Norepinephrine and Epinephrine Effect on Renal Hemodynamics

With Particular Reference to the Possibility of Vascular Shunting and Decreasing the Active Glomeruli

By John H. Moyer, M.D., and Carroll A. Handley, Ph. D.

Because increasing evidence suggests that renal ischemia resulting from various stress states plays a major role in the etiology of lower nephron nephrosis, the renal hemodynamic effect of continuous infusions of norepinephrine and epinephrine was studied in dogs. The primary response was a decrease in renal blood flow. As the rate of infusion was increased, a progressive decrease in the number of functioning glomeruli followed. Despite the decrease in renal blood flow, there is no evidence to indicate arteriovenous shunting mechanisms.

Hemorrhagic or traumatic shock causes a disproportionate decrease between renal blood flow and cardiac output. This probably represents a protective mechanism for redistribution of blood to more vital areas. Increasing evidence suggests that the renal ischemia thus produced plays a major role in the etiology of lower nephron nephrosis and its attendant renal insufficiency. The alterations in renal hemodynamics under these circumstances may be mediated via the sympathetic nervous system directly or indirectly through the release of epinephrine or other vasopressor substances, since peripheral vasoconstriction due either to sympathomimetic drugs or to sympathetic nerve activity depresses renal blood flow. Associated with the decrease in renal blood flow there may be a decrease in glomerular filtration rate. Whether or not this is due to a proportional decrease in filtration in all glomeruli, or due predominantly to a decrease in the number of active nephrons, has not been clearly demonstrated. Some investigators have presented evidence to indicate that all glomeruli are continuously perfused with blood and disclaim the possibility that the number of active nephrons can either be increased or decreased in mammals. Others have found evidence to suggest changing numbers of active nephrons. Trueta has gone so far as to suggest that under conditions of stress, entire areas of the renal cortex may be shunted out of the circulation due to subcortical or juxtamedullary arteriovenous bypasses. The following report is concerned with an evaluation of the renal hemodynamic effects of epinephrine and norepinephrine. Evidence is presented to indicate that the number of active glomeruli is decreased following the administration of both epinephrine and norepinephrine to dogs, but at the same time there is no evidence to indicate arteriovenous shunting mechanisms.

Methods

Two groups of female dogs weighing between 10 and 20 Kg. were studied. One group consisting of nine dogs received a constant infusion of epinephrine (1:100,000 dilution) and seven received an infusion of norepinephrine* (1:100,000 dilution). Four dogs in the first group and three in the second were trained dogs and received no anesthesia. The others were anesthetized with chloralose (100 mg. per Kg.), which seems to have a negligible effect on renal function. A venous catheter was passed through the external jugular vein into the left renal vein with the aid of a fluoroscope so that renal extractions (A-V) of creatinine and paraaminohippurate (PAH) could be determined. Renal plasma flow (RPF) could thus be calculated by the Fick principle \( RPF = \frac{UV}{A-V} \) using both creatinine and PAH extractions. Glomerular filtration rate (GFR) was determined by the creatinine clearance (GFR = total urinary excretion of creatinine over 30 minutes).

* Supplied through the courtesy of Mr. Kenneth M. Smoot, Winthrop-Stearns, Inc.

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UV/A). Maximum tubular reabsorptive capacity for glucose (Tm\textsubscript{g} = GFR \times A - UV) was determined. Because glucose has been observed to depress paraaminohippurate extraction\textsuperscript{18} by the renal tubules, control values for glomerular filtration rate (creatinine clearance) and renal plasma flow (paraaminohippurate and creatinine extractions) were established before and after glucose was added to the infusing solution. After the control periods were completed, the infusion of epinephrine or norepinephrine was started. The rate was regulated so that there was a definite and sustained increase in systemic blood pressure of 10 to 20 mm. Hg. At least two periods were then run after which the infusion rate was increased and the process repeated. Studies on successive periods during increasing increments of sympathetic effector organ stimulation were thus obtained. Bladder washes of distilled water were used in all but two dogs (Epi. 8 and 9) in group I. In these the ureters were catheterized in order that renal function could be studied on each kidney for comparative purposes. A needle in the femoral artery was connected to a manifold for withdrawing arterial blood samples and recording mean blood pressures. Chemical methods and technics employed have been described.\textsuperscript{13}

### Results

During control periods, the values for glomerular filtration rate, renal plasma flow and renal plasma flow as determined by the paraaminohippurate method are the ones used in the present report. When epinephrine and norepinephrine were administered, the renal plasma flow decreased progressively and inversely to the rise in blood pressure as the rate of infusion was increased. Initially, the glomerular filtration rate changed very little resulting in an increased filtration fraction. As the renal plasma flow decreased further, the glomerular filtration rate dropped off equally and progressively. A representative case showing this response is seen in table 1. This pattern

**Table 1.—Response of Kidney Functions to Increasing Rate of Infusion of Intravenous Epinephrine**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>UV/min.*</th>
<th>GFR†</th>
<th>RPF$</th>
<th>RBF$</th>
<th>FF</th>
<th>MBP**</th>
<th>RVR††</th>
<th>PAH Ext.‡‡</th>
<th>Hct.§§</th>
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<td></td>
<td></td>
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<tr>
<td>Cont.</td>
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<td>52</td>
<td>196</td>
<td>322</td>
<td>.27</td>
<td>115</td>
<td>.36</td>
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<tr>
<td>(10\textgamma/min.)</td>
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<td>52</td>
<td>126</td>
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<tr>
<td>(30\textgamma/min.)</td>
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<tr>
<td></td>
<td>1.2</td>
<td>50</td>
<td>155</td>
<td>272</td>
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<td>80</td>
<td>.29</td>
<td>75</td>
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* UV = Urine Volume—cc./min.
† GFR = Creatinine Clearance—glomerular filtration rate expressed in cc./minute.
‡ RPF = Renal Plasma Flow = A-V (PAH)' RPF
§ RBF = Renal Blood Flow = 1-Hct'
∥ FF = Filtration Fraction = GFR RPF.
** MBP = Mean Blood Pressure—Direct arterial mercury manometer.
†† RVR = Renal Vascular Resistance = MBP RBF.
‡‡ PAH Ext. = A-V A
§§ Hct = Hematocrit.
was seen in eight out of nine dogs which received epinephrine, and four out of seven which received norepinephrine. In the others, the filtration fraction did not change significantly since both glomerular filtration rate and renal plasma flow decreased proportionally, both initially and with the more rapid rate of infusion.

The effects of epinephrine (dogs Epi. 1 to Epi. 9) and norepinephrine (dogs Nor. 1 to Nor. 7) on all renal functions studied are summarized in Table 2. The results are expressed in percentage of control values considering the control figures as 100 per cent. Values which demonstrated definite changes in renal function but at the same time were most reproducible during successive study periods, were the ones chosen for this table. The relationship between glomerular filtration rate and tubular maximum for glucose is graphed in figure 1. The study periods not included in Table 2 are also included in this graph. There appeared to be no difference in response between anesthetized and unanesthetized dogs, or between left (renal vein catheterized) and right (uncatheterized) kidneys (dogs Epi. 8 and 9).

Depression of the glomerular filtration rate was associated with a parallel decrease in urine volume (UV) and except for a few instances, the ratio GFR:UV was quite constant. During the course of increasing the rate of infusion of epinephrine and norepinephrine, maximal tubular transport of glucose did not seem to be closely related to renal plasma flow, although there were similar directional changes. However, there was a close relationship between the reduction in tubular maximum and glomerular filtration rate with the reduction in the former lagging somewhat behind the latter. This resulted in a slightly reduced, but otherwise constant, GFR: TmG ratio. When the tubular maximum is plotted against glomerular filtration rate during increasing rates of infusion there is

<table>
<thead>
<tr>
<th>Dog No.*</th>
<th>Urine†</th>
<th>GFR†</th>
<th>RR†</th>
<th>RF†</th>
<th>FF†</th>
<th>Tmg†</th>
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<th>MBP†</th>
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</table>

* Epi. 1–9 received epinephrine infusion and Nor. 1–7 received norepinephrine infusion.
† See table 1 for abbreviations.
‡ Tubular maximum for glucose = GFR X Art. Cone. — UV

lar transport of glucose did not seem to be closely related to renal plasma flow, although there were similar directional changes. However, there was a close relationship between the reduction in tubular maximum and glomerular filtration rate with the reduction in the former lagging somewhat behind the latter. This resulted in a slightly reduced, but otherwise constant, GFR: TmG ratio. When the tubular maximum is plotted against glomerular filtration rate during increasing rates of infusion there is
little scatter, and the mean lies just slightly above the true median (fig. 1). At the point where renal function is markedly depressed, the tubular maximum for glucose, renal plasma flow, and glomerular filtration rate appear to have decreased to about the same degree (table 2).

In order to evaluate the effect of adrenergic blockade, imidazole hydrochloride (Regitine)* was administered to seven dogs, following which norepinephrine was administered to two and epinephrine to five. Infusion rates were those which had previously caused a decrease in renal plasma flow to 70 per cent or less of the control values. After the blockade, the infusion of norepinephrine had no significant effect on blood pressure or renal function. However, epinephrine resulted in a marked drop in blood pressure (epinephrine reversal). The drop was so marked in two of the five dogs that accurate renal function studies were not possible due to the decreased filtration pressure and resultant oliguria. The vasodilatory effect on the other three dogs was not as marked. One of these showed essentially no change, but the other two experiments were quite instructive and the results are consequently recorded in table 3. In these the renal plasma flow did not change significantly but the glomerular filtration rate decreased about 50 per cent, most likely a reflection of low hydrostatic pressure within the glomeruli. Both dogs showed a clear-cut reduction in functioning tubular mass when

![Graph showing relationship of glomerular filtration rate to maximum tubular reabsorption of glucose.](http://circ.ahajournals.org/)

**Fig. 1.** Relationship of glomerular filtration rate to maximum tubular reabsorption of glucose, expressed in per cent of control value. ○, GFR is plotted against $T_{mg}$ after epinephrine infusion, same study periods as recorded in table 2. ●, GFR is plotted against $T_{mg}$ after norepinephrine infusion, same study periods as recorded in table 2. ×, GFR is plotted against $T_{mg}$ after epinephrine and norepinephrine. These study periods are from the same experiments but represent study periods during varying rates of infusion not included in table 2.

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>UV (cc./min.)</th>
<th>GFR (cc./min.)</th>
<th>RPF (cc./min.)</th>
<th>RBF (cc./min.)</th>
<th>FF (mg./min.)</th>
<th>$T_{mg}$ (cc./min.)</th>
<th>GFR/$T_{mg}$ (cc./min.)</th>
<th>MBP (mm. Hg)</th>
<th>RVR (mm. Hg)</th>
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*Supplied through the courtesy of Dr. Jock L. Graeme, Ciba Pharmaceutical Products, Inc.

**Table 3.** Response of Renal Hemodynamics to Epinephrine before and after Adrenergic Blockade

*See table 1 for key to abbreviations.
†Two mg. per Kg. body weight.

In both dogs there was a parallel reduction in GFR and $T_{mg}$ after epinephrine alone due to a decrease in the number of active nephrons. After adrenergic blockade the vasoconstrictive response to epinephrine was replaced by vasodilatation with a drop in blood pressure. Although the GFR decreased, the $T_{mg}$ did not change since the number of active nephrons was unaltered and all tubules continued to transport glucose.
epinephrine was given alone. This did not occur when the epinephrine was preceded by sympathetic blockade (Regitine) despite the 50 per cent decrease in glomerular filtration rate.

**Discussion**

The observations in these experiments indicate that there is no essential difference in the response of the kidney to epinephrine and its possible precursor, norepinephrine, and that the first and most prominent effect is on the efferent arterioles, thus increasing the renal vascular resistance in this segment. As a result, the renal plasma flow initially decreases in the presence of a maintained glomerular filtration rate, and an increase in the filtration fraction. This has also been noted in man following the administration of epinephrine and phenylephrine (Neosynephrin). In the present experiments, the maximum tubular reabsorption of glucose did not change significantly as long as the glomerular filtration rate was maintained despite a decrease in renal blood flow. This indicates no change in the number of tubules actively reabsorbing glucose from the glomerular filtrate.

As the infusion rate is increased and the vasoconstrictive effect on the kidney becomes more prominent, the glomerular filtration rate decreases (table 1 and 2) in proportion to the decrease in renal plasma flow. In a few animals this proportionate decrease in glomerular filtration rate and renal plasma flow occurs initially without the primary decrease in renal plasma flow alone and its resultant increase in filtration fraction. Regardless of whether this proportionate decrease in renal plasma flow and glomerular filtration rate occurs initially or late, when it does occur it suggests that the afferent arterioles share in the increased vasoconstriction, and that a significant number of glomeruli may be eliminated from the renal circulation. This concept is supported most emphatically when one notes the relationship between glomerular filtration rate and maximum tubular reabsorption of glucose (tables 2 and 3 and fig. 1). At first the ratio GFR:Tm\textsubscript{e} decreases slightly and then it remains constant while both the filtration rate and tubular maximum decrease to a parallel degree. One must conclude that a reduction in equal numbers of filtering glomeruli and tubules actively transporting glucose has taken place because the concept of measuring tubular maximum is based on the fact that the blood level of glucose be maintained high enough to insure a concentration in the glomerular filtrate far in excess of the amount that the tubules are able to transport. The difference between the amount of glucose filtered and that lost in the urine represents the amount reabsorbed or transported by the tubules. Despite the fact that the glomerular filtrate might be reduced in some of the nephrons, there would remain adequate glucose to continue to measure maximum reabsorptive ability of these tubules. Under such circumstances, if the glomerular filtration rate is reduced but at the same time all the tubules continue to transport glucose at a maximum rate, then the ratio of filtration rate to tubular maximum must decrease. In the present study, the tubular maximum did not remain constant, as noted above, but rather the glomerular filtration rate and tubular maximum decreased together and their ratio remained constant, indicating a decrease in the number of active nephrons. The small but consistent decrease in the ratio because of the greater initial decrease in glomerular filtration rate does in fact indicate that some of the glomeruli are filtering at a reduced rate rather than being constricted out of the circulation. These concepts are further confirmed by table 3, showing the results of giving these animals epinephrine with the usual reduction in filtration rate and tubular maximum. However, when this was repeated following an adrenergic blocking agent, a generalized vasodilatation with a drop in blood pressure (epinephrine reversal) was noted. Apparently the kidney shared in this decrease in peripheral resistance, since the renal blood flow was not altered and the glomeruli were not eliminated from the renal circulation as they were before the blockade. However, due to a drop in systemic blood pressure, and consequently glomerular filtration pressure, the glomeruli now filtered at a reduced rate and the glomerular filtration rate decreased significantly. This resulted in a drop in the filtration fraction. At the same time,
nearly all tubules continued to reabsorb glucose. As a result, the GFR:TMg ratio decreased greatly (dogs Epi. 1 and Epi. 5, table 3). We can therefore conclude that epinephrine and norepinephrine are able to cause renal vasoconstriction to the extent that glomeruli are eliminated from the renal circulation, and that this effect can be blocked by adrenergic blocking agents. These observations are in direct contrast to the assumption that maximal tubular transport for glucose, Diodrast, and paraaminohippurate are independent of glomerular filtration rate, and that the only way that changes in tubular function can be produced is by glomerular and tubular damage or by inhibition of the transporting mechanisms.

Trueta and associates14 recently aroused interest with their assertion that neurogenic and circulatory stress as well as vasopressor drugs activate renal subcortical arteriovenous shunts, thus bypassing the normal cortical glomeruli. Since direct blood flow studies8 and renal clearance studies9 following sciatic nerve stimulation and hemorrhage have failed to confirm these observations, it seemed worthwhile to analyze the data in the present study for evidence of vascular shunting following epinephrine and norepinephrine. If blood were shunted past the normal glomeruli and renal parenchyma to any significant extent, the ratios GFR:RPF and TMg;RPF would decrease. In addition, renal venous blood should show progressively increasing amounts of oxygen (arterialization) and the extraction of paraaminohippurate should decrease since most of this substance is extracted and secreted into the tubules as the blood circulates through the peritubular capillaries after it leaves the glomeruli.12 None of these predicted alterations were observed. The filtration fraction (GFR:RPF) either increased or it did not change. A similar observation was made on the ratio of TMg;RPF (table 2). The renal venous blood did not become arterialized. The A-V oxygen difference at first did not change significantly, but as the renal blood flow became greatly reduced the oxygen content of renal venous blood progressively diminished. The extraction of paraaminohippurate showed considerable random variation (table 2), but it increased in as many animals as it decreased. This confirms a previous observation.19 Only when the renal plasma flow decreased to about 10 per cent17 of normal or below was the paraaminohippurate extraction affected consistently. Then it decreased. This may be due to the increasing importance of extraparenchymal blood flow, or may represent back diffusion of paraaminohippurate due to the low urine output.

Although more marked, the changes noted in the present studies are essentially similar to changes noted following sciatic nerve stimulation.10,11 In these latter experiments no attempt was made to determine whether the decrease in renal function associated with sciatic nerve stimulation was due to a neurogenic reflex vasoconstriction or due to the liberation of a circulating vasoconstrictive agent such as epinephrine. It may have been either or both. Certainly one might expect the liberation of epinephrine from the adrenal medulla following sensory nerve stimulation. Although the present study clearly demonstrates decreasing numbers of active glomeruli, dye injection studies suggest that this is not limited to anatomic areas, but rather that the glomeruli have a graded threshold of response to vasoconstrictive substances. The peripheral cortical glomeruli seem to have a lower threshold and may show a decrease in blood flow before the deeper ones do, but this does not indicate any shunting mechanisms. It only means that the deeper glomeruli are left to carry on whatever renal function remains.

Conclusions

1. Epinephrine and norepinephrine, when administered by continuous infusion, caused a marked reduction in renal blood flow, renal plasma flow (RPF), glomerular filtration rate (GFR), and maximum tubular transport of glucose (TMg). There was no essential difference in the response to the two drugs.

2. In the majority of instances the renal plasma flow decreased and the filtration fraction increased before changes in other renal functions became evident, apparently due to efferent arteriolar vasoconstriction. As the in-

* Not accurate due to very low urine volumes at this stage of reduced renal function.
fusion rate was increased, there followed a proportional decrease in renal plasma flow, glomerular filtration rate, and maximum tubular absorption of glucose. The GFR:Tm ratio remained constant in the face of a decrease in the absolute values of both filtration rate and tubular maximum. These changes in renal hemodynamics are probably due to a decrease in the number of active nephrons.

3. Under the conditions of the experiment and similar conditions of stress, there seems to be sufficient evidence to conclude that active nephrons in large numbers can be completely occluded from the renal circulation in dogs and that this response can be prevented by adrenergic blockade. However, there is not sufficient evidence to conclude that the sympathetic nervous system regulates the renal circulation under normal conditions or that glomeruli "wink in and out of the renal circulation" as noted by Richards and Schmidt in amphibians.

4. There is no evidence from this study to support the hypothesis that epinephrine or norepinephrine activate renal vascular shunts in dogs.

REFERENCES
Norepinephrine and Epinephrine Effect on Renal Hemodynamics: With Particular Reference to the Possibility of Vascular Shunting and Decreasing the Active Glomeruli

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