Epinephrine Levels in the Peripheral Blood During Irreversible Hemorrhagic Shock in Dogs

By Carl J. Greever, M.D., and Daniel T. Watts, Ph.D.

Dogs were bled to a mean arterial pressure of 40 mm. Hg until 10 per cent of the shed blood had automatically reinfused from an elevated reservoir. The remaining blood was then rapidly infused intravenously. The procedure was fatal to all 13 dogs. Arterial blood epinephrine levels were followed during the time of hemorrhage and the post-hemorrhagic survival period in 9 of these animals. Arterial blood epinephrine levels in the 9 dogs increased from control values of less than one μg./L. to a maximum of 29 μg./L. during early hemorrhage, and then decreased during the period of spontaneous reinfusion to 7.5 μg./L. After complete reinfusion the blood pressure returned to normal, and epinephrine disappeared from the circulation. The blood pressure then gradually failed under normovolemic conditions, and the animals died in shock after an average of 220 minutes. Blood samples obtained immediately before death when the mean arterial pressure was 45 mm. Hg contained only 3.5 μg./L. epinephrine.

Intense peripheral vasoconstriction is characteristic of all but the terminal stage of shock. Harkins, in summarizing his extensive review on the subject, described shock as a progressive vasoconstrictive oligemic anoxia. Freeman et al. emphasized the role of epinephrine not only in producing vasoconstriction but in causing shock itself. Several investigators have produced shock in dogs by the intravenous infusion of epinephrine. It has also been shown that adrenergic blocking agents protect dogs during hemorrhagic shock.

The epinephrine content of the adrenal vein blood is increased during shock in dogs, and the epinephrine content of the adrenal gland is depleted. With the development in recent years of more sensitive methods for the estimation of epinephrine it has been shown that the epinephrine content of peripheral arterial blood is significantly increased during hemorrhagic hypotension and hemorrhagic shock of short duration in dogs. Watts and Bragg have shown that arterial blood epinephrine levels of dogs decrease slowly from an initial maximum when the mean arterial pressure is held at 40 mm. Hg, indicating an exhaustion of the sympathoadrenal system. In the present experiments, the arterial blood epinephrine levels have been followed in dogs bled to a mean arterial pressure of 40 mm. Hg until 10 per cent of the shed blood had automatically reinfused from an elevated reservoir. The remainder of the blood was then rapidly infused and epinephrine levels followed until the animals died after 1 to 10 hours. The epinephrine content of the adrenal glands of the dogs dying of hemorrhagic shock was determined for comparison to the epinephrine content of the adrenals of control animals.

Methods

Mongrel dogs weighing 11 to 17 Kg. were anesthetized with 30 mg./Kg. sodium pentobarbital given intravenously. One femoral artery was cannulated for blood pressure recordings with a Statham transducer and Sanborn recorder. The other femoral artery was cannulated with a poly-
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ethylene catheter (0.070 in. I.D.) leading to a 1,000 ml. polyethylene reservoir in which the blood level was kept 51.3 cm. above the heart. That height was equivalent to 40 mm. Hg. The blood was stirred with a magnetically driven, polyethylene-covered rod and kept at 37 to 38 C. with an infra-red lamp. The dogs were given 4 mg./Kg. heparin sodium and 10 mg. heparin sodium was added to the reservoir. Blood samples were obtained from the femoral artery by means of the indwelling catheter. Respiration was recorded with a pneumograph. Pulse rates and hemorrhage volumes were noted at about 10 minute intervals.

After obtaining control blood samples, hemorrhage was started into the reservoir. Arterial blood pressure was maintained at 40 mm. Hg until 10 per cent of the maximum volume of blood collected in the reservoir had spontaneously returned to the femoral artery. The reservoir was then connected to the femoral venous cannula and the remainder of the shed blood was infused within 3 to 6 minutes. Serial blood samples were collected and other data recorded until the dogs died after an average of 186 minutes.

Blood epinephrine concentration was determined by the bioassay method of Gaddum and Leinbeck as modified by Franko et al. The rat uterus, stimulated by the timed, automatic addition of carbachol, was used as the test object in a 3 ml. muscle bath. The method is specific for epinephrine and can be used for detection in whole blood of concentrations as low as 1 /ug./L. epinephrine, depending on the sensitivity of the uteri. Samples as small as 0.3 ml. can be used. From 93 to 99 per cent of the epinephrine added to whole blood 60 seconds before assay can be recovered by the method. Blood epinephrine levels were estimated at about 10 minute intervals during the post-hemorrhage period. Final blood samples were obtained during the period of cardiovascular collapse and impending death when the blood pressure was as near 40 mm. Hg as possible for comparison to the samples obtained during the earlier hemorrhage at this same pressure.

RESULTS

Figure 1 shows a typical experiment in which a 16 Kg. male dog was bled to an arterial blood pressure of 40 mm. Hg, and maintained at this level for 135 minutes. At this time, 10 per cent of the shed blood had spontaneously reinfused, and the remainder was then rapidly infused intravenously. The post-hemorrhagic survival time for this animal was 420 minutes. The epinephrine concentration of femoral arterial blood rose rapidly during early hemorrhage, gradually declined during the period of spontaneous reinfusion, and essentially disappeared from the circulation when the blood was reinfused and blood pressure returned to a control level. The duration and volume of hemorrhage are shown on the middle graph. The two upper graphs of figure 1 show that respiratory and pulse rates were elevated throughout the periods of hemorrhage and post-hemorrhagic shock until shortly before cardiovascular collapse and death.

Table 1 summarizes the data from experiments on 9 dogs, similar to those shown in figure 1. Femoral arterial blood epinephrine levels rose from undetectable control values of less than one /ug./L. to a mean of 29 /ug./L. during early hemorrhage. This level had decreased to 7.5 /ug./L. after an average hemorrhage time of 123 minutes when 10 per cent of the shed blood had spontaneously reinfused from the reservoir. Rapid infusion of the remainder of the blood returned blood pressure

![Figure 1. Arterial blood epinephrine levels during hemorrhage and post-hemorrhagic shock in a 16.0 Kg. male dog.](http://circres.ahajournals.org/)

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TABLE 1.—Arterial Blood Epinephrine Levels during Hemorrhagic Shock in Dogs

<table>
<thead>
<tr>
<th>Wt. (Kg.)</th>
<th>Hem. vol. (ml./Kg.)</th>
<th>Hem. time (min.)</th>
<th>Post-hem. survival time (min.)</th>
<th>Epinephrine, µg./L. as base</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.0±0.9*</td>
<td>46±2.5</td>
<td>123±7.7</td>
<td>220±37</td>
<td>Control Early hem. Late hem. After reinfusion At failure Bl. pres. at failure (mm. Hg)</td>
</tr>
<tr>
<td></td>
<td>Interpretation</td>
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</tr>
<tr>
<td>p compared to control value of 0</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.1</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of mean for nine dogs.
† Epinephrine concentration below the sensitivity of the method of assay, i.e. about 1 µg./L.

The data in Table 2 show that the mean epinephrine content of the adrenal glands of control dogs was 0.76 mg./Gm. of adrenal tissue, wet weight, as compared to 0.32 mg./Gm. in adrenal glands removed from the dogs succumbing to hemorrhagic shock. This is a significant difference and shows that the epinephrine content of the adrenal glands was depleted during hemorrhagic shock.

**DISCUSSION**

The increase in peripheral arterial blood epinephrine levels, from less than one µg./L. to 29 µg./L. when dogs were bled, to 40 mm. Hg arterial pressure, probably produces significant physiological effects on the cardiovascular system. Though it is difficult to determine peripheral blood epinephrine levels at rest, the best estimates indicate that it is the range of 0.2 to 0.3 µg./L., so the increase observed during shock represents a one hundred fold increase. This increased amount in circulating epinephrine could account for the intense vasoconstriction of early shock, and the fact that adrenergic blocking agents protect dogs during hemorrhagic shock.

The steady decrease in peripheral blood epinephrine during the one to three hour period of hemorrhage at 40 mm. Hg is an indication of exhaustion of the sympathoadrenal system. Reinfusion of the blood returns the arterial pressure to approximately control levels, removes the stimulus of hypotension, and the epinephrine disappears from the circulation during the post-hemorrhagic survival period. When the blood pressure again failed under normovolemic conditions, the blood epinephrine increased, but only to a mean of 3.5 µg./L. as compared to 29 µg./L. for similar levels of blood pressure at the beginning of hemorrhage. This, plus the fact that the epinephrine content of the adrenal glands of the shocked dogs was only 42 percent as great as that in the glands from control dogs, is further indication of sympathoadrenal exhaustion during irreversible hemorrhagic shock in dogs.

Rat uteri used in these experiments for bioassay are about 100 times more sensitive to epinephrine than to levarterenol, so that

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most of the measured effect was due to epinephrine. Repeated attempts to qualitatively demonstrate an increase in levaterenol with rat colons, which would have disclosed about 50 μg/L levaterenol, were unsuccessful. This is in accord with the recent work of Manger et al. who used fluorimetric procedures to show that during hemorrhagic hypotension in dogs the epinephrine content of plasma increased from control levels of 1.0 to 7.8 μg/L, whereas plasma levaterenol increased from 2.5 to only 3.6 μg/L.

SUMMARY
Peripheral arterial blood epinephrine levels were determined in nine dogs during the various stages of the development of irreversible hemorrhagic shock. Epinephrine concentration in the arterial blood increased from control values of less than one μg/L to a maximum of 29.0 μg/L when the arterial blood pressure was held at 40 mm Hg. This represents about a hundred-fold increase in the epinephrine level in the peripheral arterial blood. This circulating epinephrine could account for the intense vasoconstriction in the early phases of shock and the fact that adrenergic blocking agents protect dogs during hemorrhagic shock.

SUMMARIO IN INTERLINGUA
Nivellos de epinephrina in sanguine periphero-arterial esseva determinate in 9 canes durante le varie stadios in le disveloppamento de irreversibile choc hemorrhagic. Le concentrazione de epinephrina in le sanguine arterial montava ab valores de controlo de minus que 1 μg/L usque al maximu de 29.0 μg/L, quando le tension de sanguine arterial eseva tenite a 40 mm de Hg. Isto representa un augmento quasi centuplo del nivello de epinephrina in le sanguine periphero-arterial. Iste circulante epinephrina explixa possibilemente le intense vasoconstriction in le prime phases de choc e etiam le facto que agente de blocage adrenergic protege le canes in stato de choc hemorrhagic.

REFERENCES
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