EPINEPHRINE SHOCK, ITS RELATION TO PLASMA EPINEPHRINE LEVEL AND THE MECHANISM OF ITS PROTECTION BY GLUCOCORTICOID

Tokuro Fukuda, Hiroyuki Okuma and Namiyo Hata

Department of Physiology, Chiba University School of Medicine, Chiba.

Since the time of ERLANGER and GASSER (1919), it has been repeatedly confirmed that the continuous intravenous infusion of epinephrine at relatively high rates causes an irreversible shock in dogs. Although the threshold rate of epinephrine infusion necessary for the induction of shock within a few hours differs according to authors, it is usually more than 5 µg/kg/min, which is a little over the maximum rate of epinephrine secretion possible in this animal. Noxious effects of epinephrine upon the cardio-vascular system are determined by the level of plasma epinephrine in arterial blood. This depends not only upon the rate of epinephrine infusion, but also upon the rate of its removal from the circulation which is known to proceed rapidly. It is well established that the rise in plasma epinephrine level attains a steady state soon after the beginning of epinephrine infusion and this level is maintained during an infusion period of a few hours. This, however, is based upon experiments with epinephrine infusion at relatively low rates (less than 5 µg/kg/min). Whether the circumstance is the same in cases of epinephrine infusion at higher rates which inevitably induce shock, has not been examined. The present experiments were designed to determine the plasma level of epinephrine during the course of the development of epinephrine shock and to examine the effect of glucocorticoid upon it, since glucocorticoid is known to protect animals against epinephrine shock.

METHODS

Mongrel dogs of both sexes, weighing about 10 kg were used in the present experiments. The animals were sedated with Nembutal (30 mg/kg, i.m.) and infused with epinephrine (Adrenalin chloride, Sankyo) into the femoral vein employing a motor driven syringe. Adrenalectomized dogs were maintained with DCA (1 mg per day) for more than one week after the operation. Blood samples were obtained from the femoral artery. Plasma catecholamine (epinephrine) was determined after the method of Weil-
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Malherbe & Bone with an additional purification of the samples through a column of Dowex 50 at pH 3.06. Usually 1 ml of plasma sample was sufficient for analysis, since the levels of plasma epinephrine were extremely high. The mean values cited in the text are given with ± SE. Blood sugar was determined after the method of Somogyi.

RESULTS

*Plasma epinephrine level of arterial blood during the course of epinephrine shock.*

With an infusion rate of 5.0 μg/kg/min the rise in plasma epinephrine level attained a steady state within 15 minutes after starting the intravenous infusion and this level (19±1.5 μg/l, n=5) was maintained throughout the infusion period of 4 hours. Shock did not occur in this series of experiments and the animals tolerated the infusion well. With an infusion rate above this, for instance 10 μg/kg/min, shock invariably ensued within a 4 hour infusion period. Thereby, the plasma epinephrine level could not remain at the high initial stationary level (101±4 μg/l, n=8) and rose progressively (FIG. 1A). At the same time, signs of central depression, such as myosis and prostration appeared and defecation followed. Apparent shock was observed only when the plasma epinephrine level attained high values such as 300–400 μg/l. In the preterminal period often a prompt rise of epinephrine level to enormous high values (more than 1000 μg/l) was observed. These values could not be expected, when the infused epinephrine was diluted with the normal circulating blood volume. It might be an artifact due to an abrupt reduction of venous return in the preterminal period.

The difficulty in removing epinephrine encountered in the case of infusion

**Fig. 1.** Plasma epinephrine level during the course of epinephrine shock.
at the rate of 10 μg/kg/min was reflected in the relationship of plasma epinephrine level in the initial stationary state to the rate of epinephrine infusion (Fig. 2). The values obtained at an infusion rate of 10 μg/kg/min were much higher than that expected from the linear relation observable at lower infusion rates, i.e. less than 3 μg/kg/min. Together with this, it became difficult to maintain the initial rate of epinephrine removal long enough and the secondary rise ensued.

The ability of the liver in removing epinephrine. It is well known that the liver is one of major sites of epinephrine removal. Whether an eventual limit in the ability of the liver to remove circulating epinephrine would be responsible for the secondary progressive rise in plasma epinephrine level above mentioned was tested. For this purpose, epinephrine was infused through the splenic vein directly to the liver at the same rate (10 μg/kg/min). As shown in Fig. 3A, the initial stationary level of plasma epinephrine was far lower than that observed in the case of intravenous infusion and this level (52±1.7 μg/l, n=5) was maintained throughout the infusion period of 4 hours. Shock did not occur and the animal tolerated the infusion well. Thus it is inferred that the liver is able to remove epinephrine rapidly in keeping the plasma epinephrine level low enough to avoid shock, when it receives epinephrine directly from the portal flow. This capacity of liver was found not to be impaired even in severe anoxemia. As shown in Fig. 3B, inhalation of 8% O₂ in N₂ did not influence the plasma epinephrine level.
Fig. 3. Effect of intraportal infusion of epinephrine on plasma epinephrine level, blood sugar concentration and mean arterial blood pressure.

Limiting factors in epinephrine removal. The limit observed in epinephrine removal in the case of intravenous infusion, therefore, may possibly be due to the presence of factors which reduce the blood flow to the liver. In order to test the significance of portal blood flow, the effect of occlusion of the

Fig. 4. Effect of occlusion of the superior mesenteric artery and the hepatic artery on the manifestation of epinephrine shock.
superior mesenteric artery just prior to the beginning of intravenous epi-
epinephrine infusion (10 µg/kg/min) was examined. As shown in Fig. 4A, the
secondary rise of plasma epinephrine level appeared far earlier than in controls
and the animal became easily shocked. On the other hand, ligation of the
hepatic artery did not substantially influence the plasma epinephrine level or
the course of shock (Fig. 4B). Thus, the reduction of portal blood flow was
found to be the major factor in decreasing the hepatic removal of epinephrine.
The increasing difficulty in removing epinephrine with an increasing rate of
infusion and the appearance of the secondary rise in the plasma epinephrine
level observed in the case of intravenous infusion should, therefore, be at-
tributed to a reduction of portal blood flow. As will be discussed later, this
has been amply confirmed to be the case.

Significance of glucocorticoid for epinephrine removal. Although glucocorticoid
is known to afford protection against epinephrine shock5), the underlying
mechanism remains unelucidated. Therefore, it was examined whether gluco-
corticoid has any effect upon the epinephrine removing capacity in case of
intravenous epinephrine infusion at a rate of 10 µg/kg/min. As depicted in
Fig. 1B pretreatment with Decadron (dexamethasone-21-phosphate: 4 mg i. m.,
one day before) lowered the initial stationary level of plasma epinephrine and
together with this, its secondary rise and shock were prevented. Thereby,
the blood sugar level was maintained high throughout the infusion period,
indicating the absence of the derangement of carbohydrate metabolism. Fig.
5 illustrates the effect of glucocorticoid upon the initial stationary level of
plasma epinephrine. In spite of a high infusion rate of 10 µg/kg/min, the
plasma level was reduced to that corresponding to an infusion rate of 5 µg/

![Fig. 5. Effect of glucocorticoid on the initial stationary level of plasma epinephrine after intravenous infusion of epinephrine at a rate of 10 µg/kg/min.](image-url)
kg/min in untreated animals. On the other hand, adrenalectomy reduced the ability of epinephrine removal and not only was the initial stationary level of plasma epinephrine raised (Fig. 5), but also the progressive rise of plasma epinephrine level was promoted and the animals became easily shocked (Fig. 1C). The blood sugar concentration often dropped to a convulsion level, and the intravenous infusion of 20% glucose solution (20 ml or more) for prevention of the convulsion could neither prevent the shock, nor reduce the elevated plasma epinephrine level. The deterioration of carbohydrate metabolism leading to a depletion of liver glycogen and hypoglycemia in the absence of glucocorticoid by itself did not seem to be responsible for the diminished ability of epinephrine removal. The effect of glucocorticoid seemed to be concerned mostly with hepatic epinephrine removal, since the plasma epinephrine level in the case of intra-portal infusion was also markedly reduced (16±6 µg/l, n=4) in comparison with that in the controls.

Autopsy findings in epinephrine shock. Epinephrine shock was found to be induced only when the plasma epinephrine level enormously high, such as 300-400 µg/l. Direct noxious effects upon the cardiovascular system would naturally be expected. On gross examination, subepicardial and subendocardial hemorrhage of the left ventricle and an accumulation of pericardial effusate were most prominently and constantly observed. The effusate was colorless clear and contained protein (3.5-4.3%). Its amounts reached 30 ml and the pericard was strained. On the other hand, the well documented hemorrhagic

TABLE 1.
Occurrence of hemorrhagic lesion of intestinal mucosa in epinephrine shock.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Cases</th>
<th>Hemorrhagic Lesions</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>−</td>
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<tr>
<td>May–June (1965)</td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>6</td>
<td>5</td>
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<tr>
<td>Adrenx.</td>
<td>5</td>
<td>4</td>
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<tr>
<td>July–August</td>
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<tr>
<td>Normal</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Adrenx.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Sept.–Oct.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Adrenx.</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Nov.–Dec.</td>
<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Adrenx.</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>March–April (1966)</td>
<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Adrenx.</td>
<td>4</td>
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</tr>
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lesion of the intestinal mucosa was, in our series of over 50 autopsies, not a constant finding and absent particularly in experiments done during the hot summer season (Table 1).

In cases of epinephrine infusion for a 4 hour period in which the plasma epinephrine level remained below 50 μg/1, i.e. with an infusion rate of 5 μg/kg/min or of 10 μg/kg/min following treatment with Decadron, no cardiac involvement was observed at autopsy and the pericardial effusate was less than 10 ml.

DISCUSSION

Poole and Watts found that during the constant infusion of epinephrine at a rate of 5 μg/kg/min in dogs, blood epinephrine concentration reached a maximum level within 5-10 minutes after the infusion was started and remained at this level throughout the period of 260 minutes. These authors failed to find the appearance of secondary rise in plasma epinephrine concentration, since they did not examine the effect of infusion at higher rates. When 10 μg/kg/min epinephrine was infused, enormously elevated plasma level of epinephrine up to 300-400 μg/1 was attained, and a typical epinephrine shock, an increasing refractoriness to the pressor effect of epinephrine, ensued. Whether the secondary rise in plasma epinephrine level occurs or not seemed to depend on the height of the initial stationary level of plasma epinephrine. In a variety of cases in which the initial level was lower than 50 μg/1, no secondary rise followed. Poole and Watts estimated the arterial blood epinephrine level corresponding to the lowest rate of infusion which has ever been reported to produce shock in dogs (3.4 μg/kg/min, Freeman et al.) as 39 μg/1 by bioassay method. Although this value is much higher than the normal level (less than 1 μg/1), it does not seem to be responsible for the induction of shock. Freeman et al. infused epinephrine at rates ranging from 3.4 up to 16.4 μg/kg/min. In their data, in the case of infusion at a rate of 3.4 μg/kg/min, it was not clear whether the animal died or was sacrificed. At any rate two cases of infusion at a rate of 4.5 μg/kg/min survived a 3 hour period of infusion. It is noteworthy that difficulty in removing epinephrine and an attendant possibility of the induction of shock appears only when epinephrine is infused at rates higher than the maximal secretion rate of endogenous epinephrine ever observed, i.e. 5 μg/kg/min.

Among the various sites of epinephrine removal, the liver seems to play the most dominant role, especially when large amounts of epinephrine is given over long periods. In this respect it was observed in one case that the removal of epinephrine in hind limb circulation, as estimated by A-V difference of plasma epinephrine concentration, completely ceased at relatively early stage during the course of intravenous epinephrine infusion at a rate of 10
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µg/kg/min. Changes in portal blood flow, which may affect hepatic removal of epinephrine, might be involved in the appearance of the secondary rise of plasma epinephrine level following a high rate infusion of epinephrine. The fact that physiological doses of epinephrine increase but pharmacological doses decrease the splanchnic blood flow(7) may support the above inference. It was also reported by LILLEHEI et al.(9) that the blood flow through the superior mesenteric artery reduced progressively almost to zero during the course of epinephrine shock.

The effect of glucocorticoid in preventing epinephrine shock has been difficult to interpret(10). It is generally assumed that glucocorticoid might protect peripheral vascular beds from damaging effects of excessive catecholamines (LEVINE and GOLDSTEIN(10)). However, there was no appreciable difference in the degree of hemorrhagic lesions of the intestinal mucosa between intact and adrenalectomized animals at autopsy. Moreover, the intestinal involvement was absent, even in adrenalectomized dogs, in epinephrine shock induced during the hot summer season. These observations are hard to reconcile with the above assumption. In this respect the here demonstrated potentiating effect of glucocorticoid upon epinephrine removal will provide a much more satisfactory explanation for its protective effect against epinephrine shock. The potential ability of the liver in removing epinephrine requires the presence of glucocorticoid. The detailed mechanism awaits further clarification.

The deleterious effect of an extremely high plasma epinephrine concentration upon the cardio-vascular system was most marked in the heart. That the hemorrhagic lesion of the intestinal mucosa is not a constant finding has also been noticed by LEWIS and NICKERSON(11). Why this lesion was absent especially in experiments during the summer season is not clear at present. At any rate, contrary to the current view(7,8), the intestinal involvement is not an absolute requisite for the induction of epinephrine shock. It may be here mentioned that the hematocrit rose soon after beginning epinephrine infusion and remained stationary throughout the infusion period whether shock occurred or not. The initial rise might be due to contraction of the spleen. The cardiac damage together with an eventual tamponade effect of the acute accumulation of pericardial effusate (EICHLER and BARFUSZ(12)) should also be considered as one of the causalities of epinephrine shock.

SUMMARY

The induction of epinephrine shock by the intravenous infusion of epinephrine (10 µg/kg/min) was characterized by an inability to maintain the initial stationary level of plasma epinephrine, leading to a progressive rise of epinephrine level up to a very high values (300–400 µg/l) within a few hours. When epinephrine was infused intra-portalally at the same rate, the arterial plasma
ne attained a far lower initial level and neither a secondary rise nor
urred during the infusion period of 4 hours. Thus the secondary
asma epinephrine level indicating the limit of epinephrine removal
ne of the intravenous infusion was found to be due to circumstances
ish participation of the potential ability of the liver in removing
ue. The well documented reduction of splanchnic blood flow with a
ogic dose of epinephrine has been suggested as the cause. The
rise in plasma epinephrine level and the attendant shock were not
ith intravenous infusion at rates less than 5 μg/kg/min during a
ision period.

Administration of glucocorticoid markedly potentiated the epinephrine
oving capacity of the liver, while adrenalectomy reduced it. This might
vide a satisfactory basis for the interpretation of the protective effect of
ucocorticoid against epinephrine shock.

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