significantly different from the corresponding temporal value in the group receiving NaCl infusion (P < 0.05).

![Figure 3](http://circres.ahajournals.org/)

**Figure 3** Five hour values for S-T segment changes (top panel) and for plasma CPK (bottom panel) are shown for sham MI and MI cats. Bar heights represent mean values and brackets indicate SEM. No significant differences were observed between sham-operated groups and MI groups receiving PGE₁ or PGE₂ infusions for either plasma CPK or S-T elevations. Untreated MI animals (i.e., MI + NaCl) and MI + PGF₂α animals showed significantly increased plasma CPK and S-T elevations compared to corresponding sham-operated groups. No significant differences were observed among any of the ischemic groups with regard to plasma CPK activities at 5 hours.

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**Table 1 Hemodynamic Responses to PGF₂α Infusion**

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>0</th>
<th>20</th>
<th>180</th>
<th>300</th>
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<tbody>
<tr>
<td>Mean Arterial Blood Pressure (mm Hg)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sham + NaCl (8)</td>
<td>153 ± 10.6</td>
<td>154 ± 9.2</td>
<td>131 ± 4.9</td>
<td>131 ± 5.8</td>
</tr>
<tr>
<td>Sham + PGF₂α (5)</td>
<td>152 ± 7.0</td>
<td>131 ± 12.1</td>
<td>113 ± 4.6*</td>
<td>111 ± 4.6*</td>
</tr>
<tr>
<td>Sham + 15-keto PGF₂α (6)</td>
<td>151 ± 7.7</td>
<td>168 ± 7.9t</td>
<td>129 ± 13.8</td>
<td>128 ± 12.7</td>
</tr>
<tr>
<td>Heat Rate (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham + NaCl (8)</td>
<td>199 ± 11.2</td>
<td>199 ± 10.3</td>
<td>161 ± 5.4</td>
<td>146 ± 4.9</td>
</tr>
<tr>
<td>Sham + PGF₂α (5)</td>
<td>195 ± 9.6</td>
<td>193 ± 6.8</td>
<td>148 ± 4.1</td>
<td>133 ± 3.4</td>
</tr>
<tr>
<td>Sham + 15-keto PGF₂α (6)</td>
<td>203 ± 9.8</td>
<td>208 ± 4.8</td>
<td>161 ± 5.2</td>
<td>143 ± 4.8</td>
</tr>
</tbody>
</table>

PGF₂α infusion = 1 μg/kg per minute. All values are means ± SEM. Numbers in parentheses are number of cats in each group.

*P < 0.05 compared to sham + NaCl.
+P < 0.05 compared to sham + PGF₂α.

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**PROSTAGLANDINS IN MYOCARDIAL ISCHEMIA/Ogletree and Lefer**
between normal, non-ischemic, and sham-ischemic cardiac tissue in these control groups. These results correlate closely with the observed elevations of plasma CPK activity in ischemic cats receiving either saline or PGF\textsubscript{2\alpha} and the absence of such elevations in sham-operated cats and ischemic cats receiving either PGE\textsubscript{1} or PGE\textsubscript{2}. However, neither prostaglandin metabolite prevented these changes in myocardial and plasma CPK activity during myocardial ischemia.

Concentrations of substances possessing free amino-nitrogen groups during myocardial ischemia. Identification of the factors responsible for changes in myocardial amino-nitrogen concentration must await further investigation.

Figure 5 illustrates percentages of myocardial cathepsin D activity remaining in bound form (i.e., intralysosomal) after tissue homogenization. Only in untreated ischemic hearts was there a significant difference between ischemic and normal myocardial tissue. No significant differences were observed between normal, non-ischemic tissue samples in the various experimental groups. Thus, prostaglandins did not significantly influence the processes responsible for the loss of myocardial substances possessing free amino-nitrogen groups during myocardial ischemia. Identification of the factors responsible for changes in myocardial amino-nitrogen concentration must await further investigation.

**Table 2** Ischemic (or Sham-Ischemic) Myocardial Amino-Nitrogen Concentration (µmoles/mg Protein)

<table>
<thead>
<tr>
<th>Myocardial area</th>
<th>NaCl</th>
<th>PGE\textsubscript{1}</th>
<th>PGE\textsubscript{2}</th>
<th>PGF\textsubscript{2\alpha}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham MI MI</td>
<td>Sham MI MI</td>
<td>Sham MI MI</td>
<td>Sham MI MI</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>1.5 0.9\textsuperscript{<strong>} 1.3 1.0\textsuperscript{</strong>} 1.7 1.1\textsuperscript{t} 1.4 1.0\textsuperscript{**}</td>
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</tr>
<tr>
<td><strong>SEM</strong></td>
<td>±0.10 ±0.10  ±0.06 ±0.08 ±0.32 ±0.16 ±0.16 ±0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>8 9 7 8 5 5 5 6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\* P < 0.05 compared to corresponding sham MI group.
\textsuperscript{t} P < 0.05 compared to sham + NaCl.
sistent with a direct enhancement in myocardial lysosomal stability by PGE, PGE, and PGF during acute myocardial ischemia. Alternatively, the reduced release of cathepsin D may be due to a secondary effect of the prostaglandins on some other process resulting in an improved lysosomal stability. All three prostaglandins used in this study appeared to significantly retard this autolytic process, although PGE, and PGE were somewhat more effective in stabilizing lysosomal membranes.

Moreover, 15-keto PGF did not significantly alter the rate of lysosomal enzyme release by isolated cat liver lysosomes when compared to vehicle controls. Similarly, 13,14-dihydro, 15-keto PGE, exerted no significant lysosomal effect in vitro. Thus, neither PG metabolite exhibited membrane-stabilizing effects on isolated lysosomes.

Discussion

In the present study, infusion of E-type prostaglandins was shown to exert a beneficial effect on several hemodynamic and biochemical changes resulting from myocardial ischemia (i.e., circulating and myocardial CPK activities and myocardial cathepsin D activity) which may result in a preservation of myocardial cell integrity.

In 1973, Hutton et al. reported that PGE, infusion (0.05-0.1 μg/kg per minute) resulted in a reduction of cardiac afterload and an increase in coronary blood flow in cats. More recently, Mjos et al. showed that PGE, prevented isoproterenol-induced myocardial injury in dogs, as evidenced by significant reductions in S-T elevation and plasma free fatty acid concentrations. Recent evidence has appeared indicating that PGE, or PGE significantly reduces cardiac work and diminishes S-T segment elevation during myocardial ischemia. PGE was further shown to improve the distribution of coronary blood flow to the ischemic dog myocardium by significantly increasing subendocardial blood flow. PGE and PGE were also shown to prevent release of membrane-bound cardiac enzymes during myocardial ischemia. Thus, there appears to be agreement that PGE infusion can be beneficial to the ischemic myocardium. However, there is no general agreement concerning the mechanisms involved, in part because of the multiplicity of biological actions of the E-type prostaglandins.

Several actions of the E-type prostaglandins could contribute to a reduction in projected infarct size during the early phase of myocardial ischemia. Hemodynamically, these agents reduce cardiac afterload (i.e., arterial blood pressure) and appear to prevent compensatory tachycardia. PGE and PGE also have been shown to exert modest negative inotropic effects of isolated cat cardiac muscle. In concert, these actions tend to decrease cardiac work and, thus, reduce myocardial oxygen demand.

Infusion of E-type prostaglandins in vivo decreases blood pressure largely by inducing peripheral vasodila-
tion. In addition, PGE has been shown to antagonize the peripheral vasoconstrictor actions of norepinephrine and angiotensin II. Thus, infusion of E-type prostaglandins is capable of maintaining blood flow despite potentially high levels of circulating pressor agents. Furthermore, coronary vasodilation by E-type prostaglan-
dins coupled with a decreased cardiac afterload, could favorably influence redistribution of myocardial blood flow toward the subendocardium, which is most severely compromised following coronary occlusion. Alternatively, the E-type prostaglandins may exert effects on redistribution of coronary flow by opening of coronary collateral vessels. Moreover, these postulated effects may occur even in the presence of a reduced afterload on the heart, as is thought to be the case with nitroglycerin.

In conjunction with its nonspecific antagonism of pressor agents on vascular smooth muscle, PGE, has been shown to inhibit release of norepinephrine from myocardial nerve terminals in response to cardiac sympathetic nerve stimulation. This counterbalancing of the activated sympathetic nervous system would help explain the reduced cardiac effort observed during myocardial ischemia with PGE, infusion. This would prevent deleterious effects of catecholamine release during sustained cardiac sympathetic activation, including prevention of regional myocardial ischemia and increased myocardial oxygen demand. Furthermore, catecholamine release is largely responsible for enhanced lipolysis during myocardial ischemia. The resulting increase in circulating free fatty acids stimulates myocardial metabolism and may contribute to arrhythmogenesis. Among its other effects, PGE, directly inhibits lipolysis and platelet aggregation. Thus, PGE, not only modulates catecholamine release but also directly antagonizes potentially harmful effects of catecholamines. Moreover, PGE has been shown to be an antiarrhythmic agent.

Apparently, prostaglandins do not exert significant effects on myocardial proteolysis at least with respect to the accumulation of small amino compounds. We have previously shown that ischemic myocardial tissue undergoes a significant reduction in free amino-nitrogenous compounds. This may be due to the extensive cellular membrane damage which does not allow the retention of small molecules by myocardial cells in the ischemic area, or these amino compounds may be consumed more rapidly in myocardial ischemia.

Some other beneficial actions of E-type prostaglandins which may be of value in myocardial ischemia are related to membrane effects of these agents. Prostaglandins have been shown previously to stabilize lysosomal membranes, and in the current study prostaglandin infusion was associated with prevention of myocardial lysosomal disruption in the ischemic region. Lysosomal disruption would have the effect of liberating lysosomal proteases and phospholipases which could damage adjacent cellular membranes and degrade or denature vital cellular proteins. Prevention of lysosomal disruption and inhibition of lysosomal enzymes has been shown to be of significant value in minimizing cellular damage during myocardial ischemia. Moreover, prostaglandins may exert more generalized membrane-stabilizing effects, thus directly preventing damage to myocardial sarcolemmal membranes as well as maintaining the integrity of red blood cell membranes. In this regard, PGE, has been shown to enhance red blood cell deformability and, thus, may promote greater oxygen delivery to the coronary microcirculation.

The protective action of prostaglandins observed in this
study does not appear to be due to the major metabolites of these agents. Both 15-keto PGE$_2$ and 13,14-dihydro, 15-keto PGE$_1$ were essentially devoid of a protective effect on the myocardium. Neither metabolite prevented loss of CPK from ischemic myocardial tissue, accumulation of CPK in plasma, or elevation in S-T segment during 5 hours of ischemia. It is possible that other metabolites play a role in the protective effect, but these are not commonly available for study.

In summary, infusion of E-type prostaglandins during myocardial ischemia significantly reduced arterial blood pressure without producing significant changes in heart rate. These actions resulted in an overall reduction of a pressure-rate index which is an indicator of myocardial oxygen demand. During 5 hours of myocardial ischemia, PGE$_1$ and PGE$_2$ infusion prevented significant S-T segment elevation. PGE$_1$ and PGE$_2$ also prevented release of CPK and cathepsin D from ischemic myocardial tissue. However, treatment with the E-type prostaglandins did not prevent significant decreases in myocardial amino-nitrogen activity in ischemic tissue, and thus prostaglandin infusion did not prevent ischemia-induced reduction of intracellular compounds containing free amino-nitrogens. These results indicate that E-type prostaglandins preserve myocardial integrity during acute myocardial ischemia, probably by reducing myocardial oxygen demand and stabilizing myocardial lysosomal membranes. However, other mechanisms which were not investigated in this study may also be involved in this protective effect of the prostaglandins.

Acknowledgments

We gratefully acknowledge the technical assistance of Mary Ann Gaffney and Cathleen Shupe in the biochemical analyses and Richard Levin for surgical assistance. We also wish to thank Dr. John Pike of the Upjohn Company, Kalamazoo, Michigan, for the generous supply of prostaglandins and their metabolites used in this study.

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Prostaglandin-induced preservation of the ischemic myocardium.
M L Ogletree and A M Lefer

Circ Res. 1978;42:218-224
doi: 10.1161/01.RES.42.2.218

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