Protective Action of Methylprednisolone on the Myocardium during Experimental Myocardial Ischemia in the Cat

By James A. Spath, Jr., David L. Lane, and Allan M. Lefer

ABSTRACT

Cats subjected to coronary artery occlusion were used to study the effect of methylprednisolone on the release of lysosomal acid hydrolases and creatine phosphokinase (CPK) from ischemic myocardial tissue. Plasma CPK activity was increased significantly 2 hours after occlusion and increased eightfold 5 hours after ligation in vehicle-treated cats. Intravenous administration of methylprednisolone (30 mg/kg) 30 minutes before or 60 minutes after occlusion significantly limited the increases in plasma CPK activity to values only slightly greater than those observed in sham-operated cats. Plasma activities of the lysosomal hydrolases, β-glucuronidase and cathepsin D, were comparable in all groups of cats and did not change during the 5-hour observation period. Nevertheless, cathepsin D and β-glucuronidase activities were reduced 41% and 33%, respectively, in the ischemic portion of the myocardium of untreated cats subjected to coronary artery ligation. The CPK activity of the ischemic myocardium was reduced 43% in these cats. Pre- or posttreatment of cats with methylprednisolone prevented the decline in CPK and lysosomal hydrolase activity of ischemic myocardium. These data indicate that lysosomal disruption is a consequence of myocardial ischemia and that pre- or posttreatment with methylprednisolone prevents the leakage of myocardial lysosomal and cellular enzymes. Moreover, the methylprednisolone-induced stabilization of myocardial membranes appears to be related to the ability of glucocorticoid to limit infarct size following myocardial ischemia.

KEY WORDS
S-T segment elevation lysosomal hydrolases creatine phosphokinase β-glucuronidase cathepsin D

Twenty years ago, cortisone was reported to limit myocardial damage following acute myocardial ischemia (1). However, these results have been challenged by others (2, 3) and the postulated mechanism of action of cortisone in this report, improvement in intercoronary collaterals, has not been verified (3). More recently, Libby et al. (4) have shown that pharmacologic doses of cortisol limit the severity and the extent of the infarct 24 hours after coronary artery occlusion in dogs. Several possibilities have been proposed to explain this infarct-reducing effect including coronary vasodilation, increased myocardial contractility, and stabilization of myocardial cell membranes. Brachfeld (5) has suggested that disruption of cardiac lysosomes within the ischemic myocardium promotes cardiac damage following occlusion of a coronary artery. Although previous investigations have shown alterations in cardiac lysosomal enzyme content following coronary artery occlusion (6, 7), most of these studies have been directed toward examination of changes in cardiac enzyme activities 24 hours or more after coronary artery occlusion. Furthermore, the effect of glucocorticoids on the lysosomal hydrolase activity of ischemic myocardial tissue has not been investigated. Thus, the present study was undertaken to quantify the release of myocardial lysosomal hydrolases following coronary artery occlusion and to investigate the effects of glucocorticoids on myocardial enzyme release during acute myocardial ischemia.

Methods

CORONARY ARTERY OCCLUSION

Adult male and female cats (2.5-3.8 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv). Their tracheas were cannulated and positive-pressure respiration was instituted with a Harvard respirator. Catheters were placed within the right external jugular vein and the left common carotid artery of each cat and positioned to allow recording of central venous pressure and mean arterial blood pressure, respectively. Pressures were recorded continuously using appropriate Statham transducers coupled to a Beckman type R Dynograph. Needle
GLUCOCORTICOID IN MYOCARDIAL ISCHEMIA

A silk ligature was tied around the artery. The resultant ischemic surrounding tissue about 13-15 mm from the coronary ostium. A coronary artery. The left coronary artery was dissected free of surrounding tissue and a 3-0 silk ligature was placed under the vessel. In cats subjected to acute myocardial ischemia, the ligature was tied tightly around the left coronary artery 13-15 mm from the coronary ostium (Fig. 1). Twenty-six cats were subjected to either a sham operation or 5 hours of myocardial ischemia following occlusion of the coronary artery. Cats subjected to myocardial ischemia were given either 30 mg/kg of methylprednisolone sodium succinate (Solu-medrol, Upjohn) or an equal volume of diluent (0.9% benzyl alcohol in sterile water) in the jugular vein catheter. Methylprednisolone was administered slowly over 10 minutes beginning either 30 minutes prior to or 60 minutes after occlusion of the coronary artery. Sham-operated cats were given methylprednisolone 30 minutes prior to the start of the experiment.

SAMPLING AND HOMOGENIZATION OF CARDIAC TISSUE

Samples of arterial blood (4 ml) were withdrawn from the carotid catheter just prior to occlusion and 1, 2, 4, and 5 hours after occlusion. Blood samples were drawn from sham-operated cats at the same time. Blood loss was replaced with an equal volume of Kreb's-Henseleit solution warmed to 37°C. Blood was collected in polyethylene tubes containing 2 drops of sodium heparin (1,000 units/ml, Upjohn, beef lung) and kept at 4°C until centrifugation. Blood was centrifuged at 2,400 g for 15 minutes. The plasma was decanted and treated as described in the following section. At 5 hours, the hearts were excised, rinsed in 0.9% NaCl solution at 4°C, rapidly weighed, and placed in cold 0.25M sucrose. The hearts from cats subjected to myocardial ischemia were divided into ischemic and normal left ventricle by inspection of the coronary vessels, endocardium, and epicardium. Thus, tissue supplied by arterial branches distal to the ligature appeared as a cyanotic area having patchy subendocardial hemorrhagic regions.

Ischemic or nonischemic tissue was homogenized in 0.25M sucrose (1:10 w:v) containing 1 mM ethylenediaminetetraacetic acid and 0.1 mM mercaptoethanol for the determination of myocardial creatine phosphokinase (CPK) activity (8). The tissue preparations for the CPK determinations were treated according to the method of Kjekshus and Sobel (9). Additional ischemic or adjacent normal ventricular tissue was minced and homogenized in 0.25M sucrose (1:10 w:v) for subsequent determination of lysosomal enzymes. Each sample of myocardium was homogenized twice for 15 seconds using a Virtis homogenizer at a speed setting of 9.0. The homogenates were centrifuged at 800 g for 10 minutes. The supernatant fractions were centrifuged at 36,000 g for 30 minutes at 4°C. Samples of supernatant fluid were assayed for β-glucuronidase and cathepsin D activities in the presence and the absence of Triton X-100. Cardiac homogenates from sham-operated cats were derived from left ventricular tissue anatomically equivalent to the ischemic and normal areas present in ischemic hearts.

BIOCHEMICAL DETERMINATIONS

Samples of plasma and supernatant fluid from the cardiac homogenates were analyzed for activities of the lysosomal hydrolases, cathepsin D and β-glucuronidase, using the method of Anson (10) and Talalay et al. (11), respectively. The protein concentration of plasma and of supernatant fluid from the cardiac homogenates was determined using the Biuret method (12). The β-glucuronidase activity is expressed in Fishman units computed as micrograms of phenolphthalein released per hour per milligram of protein at 37°C using phenolphthalein glucuronide as substrate. Cathepsin D activity is expressed as milliequivalents of tyrosine × 10⁻⁴ released from bovine hemoglobin per milligram of protein per hour at 37°C. CPK activities of plasma and supernatant fluid from cardiac homogenates were determined according to the method of Rosalki (8). CPK activity is expressed as international units per milligram of protein. One international unit of CPK is that activity which transfers 1.0 µmole of phosphate from phosphocreatine to adenosine diphosphate (ADP) per minute at pH 7.4 and 30°C.

Results

Table 1 reports the hemodynamic effects of the sham operation or the acute myocardial ischemia in 24 cats given methylprednisolone or its vehicle. Sham-operated cats given methylprednisolone exhibited a stable heart rate, mean arterial blood pressure, and cardiac output for 5 hours. Furthermore, all groups of cats were comparable with respect to all hemodynamic indexes studied prior to coronary occlusion. Occlusion of the left coro-

[FIGURE 1]

Diagrammatic representation of the site of occlusion of the left coronary artery. The left coronary artery was dissected free of surrounding tissue about 13-15 mm from the coronary ostium. A silk ligature was tied around the artery. The resultant ischemic area of the left ventricle (stippled) constituted about 20% of the total cardiac weight.

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TABLE 1
Hemodynamic Effects of Acute Myocardial Ischemia in Methylprednisolone- and Vehicle-Treated Cats

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Group</th>
<th>MABP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>CO (ml/min)</th>
<th>MABP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>CO (ml/min)</th>
<th>MABP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>CO (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Sham MI + MP (6)</td>
<td>97 ± 9</td>
<td>162 ± 11</td>
<td>343 ± 54</td>
<td>97 ± 9</td>
<td>162 ± 8</td>
<td>336 ± 49</td>
<td>106 ± 7</td>
<td>146 ± 10</td>
<td>352 ± 31</td>
</tr>
<tr>
<td>30</td>
<td>MI + vehicle (7)</td>
<td>116 ± 7</td>
<td>160 ± 10</td>
<td>390 ± 66</td>
<td>96 ± 5*</td>
<td>125 ± 13*</td>
<td>302 ± 69</td>
<td>106 ± 7</td>
<td>122 ± 12*</td>
<td>297 ± 70</td>
</tr>
<tr>
<td>180</td>
<td>MI + MP-Pre (6)</td>
<td>117 ± 7</td>
<td>158 ± 12</td>
<td>394 ± 77</td>
<td>104 ± 6†</td>
<td>132 ± 16</td>
<td>375 ± 75</td>
<td>109 ± 6</td>
<td>143 ± 7</td>
<td>349 ± 73</td>
</tr>
<tr>
<td>300</td>
<td>MI + MP-Post (5)</td>
<td>124 ± 5</td>
<td>161 ± 10</td>
<td>371 ± 49</td>
<td>99 ± 7*</td>
<td>149 ± 5</td>
<td>317 ± 39</td>
<td>105 ± 5</td>
<td>140 ± 5</td>
<td>272 ± 43</td>
</tr>
</tbody>
</table>

All values are means ± SE. Coronary artery occlusion occurred at 0 minutes. MABP = mean arterial blood pressure, HR = heart rate, CO = cardiac output, MI = myocardial ischemia, MP = methylprednisolone, MP-Pre = pretreatment with methylprednisolone, and MP-Post = posttreatment with methylprednisolone. Number of samples tested is given in parentheses.

* P < 0.02 compared to value at 0 minutes.
† P < 0.05 compared to value at 0 minutes.

Coronary artery resulted in a significant decrease (P < 0.05 to < 0.02) in mean arterial blood pressure 30 minutes postocclusion in all groups of cats. Cats given the vehicle also exhibited a significant decrease in heart rate 30 minutes after ligation of the left coronary artery (P < 0.05 to < 0.02).

Thus, the degree of myocardial ischemia induced in our preparation produced only moderate hemodynamic changes. However, in about 20% of the cats, ventricular fibrillation occurred spontaneously within the first hour following occlusion. These cats were successfully converted to sinus rhythm by using a Medtronic internal-external defibrillator. Fibrillation per se with rapid conversion to sinus rhythm apparently did not significantly alter the mean hemodynamic parameters measured or the rate of release of enzymes in these experiments, since these cats were indistinguishable from the majority of cats not experiencing fibrillation. A few cats with multiple fibrillations were not used.

Table 1 does not include data from two cats. In one of these cats, the mean arterial blood pressure fell to 50 mm Hg following ligation of the coronary artery and was sustained at this hypotensive level for the duration of the experiment. This cat was clearly in a state of cardiogenic shock. In the other cat, coronary artery occlusion failed to produce significant hemodynamic or electrocardiographic changes. The cat in cardiogenic shock exhibited a considerably greater loss of myocardial enzymes than was usual in cats subjected to coronary artery ligation, and the unaffected cat exhibited only very slight changes in myocardial enzyme activity. Both cats were excluded from statistical evaluation.

Ligation of the left coronary artery typically produced an elevation of the S-T segment of lead III of the ECG and an enlarged T wave. Figure 2 illustrates a representative ECG recording from a cat prior to coronary artery occlusion (A) and at 5 hours postocclusion (B) in an untreated cat. The mean elevation of the S-T segment of the ECG during the course of the experiments in all groups of cats is shown in Figure 3. Sham-operated cats exhibited no significant elevation of the S-T segment during the 5-hour experimental period. In contrast, marked elevations of the S-T segment occurred at 20-60 minutes in all groups of cats.

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

Typical lead III electrocardiogram of an untreated cat before (A) and after (B) occlusion of the left coronary artery. Coronary artery occlusion produced a significant elevation of the S-T segment and enlargement of the T wave of the electrocardiogram.
Ile…

Effect of methylprednisolone (MP) or its vehicle on the elevation of the S-T segment in cats subjected to acute myocardial ischemia (MI) by occlusion of the left coronary artery. All values are means ± SE for five to seven cats in each group. Sham-operated cats given methylprednisolone showed an absence of S-T segment elevation over the entire 5-hour experimental period. Occlusion of the left coronary artery initially produced similar elevation of the S-T segment in all three groups of cats subjected to occlusion. The S-T segment of vehicle-treated cats (MI + Vehicle) remained elevated for the duration of the experiment. However, S-T segment elevation declined to control values 2-5 hours after occlusion in cats subjected to myocardial ischemia and pretreated with methylprednisolone (MI + MP-pre) or posttreated with methylprednisolone (MI + MP-post).

experiencing coronary artery occlusion. The S-T segment remained elevated for the entire experimental period in the untreated cats. However, pre- or posttreatment of ischemic cats with methylprednisolone was associated with a significant reduction in the S-T segment elevation 2-5 hours after coronary artery occlusion. Despite differences in the rate of decline of the S-T segment voltage toward preocclusion levels, the degree of elevation of the S-T segment in both glucocorticoid-treated groups of cats after 5 hours of ischemia was not significantly different from that in sham-operated cats.

In addition to electrocardiographic changes, alterations in the activity of plasma CPK occurred following coronary artery occlusion. Figure 4 summarizes the plasma CPK activities in the four experimental groups. A significant elevation in plasma CPK activity was observed as early as 2 hours after coronary artery occlusion in untreated cats. These cats exhibited an eightfold increase in plasma CPK activity 5 hours after coronary artery occlusion. In contrast, sham-operated cats exhibited only a slight increase in plasma CPK activity at 5 hours. Moreover, pre- or posttreatment of cats with methylprednisolone markedly limited the plasma CPK activity 5 hours after coronary artery occlusion to values about three times the control activities.

In contrast to the plasma CPK activity, the plasma activities of β-glucuronidase and cathepsin D did not change significantly following occlusion of the left coronary artery. This finding is not surprising in view of the fact that neither arterial blood pressure nor aortic flow declined to values found in shock during the course of the experiments.

A very consistent pattern of alterations in myocardial enzyme activity occurred in response to coronary artery occlusion. Figure 5 presents the CPK activity of ischemic and nonischemic cardiac tissue in all four groups of cats. There was no significant difference in the CPK activity of normal or presumptively ischemic myocardial tissue in sham-operated cats. However, the CPK activity of ischemic myocardium in cats subjected to coronary artery ligation and given steroid vehicle was reduced 43% compared with that of adjacent normal myocardium. This loss of myocardial CPK activity was effectively prevented by either pre- or posttreatment with methylprednisolone. In addition,
Effect of pre- or posttreatment with methylprednisolone on the myocardial CPK activity of normal or ischemic myocardium (MI). All values are means ± SE. Numbers at the bottom of each bar indicate the number of myocardial samples studied. Ischemic myocardial tissue obtained from vehicle-treated cats (MI + Vehicle) shows a 43% decrease compared with adjacent normal left ventricle. Pre- or posttreatment of cats with methylprednisolone prevented the decrease in the CPK activity of ischemic heart tissue. The myocardial CPK activity of normal or ischemic myocardium of cats treated with methylprednisolone was similar in all cats.

The CPK activity of normal, nonischemic myocardium excised from ischemic hearts of untreated cats was not significantly different from CPK activities measured in all other samples of myocardium. These findings provide evidence that the ischemic myocardium undergoes a marked loss of CPK and are consistent with the concept that a very large fraction of the increase in plasma CPK activity arises from the ischemic area of the heart.

Myocardial activities of the lysosomal hydrolases, β-glucuronidase and cathepsin D, underwent changes that were quantitatively similar to those observed for myocardial CPK activity (Fig. 6). Cathepsin D and β-glucuronidase activities were decreased in the ischemic portion of the myocardium 41% and 33%, respectively, in untreated cats 5 hours after occlusion. However, the activities of the lysosomal hydrolases of adjacent, nonischemic myocardium in the same heart were not significantly different from the activities of these enzymes measured in hearts obtained from sham-operated cats. Moreover, pre- or posttreatment with methylprednisolone prevented the decrease in β-glucuronidase and cathepsin D activity observed in the ischemic myocardium obtained from vehicle-treated cats. In addition to total myocardial β-glucuronidase and cathepsin D activities, the percent of each enzyme in the free or nonsedimentable form was also determined. These data are summarized in Table 2. Both enzymes were distributed in a similar manner; about 50% of the enzyme activities existed in the free form after homogenization in the myocardium of sham-operated cats. This value increased to about 75% after ligation. Methylprednisolone, either pre- or posttreatment, largely prevented the postocclusion increase in the free activity of both enzymes in the ischemic portion of the myocardium. These find-

TABLE 2

<table>
<thead>
<tr>
<th>Group</th>
<th>β-Glucuronidase</th>
<th>Cathepsin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham MI + MP (5)</td>
<td>49.8 ± 3.7</td>
<td>52.2 ± 2.6</td>
</tr>
<tr>
<td>MI + vehicle (4)</td>
<td>73.3 ± 1.5</td>
<td>73.9 ± 2.6</td>
</tr>
<tr>
<td>MI + MP-Pre (4)</td>
<td>59.7 ± 1.7*</td>
<td>58.3 ± 2.7*</td>
</tr>
<tr>
<td>MI + MP-Post (5)</td>
<td>50.8 ± 1.9*</td>
<td>53.3 ± 1.8*</td>
</tr>
</tbody>
</table>

All values are mean percent free (i.e., unbound, nonsedimentable) lysosomal enzyme activities ± SE. See Table 1 for abbreviations. Number of samples tested is given in parentheses.

* P < 0.01 from methylprednisolone + vehicle group.
ings suggest that a marked degree of lysosomal disruption occurs in the ischemic portion of the myocardium of untreated cats and that methylprednisolone is an effective agent in preventing this loss of lysosomal enzyme activity during myocardial ischemia.

Discussion

Ligation of the left coronary artery produced a relatively consistent ischemic area constituting about 25% of the heart. This degree of myocardial ischemia, although considerable, usually failed to produce a state of cardiogenic shock. Nevertheless, the hemodynamic status of the cats subjected to coronary artery ligation was altered as evidenced by the early decrease in arterial blood pressure and heart rate. Furthermore, ischemic cardiac tissue in untreated cats exhibited significant losses of β-glucuronidase, cathepsin D, and CPK activities. The magnitudes of these decreases compared closely with those reported by Leighty et al. (13) for β-glucuronidase and cathepsin D activities in dogs subjected to asphyxia and to those reported by Kjekshus and Sobel (9) for CPK following coronary artery occlusion in rabbits.

Cellular potential changes are among the earliest myocardial alterations associated with occlusion of a coronary artery. Recently, Maroko et al. (14) have shown that the degree of S-T segment elevation recorded 15 minutes after coronary artery occlusion correlates closely with infarct size assessed by histological examination and by analysis of plasma CPK activity 24 hours later. In the present study, the magnitude of the elevation of the S-T segment of the ECG 20-40 minutes after occlusion was similar in all groups of ischemic cats. However, alterations in the S-T segment 2-4 hours after coronary occlusion accurately projected the degree of myocardial cellular damage. In untreated cats, the S-T segment remained elevated for the entire 5-hour period, and the cardiac CPK and lysosomal enzyme activities measured 5 hours after occlusion were markedly reduced. In contrast, cats receiving methylprednisolone exhibited a decline in S-T segment elevation 2-5 hours after occlusion and only a slight loss of myocardial enzyme activity 5 hours after occlusion. These findings suggest the presence of a critical period during which the ischemic area can be modified by drugs. In our experiments in cats, this critical period appeared to be about 2 hours. However, under different experimental conditions, this period can be as long as 6 hours (4).

Shell and Sobel (15) have previously reported an increase in plasma CPK activity 3 hours after occlusion of the left anterior descending coronary artery in dogs. In cats, we found a significant increase in plasma CPK activity 2 hours after occlusion, which progressively increased over the next 3 hours. In contrast to the plasma CPK activity, the plasma activities of the lysosomal acid hydrolases, cathepsin D and β-glucuronidase, did not increase in either sham-operated cats or cats subjected to myocardial ischemia.

These findings are not surprising since Glenn et al. (16) have shown that plasma lysosomal hydrolases are normally rapidly cleared by the action of the reticuloendothelial cells in the liver and spleen. During severe hypotension or in protracted shock, this clearance mechanism is impaired and lysosomal hydrolases accumulate in peripheral plasma. Such was not the case in our model of myocardial ischemia. However, we did observe a decrease in myocardial lysosomal enzymes and an increase in fragility of myocardial lysosomes in myocardial ischemia. These findings are consistent with the observations in dogs of Ricciutti (17, 18).

Thus, it is possible to demonstrate early changes in the activities of cardiac enzymes in ischemic cardiac tissue. However, treatment with methylprednisolone prevented the decreases in cardiac enzyme activities and significantly prevented the increase in plasma CPK activity found following coronary artery occlusion. Moreover, administration of methylprednisolone was associated with a decline in the elevation of the S-T segment of ischemic hearts 2-5 hours after occlusion associated with the preservation of myocardial CPK activity. In this regard, posttreatment with glucocorticoid appeared to be as effective as pretreatment in normalizing the electrical potential of the myocardium. Some degree of reversible damage of cardiac cells occurs between 20 minutes and 2 hours of experimental myocardial infarction in the absence of any therapeutic intervention (5). However, after 2 hours of ischemia, progressive damage occurs which might be difficult to reverse. Since the biological half-life of methylprednisolone in plasma is about 80 minutes (19), it is likely that administration of methylprednisolone 60 minutes after occlusion provides a higher plasma concentration of glucocorticoid than pretreatment at the potentially critical time (i.e., about 2 hours after occlusion) when ischemic cellular alterations would tend to be most severe. Libby et al. (4) have reported that administration of pharmacologic amounts of hydrocortisone up to 6 hours after experimental myocardial infarction in dogs reduces...
infarct size assessed by alterations in myocardial CPK and subsequent histological examination 24 hours after coronary artery occlusion. However, in high doses hydrocortisone exerts mineralocorticoid effects, and no vehicle controls were used. Our results with methylprednisolone suggest that it is indeed the glucocorticoid activity independent of the vehicle that protects the myocardium. Moreover, we found that the glucocorticoid limits infarct size within 5 hours following coronary artery occlusion, a finding which suggests that early treatment of myocardial ischemia might help prevent cardiac damage.

The mechanism by which glucocorticoid limits infarct size is not clear, although it has been suggested that the beneficial effect of the steroid results from (1) an antiarrhythmic, (2) a vasodilator, (3) a positive inotropic, or (4) a membrane-stabilizing effect. In our experiments, administration of methylprednisolone prevented some degree of bradycardia observed following coronary artery occlusion. However, we noticed no antiarrhythmic effect in cats given methylprednisolone and subjected to acute myocardial ischemia. Neither do our results provide support for the view that glucocorticoids produce either a positive inotropic or a vasodilator effect. The central venous pressures of sham-operated, vehicle-treated or steroid-treated cats were similar throughout the experimental period at times when the cardiac output either did not change or decreased slightly. These data are not consistent with either an overt positive inotropic effect of methylprednisolone or the prevention of a negative inotropic effect in myocardial ischemia. Moreover, the total peripheral resistances of untreated cats subjected to coronary artery occlusion were very similar to those of methylprednisolone-treated cats throughout the entire experimental period. Moreover, administration of methylprednisolone over a 10-minute period failed to evoke even a transient change in total peripheral resistance. Thus, in our experiments, we cannot attribute the beneficial effect of glucocorticoid to a transient or a sustained systemic vasodilating effect. However, our experiments provide no information on a direct coronary vasodilator effect of glucocorticoids, although these agents in general do not exert significant vasodilation in individual vascular beds (20).

Our results are consistent with the view that methylprednisolone stabilizes myocardial membranes in the ischemic heart and retards cell disruption following acute myocardial ischemia. We have observed an enhanced fragility of lysosomes and a substantial loss of lysosomal hydrolases from the ischemic myocardium of untreated cats during the early stages of myocardial ischemia. These changes are significantly reduced in glucocorticoid-treated cats, indicating that methylprednisolone induced a membrane stabilization at some site in the myocardial cell. The site of action of methylprednisolone in preventing the release of myocardial enzymes from ischemic myocardial cells might be the cell membrane, the membrane of subcellular organelles such as lysosomes, or both. Our findings do not allow us to differentiate among these possibilities.

It is conceivable that methylprednisolone protects the myocardium indirectly by some metabolic action such as making more circulating glucose available for myocardial metabolism. We have no direct data to corroborate this possibility. However, high doses of methylprednisolone have been shown to increase the turnover rate of glucose (i.e., increase the rates of production and utilization of glucose to a similar degree) without notably changing plasma glucose concentration (21). Therefore, the dramatic effect of methylprednisolone on the prevention of myocardial enzyme leakage is probably not primarily due to an increase in plasma glucose concentration.

Acknowledgments

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GLUCOCORTICOID IN MYOCARDIAL ISCHEMIA


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