Role of the Autonomic Nervous System in the Renal Vasoconstriction Response to Hemorrhage in the Rabbit

By Paul I. Korner, M.D., Gordon S. Stokes, M.D., Saxon W. White, M.B., and John P. Chalmers, M.B.

ABSTRACT
In normal unanesthetized rabbits with intact autonomic effectors, rapid removal of 26% of the blood volume resulted in prolonged renal vasoconstriction. This response was completely absent in rabbits without functioning autonomic effectors (after guanethidine treatment + adrenalectomy + atropine), despite the greater arterial hypotension in this group. The effects of removing 26% and 32% of the blood volume were compared in the normal innervated and chronically surgically denervated kidney of the same animal. After 26% hemorrhage, the vessels of both kidneys constricted, but the response was significantly greater on the innervated side; reduction in GFR was the same in both kidneys. After 32% hemorrhage the renal constrictor response was greater than after 26% hemorrhage, the difference largely resulting from additional humoral effects, as estimated by the greater vasoconstriction observed in the hypersensitive surgically denervated kidney at this level of hemorrhage; GFR also fell more on the denervated side. The results indicate that sympatho-adrenal activity is essential in the production of renal vasoconstriction after hemorrhage, and suggest that this response is normally produced by the synergistic action of increased sympathetic nerve activity and humoral effects, including those of the adrenal catecholamines.

ADDITIONAL KEY WORDS angiotensin sympatho-adrenal system renal blood flow denervation hypersensitivity epinephrine glomerular filtration rate autoregulation neurohumoral synergism

After severe hemorrhage there is a large increase in sympatho-adrenal activity (1-3), but there is also increased secretion of other constrictor substances such as angiotensin and vasopressin (2, 4, 5). The relative importance of the autonomic effectors and of the other constrictor agents in the production of renal vasoconstriction after hemorrhage has not been defined, and there is also doubt concerning the relative contribution of sympathetic nerves and adrenal medullary hormones in the constrictor response (6-12). In recent experiments in unanesthetized rabbits, reproducible general circulatory effects were obtained by rapid removal of a fixed fraction of each animal's own blood volume without retransfusion (13). This technique has been used in the experiments reported in this paper to examine the role of the autonomic nervous system in the control of the renal circulation after hemorrhage in normal rabbits and in "de-efferented" rabbits without functioning autonomic effectors. The relative role of the sympathetic nerves and adrenal hormones in the renal response has been assessed by examining the effects of hemorrhage in the innervated and chronically denervated kidney.

Methods
New Zealand White rabbits crossbred with the New Zealand Giant strain were used in these experiments (mean body weight 2.6 kg; range 2.3 to 3.5 kg). Three groups were studied; the first was normal rabbits. The second group con-
sisted of de-efferented rabbits, bilaterally adrenal-ectomized 9 to 10 days before the experiment and maintained on daily injections of 2 mg cortisone acetate and 1.5 mg deoxycorticosterone acetate im (14). From the fourth postoperative day they were given a 5- or 6-day course of guanethidine sulfate (Ismelin, Ciba) of 12.5 mg/kg per day iv to produce sympathetic nerve block and depletion of tissue catecholamines (15-17); vagal block was produced by administration of atropine sulfate at an initial dose of 2 mg iv, followed by alternating doses of 1.0 and 0.5 mg every 15 min. Atropine, by abolishing reflex vagal effects on the heart, slows the recovery in cardiac output after hemorrhage compared with the response of animals subjected to guanethidine treatment plus adrenalectomy (13). In the third group of rabbits, the left kidney had been surgically denervated 7 to 10 days before the test by cutting all visible nerves lying in the renal pedicle about 1 cm from the hilum of the kidney and stripping the adventitia from the renal artery over a distance of about 1 cm (18).

In one series of experiments, blood flow in the left renal vein was measured in normal and de-efferented rabbits using a local thermodilution method, with a fine thermistor-containing double-lumen catheter (19, 20) inserted 4 to 10 days before an experiment under sodium pentobarbital anesthesia (initial dose 30 to 40 mg/kg iv, supplemented as required). The catheter was inserted directly through the vein wall and fixed in position with 2 or 3 drops of methyl 2-cyanoacrylate or isobutyl acrylate (Ethicon, Inc.) (20). A mechanical injector was used to inject rapidly 0.4 to 0.55 ml of 5.5% dextrose at room temperature through a fine slit, 11 to 12 mm upstream from the thermistor bead. Thermodilution curves were recorded on a Sanborn polybeam recorder (Fig. 1), using a linearizing circuit (20). Renal vein flow was calculated from the thermodilution curves using the formulae and corrections described previously (19, 20).

Renal clearance experiments were performed in animals with the left kidney surgically denervated 7 to 10 days before an experiment, and in sham-operated animals with both kidneys innervated. On the day of the experiment, the ureters were cannulated through a lower abdominal incision, using light sodium thiopentone anesthesia and infiltration of the abdominal wall with 0.5% lignocaine HCl, as previously described (18). A fine esophageal catheter was inserted in the neck for administering water. The animals recovered rapidly from the operation and were placed in their rabbit boxes. Control observations began 3 hours after recovery from the anesthetic. During the operation and throughout the observation period, high urine flows of 0.3 to 0.6 ml/min per kidney were maintained by infusing 5% mannitol in Ringer-Locke solution at the rate of 0.7 ml/min by means of a motor-driven syringe. The animals were given 30 ml of warm tap water during the operation through the esophageal catheter, and 10 ml every hour thereafter. Infusion solutions containing creatinine for measurement of glomerular filtration rate (GFR) (21), paraaminohippurate (PAH), and mannitol in Ringer-Locke solution were administered as previously described (18, 21, 22). In a few experiments a renal vein catheter was inserted through the lumbo-adrenal vein (21) to determine renal PAH extraction ratio under various conditions (see Tables 2 and 3). All urine collection periods were of 10-min duration. Four 2-ml arterial blood samples were taken, one during the control period and three at 20-min intervals following hemorrhage. The blood sampling offset to some extent the greater fluid "replacement" rate in the clearance series compared with the local thermodilution series. The effectiveness of renal denervation was tested during inhalation of 8% O₂, when there is renal vasoconstriction only on the innervated side (21) (Fig. 8). In view of the hypersensitivity to the constrictor action of infused epinephrine (Fig. 6), the surgical denervation probably resulted in significant degeneration of nerve fiber and depletion of terminal norepinephrine stores.

The effects of infusion of epinephrine bitartrate (0.6 to 1.2 µg/kg per min iv) and of synthetic angiotensin II (Hypertensin, Ciba) (0.1 µg/kg per min iv) were examined in 5 normal rabbits. In these experiments, 0.9% NaCl was administered at the rate of 0.35 ml/min. On the day of the experiment, both central ear arteries
and the right atrium were catheterized with polyvinylchloride catheters, and a metal tracheotomy tube was inserted into the trachea using local anesthesia as described previously (18, 23). Just before each experiment, the blood volume was measured in each animal from the estimated red cell volume using $^{51}$Cr and the arterial hematocrit ratio corrected for trapped plasma and "body" hematocrit (13). The animals were given 500 IU/kg heparin iv. Control observations of renal blood flow were obtained, together with measurements of ear artery pressure and heart rate (23); 26% or 32% of the blood volume of each animal was then bled from one ear artery into a burette at a rate of approximately 2 ml/min over a period of 15 to 20 min. Blood was not reinfused into these animals, but the blood volume gradually recovered 3 to 4 hours after hemorrhage because of spontaneous reabsorption of extravascular fluid (13).

In each series of experiments, the timing of the various procedures was always the same in each animal. In the thermodilution series, two values of each variable were obtained in each animal during each of the selected time intervals shown (Fig. 2), and these were averaged for each time interval. In any series, the mean value of each variable for a given time interval was determined for all the animals in the group. The standard error of the mean of a single time interval was calculated for each variable by analysis of variance (24) from the error mean square (EMS) after subtracting "between animals" and "between times" from the total sums of squares. The standard error of a single time interval is $(EMS/n)^{1/2}$, where $n =$ number of animals in the group, and is represented graphically by the symbol on the left of each variable, e.g. Figure 2, which shows ±1 se extending from the mean control value. In assessing the significance of the difference between two time intervals, the appropriate se diff. = $(2\ EMS/n)^{1/2}$. In order to facilitate comparisons between the various measurements, the average effects at each time interval in the group have been mostly expressed as the percentages of the mean initial control value (Fig. 2).

Results

EFFECT OF HEMORRHAGE IN NORMAL AND "DE-EFFERENTED" RABBITS

The average resting renal blood flow and arterial pressure in normal rabbits was closely similar to corresponding values in de-efferented rabbits (adrenalectomy and treatment with guanethidine and atropine), but the mean heart rate of the latter group was significantly below normal value (Table 1).

<p>| TABLE 1 |
|-------------------------------|-------------------------------|
| <strong>Initial Control Values in 4 Normal and 4 &quot;De-efferented&quot; Unanesthetized Rabbits</strong> |
|-------------------------------|-------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Normal</strong></th>
<th><strong>&quot;De-efferented&quot;</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td><strong>Mean ± SE</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>2.9 ± 0.2</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td><strong>Renal blood flow (ml/min per kidney)</strong></td>
<td><strong>Mean ± SE</strong></td>
</tr>
<tr>
<td>71 ± 2.5</td>
<td>67 ± 3.6</td>
</tr>
<tr>
<td><strong>Ear artery pressure (mm Hg)</strong></td>
<td><strong>Mean ± SE</strong></td>
</tr>
<tr>
<td>83 ± 2.3</td>
<td>81 ± 2.9</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td><strong>Mean ± SE</strong></td>
</tr>
<tr>
<td>260 ± 5.5</td>
<td>228 ± 2.5</td>
</tr>
</tbody>
</table>

The result from each animal is the mean of 4 determinations.

In normal rabbits with autonomic effectors intact, removal of 26% of the blood volume resulted in prompt reduction in renal blood flow to 58% of initial control and elevation in renal vascular resistance to 135% of control (Fig. 2, left). The renal vasoconstriction was sustained for the remaining 4 hours of the experiment. Removal of 32% of the blood volume was accompanied by more pronounced reduction in RBF and rise in renal vascular resistance in 2 rabbits, despite the more marked arterial hypotension produced by the more severe hemorrhage (Fig. 3, left).

In the de-efferented animals without functioning sympatho-adrenal and cholinergic ef-
factors, removal of 26% of the blood volume produced a significantly greater reduction in arterial pressure, but despite this, the initial fall in renal blood flow was less marked than in the normal rabbits, and its subsequent rate of recovery was more rapid although the arterial pressure remained low (Fig. 2, right). The mean renal vascular resistance fell progressively during the 4 hours following hemorrhage. In all animals, the hypotension at the onset of bleeding was accompanied by a brief reduction in renal vascular resistance (Fig. 3, right), suggestive of autoregulation of renal blood flow. It was not possible to subject de-efferented animals to more severe degrees of hemorrhage.

The experiments show that renal vasoconstriction after hemorrhage does not occur in rabbits that have no functioning autonomic effectors.

**EFFECT OF HEMORRHAGE ON THE INNERVATED AND SURGICALLY DENERVATED KIDNEY**

The role of increased sympathetic nerve activity and of humoral factors was assessed by simultaneous measurement, for 1 hour after hemorrhage, of renal blood flow, GFR, and urine flow in the innervated and surgically denervated kidney. In these experiments, adequate urine flow was maintained following hemorrhage (Fig. 4), and the renal PAH extraction ratios were not altered significantly (Table 2), thus validating the use of the PAH
TABLE 3
Effects of Intravenous Infusion of Epinephrine Bitartrate and of Angiotensin II on Renal Extraction of PAH in Rabbits with Innervated Kidney or Chronically Denervated Kidney

<table>
<thead>
<tr>
<th>State</th>
<th>Percent renal extraction of PAH</th>
<th>Epinephrine*</th>
<th>Angiotensin†</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innervated</td>
<td>97.3 96.4 98.8 98.0 97.8 99.0 97.6</td>
<td>96.8 91.6 98.0 91.9 90.6</td>
<td>92.4</td>
<td></td>
</tr>
<tr>
<td>Denervated</td>
<td>91.0 91.7 91.6 91.7 90.6 92.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Epinephrine bitartrate, 1.2 µg/kg per min.
†Angiotensin II, 0.1 µg/kg per min.

Bleeding the animals of 32% of their blood volume resulted in a significant reduction in renal blood flow and rise in vascular resistance in both kidneys (Figs. 4 and 5, left). The renal blood flow fell significantly more on the innervated side than on the denervated side, indicating that neural as well as humoral factors contribute to the renal vasoconstriction at this level of hemorrhage. The innervated-denervated ratio of renal blood flow fell from its mean control value of 0.93 to an average value of 0.81 for the first 50 min after bleeding (s = diff. ± 0.037; P = 0.001), but after 1 hour the differences between the two sides were no longer present, despite continuing vasoconstriction in both kidneys. During the first 50 min, the renal blood flow was reduced to 58% of initial control (mean initial control, 43 ± 2.3 ml/min per kidney) in the innervated kidney, and to 68% of initial control in the chronically denervated kidney (mean control 46 ± 2.5 ml/min per kidney). The corresponding values for renal vascular resistance were 147% and 127% of their respective controls.

Walker et al. (25) have shown that the adrenal catecholamine secretion rate after bleeding varies with the fraction of the blood volume removed, and accordingly the effects of more severe hemorrhage on renal function were investigated. After removing 32% of the blood volume, the reduction in renal blood flow and rise in vascular resistance in the normal innervated kidney were significantly greater than after 26% hemorrhage, the former falling to 46% of control and the latter rising to 157% of control (Fig. 4). The greater prominence of humoral effects at this level of hemorrhage is suggested by the lesser change in renal blood flow and increase in vascular resistance in the chronically denervated kidney.
An increase in sympathetic neural activity reflexly evoked by arterial hypoxia (22), and under these conditions, vasoconstriction and reduction in renal blood flow were observed only in the innervated kidney (Fig. 6). The results indicate that the chronically denervated kidney is hypersensitive to epinephrine and angiotensin and that hypersensitivity to the former is dose dependent. The results obtained after 32% hemorrhage are thus consistent with a renal

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Mean Left-Right Ratio of Renal Blood Flow, Glomerular Filtration Rate, and Urine Flow from 3 Rabbits Bleed 32% of Their Blood Volume and 1 Rabbit Bleed 68% of Their Blood Volume</th>
<th>(N = 4)</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
<th>110</th>
<th>120</th>
<th>130</th>
<th>140</th>
<th>150</th>
<th>160</th>
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<tbody>
<tr>
<td>Renal blood flow</td>
<td>2.92</td>
<td>2.92</td>
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<td>2.92</td>
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<td>2.92</td>
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<tr>
<td>Glomerular filtration rate</td>
<td>2.92</td>
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<tr>
<td>Urine flow</td>
<td>2.92</td>
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<td>2.92</td>
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The greater reduction in renal blood flow on the chronically denervated side after 32% hemorrhage suggests that the renal vasculature of this kidney is hypersensitive to humoral substances. The relative effects on innervated and denervated kidneys of intravenous infusions of epinephrine (0.6 to 1.2 μg/kg per min) and of angiotensin (0.1 μg/kg per min) were examined in 5 rabbits. The effect on renal blood flow was similar in the innervated and the denervated kidneys in 3 rabbits given epinephrine at the rate of 0.6 μg/kg per min; the innervated-denervated ratio of renal blood flow changed from a control value of 0.97 to 0.99 (SEM diff. ± 0.025). However, with a dose of 1.2 μg/kg per min, the denervated kidney had significantly greater reduction than the normal kidney (Fig. 6), the mean innervated-denervated ratio changing from its control value of 0.94 to 1.08 (SEM diff. ± 0.03). Similar greater constriction on the denervated side was observed after administration of angiotensin (Fig. 6). A further test was carried out in these animals to examine the effects of an increase in sympathetic neural activity reflexly evoked by arterial hypoxia (22), and under these conditions, vasoconstriction and reduction in renal blood flow were observed only in the innervated kidney (Fig. 6). The results indicate that the chronically denervated kidney is hypersensitive to epinephrine and angiotensin and that hypersensitivity to the former is dose dependent. The results obtained after 32% hemorrhage are thus consistent with a renal

rhage was suggested by the significantly greater reduction in renal blood flow in the chronically denervated kidney than in the innervated kidney for the first 30 min after hemorrhage, as indicated by the significant rise in the innervated-denervated ratio from its control value of 0.92 to an average value of 1.29 for the first 30 min after bleeding (SEM diff. ± 0.12; P < 0.01) (Fig. 5, right). This difference between the two kidneys was present for only a relatively brief period, and 1 hour after hemorrhage the differences between the two kidneys were no longer statistically significant.
hypersensitivity response in the denervated kidney to quite large amounts of adrenal catecholamines, angiotensin, or both.

In the innervated kidney, the GFR was less markedly reduced than the renal blood flow after removal of 26% of the blood volume, and the filtration fraction increased significantly (Fig. 4, left). The reduction in GFR was similar in the innervated and denervated kidneys, and there was no significant change in the innervated-denervated ratio of GFR (Fig. 5, left). The reduction in urine flow was significantly greater on the innervated side after 26% hemorrhage (Fig. 5, left). After 32% hemorrhage, the rise in filtration fraction in the innervated kidney was less marked than after 26% hemorrhage (Fig. 4, right). The urine flows decreased more in the chronically denervated kidney, thus following the pattern of renal blood flow and GFR changes at this level of hemorrhage (Fig. 5, right).

In 3 sham-operated rabbits with both kidneys innervated, removal of 26% of the blood volume did not significantly alter the left-right ratios of renal blood flow, GFR, and urine flow, and these ratios also remained essentially unchanged in 1 animal subjected to 32% hemorrhage (Table 4).

Discussion

The experiments demonstrate that increased activity of the autonomic nervous system is necessary for the production of renal vasoconstriction after hemorrhage, since this response was completely absent in de-efferented animals without functioning autonomic effectors. It is probable that the reflexly increased activity of the sympatho-adrenal system is the essential element in the constrictor response of normal animals, since the existence of cholinergic renal vasomotor fibers is considered improbable (9, 26). In the de-efferented animals, the initial fall in renal vascular resistance soon after bleeding began is suggestive of intrarenal autoregulation (9, 11). The rapid return in renal vascular resistance to control values could be explained by a poor autoregulatory response, since the arterial perfusion pressure is somewhat beyond the range of efficient autoregulation (27), but it could also result from the weak action of an intrarenally produced vasoconstrictor substance. However, the progressive decline in renal vascular resistance in the de-efferented group suggests that any action by such constrictor agents must be slight and evanescent in the absence of functioning sympatho-adrenal effectors.

The contribution of sympathetic nerve activity and humoral agents has been assessed in the clearance experiments. The effects in the surgically denervated kidney in otherwise intact animals indicate that part of the renal vasoconstriction after hemorrhage is due to activity of humoral agents in the absence of sympathetic nerves. After removal of 26% of the blood volume, the renal vasoconstriction...
is more pronounced in the innervated kidney, in which both neural and humoral activity were present, than in the denervated kidney, acted on only by humoral substances. The initial dominance of renal sympathetic nerve activity is probably greater than indicated in Figure 5, in view of the likelihood of a hypersensitivity response to humoral agents on the chronically denervated side. The return to initial control values in the innervated-denervated ratios of renal blood flow 1 hour after hemorrhage, with persistent vasoconstriction in both kidneys, can be explained by an increase in both sympathetic nerve activity and humoral activity, since the extra constriction ascribable to humoral hypersensitivity of the chronically denervated kidney will offset the greater constriction due to neural activity on the innervated side.

After 32% hemorrhage, the rise in vascular resistance in the normal kidney was about 10% greater than after 26% hemorrhage. Humoral effects probably accounted for the bulk of the difference, since the marked hypersensitivity response of the chronically denervated kidney indicates that greater amounts of vasoactive humoral substances are present after this degree of hemorrhage than after removal of 26% of the blood volume. One hour following a 32% hemorrhage, the renal blood flow in the innervated, and that in the denervated, kidney were again not significantly different despite continuing vasoconstriction in both kidneys. This suggests that at this level of hemorrhage also the hypersensitivity response of the chronically denervated kidney matches the neurally mediated vasoconstriction of the innervated side. At both levels of hemorrhage, the results suggest a synergistic action between sympathetic nerve activity and humoral factors. In the period immediately following hemorrhage, either the neural or humoral components play a somewhat more important role in the constrictor response, depending on the severity of hemorrhage, but after about 1 hour this preponderance of one component is no longer apparent, despite continuing vasoconstriction for at least 4 hours. It is very probable that the adrenal medullary catecholamines contribute to the humoral effects, since in the rabbit they have been found to play a complementary role with increased sympathetic nerve activity in the reflex maintenance of the arterial pressure following hemorrhage (13). The demonstration by Carriere et al. (28) that the renal cortex is the chief site of post-hemorrhagic renal vasoconstriction is in agreement with the suggestion of a synergistic action between sympathetic nerve activity and humoral effects, including those of adrenal catecholamines, since some of the effects of the latter would potentiate the effects of the renal vasomotor nerves which terminate at this site (26).

The finding in the chronically denervated kidney of hypersensitivity to the action of angiotensin in the present experiment differs from the results obtained by McGiff and Fasy (29) with similar doses of angiotensin in the acutely denervated dog kidney. In the dose used in the present experiments, angiotensin acts as a powerful release agent for adrenal catecholamines (30, 31), and the hypersensitivity response to angiotensin could be mediated through release of epinephrine by the adrenal medulla, since this accounts for over 98% of adrenal catecholamines in the rabbit (3, 17). The present experiments do not, however, exclude a direct vascular action of angiotensin. Interaction between the effects of the sympa-tho-adrenal system and the renin-angiotensin system is probably of importance in the renal vasoconstriction after hemorrhage. Renin release, and presumably greater production of angiotensin (4), are augmented by increased amounts of circulating adrenal medullary hormones (32) and by increased sympathetic nerve activity (33). The findings in the present experiments suggest that the increased sympa-tho-adrenal activity during and after hemorrhage can account adequately for the renal vasoconstriction, but do not exclude synergistic action with the renin-angiotensin system. However, any renin-angiotensin or other constrictor substance which may be released in hemorrhage cannot by itself produce renal vaso-
constriction in the absence of sympatho-adrenal activity.

**Acknowledgments**

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**References**


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