Effect of hemorrhage and vasopressor agents on distribution of renal blood flow

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METHODS

Studies were performed on mongrel dogs weighing between 13 and 23 kg. All animals were deprived of food and water for 18-24 hr before the study. The dogs were anesthetized with pentobarbital (30 mg/kg) and were subsequently given small maintenance doses as necessary. An endotracheal tube was inserted and the animals were ven-

Impact of hemorrhage and vasopressor agents on distribution of renal blood flow. Am. J. Physiol. 222(5): 1125-1131. 1972.—Studies were performed in the dog in which the distribution of renal cortical blood flow was determined with the radioactive microsphere method. Three experimental models were evaluated: 1) hemorrhagic hypotension, 2) intrarenal infusion of norepinephrine (4 μg/min), and 3) intrarenal infusion of angiotensin (100 ng/min). In all 10 hemorrhage studies, there was a marked alteration in the distribution of blood flow with a decrease in flow to outer cortical nephrons and a concomitant increase in the fraction of flow to inner cortical nephrons. In 11 studies, norepinephrine decreased total blood flow 49%, but had no effect on the fractional distribution of blood flow. Similarly, in 12 studies angiotensin II decreased total blood flow 41%, but there was no alteration in zonal distribution of blood flow. In a separate series of experiments, a comparison was made of the change in total renal blood flow, vascular volume, and mean transit time as measured by the indocyanine green indicator-dilution technique during hemorrhage and norepinephrine administration. There was no significant difference in the decrease in total blood flow and vascular volume or the increase in transit time between the two experimental maneuvers. Therefore, these results indicate that there are definite differences in the distribution of cortical blood flow during hemorrhage and vasopressor infusion and that the redistribution of flow which occurs during hemorrhage is not due to the humoral release of either norepinephrine or angiotensin.

norepinephrine; angiotensin II; microsphere method; shock; catecholamines; renin

It has been suggested that alterations in the intrarenal distribution of blood flow may be an important regulator of sodium balance. Carrière, Thorburn, O'Morehoo, and Barger (11), using the 85Kr washout technique, found that there was a marked decrease in outer cortical and an increase in inner cortical blood flow during hemorrhagic hypopension. From this data and other experiments, Barger (3, 5, 18) has suggested that a redistribution of blood flow to inner cortical nephrons may decrease sodium excretion by increasing flow to the juxtamedullary nephrons which are longer and could conceivably have a greater capacity to reabsorb sodium. Conversely, any circumstance in which blood flow was redistributed to the shorter outer cortical nephrons may lead to a natriuresis if these nephrons had a more limited capacity for sodium reabsorption.

Carrière (9) and Carrière and Friborg (10) have presented data also utilizing the inert gas-washout technique, which indicates that both norepinephrine and angiotensin decrease outer cortical blood flow while norepinephrine increases outer medullary blood flow and angiotensin increases inner cortical blood flow. Since both of these pressor agents are present in markedly increased amounts during hemorrhage (20, 27), it might be construed from this data that the excessive humoral release of norepinephrine and/or angiotensin was responsible for the redistribution of blood flow found during hemorrhagic hypotension. However, other investigators have not found a similar disproportionate change in the distribution of blood flow during either hemorrhagic hypotension or vasopressor administration. Aukland and Wolgast (1, 2), using the more direct technique of placement of a hydrogen-sensitive platinum electrode, demonstrated a proportional decrease in total renal blood flow and outer medullary flow during intrarenal angiotensin infusion and hemorrhagic hypotension. Similar results were found using heating thermocouples during intravenous angiotensin infusion (13).

Recently, several groups (17, 22, 23) have modified the radioactive microsphere technique as originally described by Rudolph and Heymann (19) and Wagner and associates (25) to measure regional blood flow in the renal cortex. This method is simple, reproducible, does not necessitate any undue manipulation of the kidney, is an index of glomerular blood flow, and offers the definite advantage of precise cortical localization (17, 22, 23).

Using the radioactive microsphere technique, we have reevaluated the effect of hemorrhage and vasopressor administration on the distribution of renal blood flow. Our results indicate that hemorrhagic hypotension does, indeed, cause a marked redistribution of cortical blood flow to inner cortical nephrons. In contrast, although total blood flow was halved, the fractional distribution of blood flow remained constant following the intrarenal infusion of either norepinephrine or angiotensin.
tilated with a Harvard respirator. Cannulas were inserted in a leg vein for infusions and in the femoral artery for blood pressure measurements and blood collection. A Goodall-Lubin standard wall catheter was placed in the left ventricle by retrograde threading from either the left carotid or femoral artery. There was no difference in the experimental results obtained with the two methods of placement of the left ventricular catheter. Both ureters were cannulated through a suprapubic incision. In the drug studies, a 23-gauge hooked needle was placed in the orifice of the left renal artery and kept open with an infusion of Ringer solution at a rate of 0.4 ml/min throughout the study. A catheter was placed in the left renal vein for measurement of para-aminohippurate (PAH) extraction. An infusion was given to establish and maintain a PAH concentration of 2 mg/100 ml.

Radioactive microspheres (3M Company, St. Paul, Minn.) were used to measure regional blood flow in different areas of the renal cortex. Approximately 450,000 microspheres (15-20 μ) 15 ± 1 μ in diameter were given with each injection. The nuclides used were ⁸⁸Sr and ¹⁴¹Ce. The sequence of injection of the two nuclides was varied from experiment to experiment. The nuclide to be injected was suspended in a 1-ml solution of 10 % dextran and was injected through the left ventricular catheter in approximately 10 sec and then flushed with another 20 ml of saline. There was no change in heart rate, mean pressure, or pulse pressure after a microsphere injection.

At the end of the experiment, the kidney was removed. Three or more sections were obtained from different portions of the kidney, and each section was then divided into four equal zones as previously described (23). These zones were called zones 1, 2, with zone 1 the most outer cortical zone and zone 4 the most inner cortical zone. Each piece of tissue was placed in a preweighed Packard gamma counting tube, reweighed, and counted in a Packard Auto-Gamma counter. The sample was placed on the bottom of the counting vial and counted for 5 min. No geometric effect was found by counting the tissue sections in the manner described. Strontium ⁸⁸ was counted at the .510 Mev peak and ¹⁴¹Ce was counted at the .145 Mev peak. No correction was necessary for the ⁸⁸Sr counts, but 15 % of the ⁸⁸Sr counts was subtracted to obtain the true ¹⁴¹Ce counts.

Three types of experimental procedures were performed with this method.

1) In 10 studies, the distribution of blood flow was determined before and during hemorrhagic hypotension. After the initial microsphere injection, the animal was bled into a reservoir to a mean arterial pressure between 60 and 70 mm Hg and was maintained at this pressure by adjusting the height of the reservoir. Thirty minutes after stabilization, a second injection of microspheres was given.

2) In 12 studies the distribution of blood flow was determined before and during the intrarenal infusion of norepinephrine (Winthrop Laboratories, New York City), 4 μg/min, in the left renal artery.

3) In 11 studies similar measurements were made before and during the administration of angiotensin II (Ciba Pharmaceutical Company, Summit, N.J.), 100 ng/min, in the left renal artery. In both groups 2 and 3 studies, the second injection of microspheres was given 30 min after the administration of the appropriate agent had begun. In groups 2 and 3, three 15-min clearance collections were obtained in both the control and experimental periods. In all three groups, the microsphere results were obtained from the left kidney.

*p-Aminohippurate was determined by the method of Bratton and Marshall (6).

In a separate series of studies, renal blood flow, mean transit time, and renal vascular volume were determined with the indocyanine green dye dilution method described by Kioschos, Kirkendall, Valenca, and Fitz (16). Indocyanine green, 1.25 mg in 1 ml of solvent, was injected into the left renal artery while blood was being withdrawn at a rate of 30 ml/min from a renal vein catheter connected to the cuvette of a Gilford densitometer. Three or more curves were obtained in each period and were recorded on a Sanborn direct-writing oscilloscope. Two groups of experiments were performed: 1) In four studies, dye-dilution curves were determined before and during hemorrhagic hypotension induced in identical fashion to the group 1 animals of the microsphere studies; 2) in five studies, measurements were obtained before and during the intrarenal infusion of norepinephrine, 4 μg/min. The experimental values were obtained 30 min after the norepinephrine infusion had begun.

Calculations

**Microsphere studies.** Renal blood flow (RBF) was determined by the following formula:

$$\text{RBF (ml/min)} = \frac{C_{\text{PAH}}}{E_{\text{PAH}} (1 - \text{Hct})}$$

where $C_{\text{PAH}}$ is the clearance of PAH, $E_{\text{PAH}}$ is the renal extraction of PAH, and Hct is the arterial hematocrit.

The uncorrected percent of renal blood flow per cortical zone ($P_z$), percent of flow per gram, was determined by dividing the counts per minute per gram of tissue in the respective zone ($CPM_z$) by the total for all four cortical zones ($CPM_T$).

The corrected percent of renal blood flow per cortical zone was determined by the following formula:

$$\text{corrected percent zonal blood flow (P'_z)} = \frac{CPM_z \times W_{tz}/CPM_T}{W_{tz} \times W_T}$$

where $W_{tz}$ is the weight of the zone and $CPM_T$ is the total counts per minute per gram times the zonal weight for all four zones. As has been shown previously (23), there is no qualitative difference between uncorrected and corrected values. Therefore, only the latter will be presented in the text.

$W_{tz}$ was obtained using the derivation of the volume of the four critical zones obtained by McNay and Abe (17) in which the percent of renal volume was found to be 21, 22, 17, and 12 % in zones 1-4, respectively. Therefore:

$$W_{tz} = V_z \times W_T$$

where $V_z$ equals the volume of the respective zone and $W_T$ equals the kidney weight.

Zonal blood flow ($BF_z$) was estimated by the following
INTRARENAL DISTRIBUTION OF BLOOD FLOW

The formula:

\[ BF_z = P_z' \times RBF \]

Zonal perfusion rate was determined by dividing BF\(_z\) by Wt\(_z\).

**Dye-dilution studies.** Total renal blood flow was calculated from the formula:

\[ RBF = \frac{I \times s \times f}{S \times i} \]

where I = quantity of dye injected in the renal artery (ml), i = quantity of dye used for calibration (ml), S = area under the flow curve (cm\(^2\)), s = area under the calibration curve (cm\(^2\)), and f = rate of flow through the recording system (ml/min).

Mean transit time (MTT) was calculated from the formula:

\[ MTT = AT + \frac{\sum t_i}{\sum c} - F \]

where AT is the appearance time of the dye, c is the concentration of the dye at time t, t is the measured time after appearance of the dye, and F is a correction factor for the delay in appearance of the dye because of the dead space of the collection tubing. This was obtained by in vitro injection of dye in the same withdrawal system in each experiment.

renal blood volume = MTT \times RBF

### RESULTS

**Hemorrhage Studies**

The summary of the results for all 10 hemorrhage studies is presented in Table 1 and Fig. 1. The percent of blood flow in outer cortical zone 1 decreased in each of the 10 studies with a mean change from 45 ± 2 to 30 ± 2% (P < .001). There was no mean change in zone 2, while fractional blood flow distribution of renal blood flow during angiotensin infusion. The mean percent distribution of blood flow was 49 ± 1, 30 ± 1, 15 ± 1, and 6 ± 1% in zones 1-4, respectively, in the control period and were unchanged at 48 ± 2, 31 ± 1, 15 ± 1, and 6 ± 1% during norepinephrine (Fig. 2). Zonal blood flow decreased 50, 47, 50, and 42% in zones 1-4, respectively, while total blood flow decreased 49% (Table 2). Zonal perfusion rate in each zone fell in a similar manner (Table 2).

### Hemorrhage Studies

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</table>

All values are the mean of three or more sections in the same kidney. C = control period. E = hemorrhagic hypotension period.

Increased from 18 ± 1 to 26 ± 1% in zone 3 (P < .001) and from 8 ± 1 to 14 ± 1% in inner cortical zone 4 (P < .001). Because of the low urinary flow rates during hemorrhage, the change in total renal blood flow was not obtained in these studies. However, in seven other studies performed with an identical design, total renal blood flow measured with a Medicon electromagnetic flowmeter fell from 222 to 119 ml/min, a decrease of 46%.

### Norepinephrine Studies

A summary of the norepinephrine studies is presented in Table 2 and Fig. 2. There was no consistent change in systemic blood pressure during the intrarenal infusion of norepinephrine, and the mean change from 124 to 127 mm Hg was not statistically significant. Renal blood flow fell in each study with a mean change from 206 ± 23 to 106 ± 15 ml/min. The mean percent distribution of blood flow was 49 ± 1, 30 ± 1, 15 ± 1, and 6 ± 1% in zones 1-4, respectively, in the control period and were unchanged at 48 ± 2, 31 ± 1, 15 ± 1, and 6 ± 1% during norepinephrine (Fig. 2). Zonal blood flow decreased 50, 47, 50, and 42% in zones 1-4, respectively, while total blood flow decreased 49% (Table 2). Zonal perfusion rate in each zone fell in a similar manner (Table 2).

### Angiotensin Studies

The results of all studies are summarized in Table 3 and Fig. 3. Systemic blood pressure was not significantly altered. Total renal blood flow fell in each study with a mean fall from 181 ± 16 to 106 ± 18 ml/min. As with norepinephrine, there was no significant alteration in the fractional distribution of renal blood flow during angiotensin infusion. The mean percent distribution of blood flow in the control period was 45 ± 3, 31 ± 1, 17 ± 1, and 8 ± 1 and remained unchanged at 46 ± 3, 31 ± 1, 17 ± 1, and 6 ± 1 during angiotensin infusion. Zonal blood flow decreased...
decrease in renal vascular volume from 18.3 to 13.4 ml. Mean total blood flow decreased from 210 to 96 ml/min in association with the increase in MTT from 5.5 to 8.0 sec and a decrease in renal vascular volume from 18.3 to 13.4 ml. Similar alterations were found in the norepinephrine studies. Renal blood flow decreased from 236 to 112 ml/min. MTT increased from 5.5 to 9.3 sec, and renal vascular volume decreased from 20.8 to 16.0 ml. There was no statistical difference between the change in renal blood flow, MTT, or renal vascular volume in the hemorrhage and norepinephrine studies.

**DISCUSSION**

The results of the present study indicate that hemorrhagic hypotension is associated with a redistribution of renal cortical blood flow to inner cortical nephrons. In contrast, neither norepinephrine nor angiotensin altered the fractional distribution of zonal blood flow.

These results do not totally agree with previous data obtained with other methods of evaluating the intrarenal distribution of blood flow. Although Carrière et al. (11) and Grandchamp and associates (12), using the inert gas method, and Slotkoff et al. (22), using the microsphere method, have found a similar pattern of redistribution of blood flow during hemorrhage as was found in the present study, Aukland and Wolgast (2) found no redistribution of blood flow with the hydrogen electrode method. In addition, Aukland (1) found no alteration in the distribution of blood flow with either norepinephrine or angiotensin (1), while Carrière (9) and Carrière and Friberg (10) found that both drugs disproportionately decreased outer cortical blood flow. The reasons for these disparate results are not clear, but seemingly relate primarily to differences in the technical and interpretative aspects of the methods utilized.

There are two possible explanations for the apparent differences found with the inert gas technique when compared with the microsphere method during vasopressor administration. First, terminology used to differentiate the different cortical zones is not similar. There are two main components of the $^{85}$Kr washout curve. Component I is thought to represent the majority of cortical blood flow, and component II is presumed to be a function of inner cortical and outer medullary blood flow. These two components account for approximately 80 and 15% of the total flow, respectively.
Although a definite comparison between the methods cannot be made with certainty, it would seem that component I of the gas method would be analogous to zones 1–3 of the microsphere technique and component II would be related to zone 4 of the sphere method. Even with these correlations, immediate disparities are apparent, since Carrière and Friberg (9, 10) have found with vasopressor administration of renal blood flow in component II increases, while we find no evidence of a disproportionate alteration in zone 4 with the sphere method.

Second, the component of flow that each technique measures may not necessarily be comparable. McNay and Abe (17) and Stein and associates (23) have both demonstrated that microspheres of the size used in this study are trapped exclusively in glomerular capillaries. This would indicate that the distribution of the microspheres would be an index of glomerular perfusion rate in different groups of nephrons. In contrast, the inert gas technique measures peritubular capillary blood flow. Since the postglomerular circulation of the juxtamedullary glomerulus is arranged in such a manner that blood leaving the glomerulus may flow through peritubular capillaries of the cortex or outer medulla as well as the vasa recta, it is possible that glomerular and peritubular capillary blood flow may not be altered in a parallel fashion and that apparent discrepancies would therefore be found between these methods.

No change in the distribution of renal blood flow was found with the hydrogen electrode method during hemorhagic hypotension (2). This conclusion was based on comparing the change in total renal blood flow with the change in outer medullary hydrogen clearance. The authors did not

### TABLE 3. Summary of angiotensin microsphere studies

<table>
<thead>
<tr>
<th>Exp No.</th>
<th>Corrected Percent Distribution to Cortical Zone</th>
<th>Zonal Blood Flow Cortical Zone, ml/min</th>
<th>Total Renal Blood Flow, ml/min</th>
<th>Zonal Perfusion Rate Cortical Zone. ml/min per g</th>
<th>Renal Blood Flow, ml/min per g</th>
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<td>100 78</td>
<td>8.8 6.9</td>
<td>4.3 3.6</td>
</tr>
</tbody>
</table>

Each value represents the mean of at least three different sections. C = control period. A = angiotensin period.
quantitate nutrient blood flow in different areas of the renal cortex. It is possible that the apparent discrepancies in results are again related to the functional differences in the parameters measured with the methods. If hemorrhage significantly alters hemodynamics beyond the juxtamedullary glomeruli, it would not necessarily follow that changes in outer medullary nutrient blood flow as measured with the hydrogen electrode method would parallel juxtamedullary glomerular perfusion rate as measured with the microsphere method (zone 4).

McNay and Abe (17), Stein et al. (23), Slotkoff and associates (22), and Katz et al. (15) have all presented data indicating that the radioactive microsphere method is simple, reproducible, and does reflect alterations in glomerular blood flow. Special emphasis was given by each group of investigators to determine whether microspheres could be significantly affected by the phenomenon of “axial streaming.” McNay and Abe (17) found that the distribution of blood flow was quite similar with microspheres of different size and density. In contrast, Katz and associates (15) found that 30-μ beads did have a greater concentration in outer cortical nephrons than the 15-μ size, although there was no difference between 7- and 15-μ spheres. These data suggest that the larger heads may stream but that the smaller sizes as used in the present study are not significantly affected by this phenomenon (15). Stein and associates (23) found that acetylcholine, an agent which increases total renal blood flow and the velocity of blood flow through the kidney (24), caused a redistribution of cortical blood flow to inner cortical nephrons. If axial streaming was the primary determinant of the distribution of the microspheres, acetylcholine would have caused the opposite pattern of blood flow distribution, since an increase in the velocity of blood flow will enhance axial streaming (8). Additionally, Slotkoff and associates (22) found no differences in the number of spheres per glomerulus in outer and inner cortical sections. Recently, Wallin et al. (26) have utilized radioactive antiglomerular basement-membrane antibody to measure regional plasma flow in the kidney. Although discrepancies were found between this technique and the microsphere method during saline diuresis in the rat, those authors noted a similar change in the distributional pattern with the two methods during volume expansion in the dog.

The results of the present study lend further evidence to the view that the distribution of the microspheres is not affected primarily by the velocity of blood flow. The indicator-dilution technique was used to compare the intrarenal hemodynamic changes during hemorrhage and vasopressor administration. As is shown in Table 4, there were similar decreases in renal blood flow and renal vascular volume in association with a comparable increase in mean transit time in the hemoglobin and noradrenergic studies. This would indicate that the velocity of blood flow was decreased to the same extent with both experimental models, although divergent effects on the distribution of blood flow were found.

In the light of the present results, there are several possible explanations for the redistribution of renal cortical blood flow during hemorrhage. First, although the noradrenergic results indicate that there is uniformity of adrenergic receptor sites from zone to zone, they do not exclude differences in adrenergic innervation between groups of nephrons as a possible mechanism of the redistribution. However, recent studies in our laboratory which failed to demonstrate any alteration in the intrarenal distribution of blood flow during low-frequency renal nerve stimulation (unpublished observations) are against this possibility. Second, although angiotensin infusion did not cause a selective fall in outer cortical blood flow, it is still possible that the local release of renin predominantly located in outer cortical nephrons (7) may cause preferential vasoconstriction of outer cortical nephrons independent of the increased humoral concentrations of this pressor substance in hemorrhage. Third, changes in perfusion pressure per se may be of importance in determining the distributional pattern during hemorrhage. This is especially attractive in view of the results of McNay and Abe (17) who found a similar alteration in the intrarenal distribution of blood flow during aortic constriction.

Stein and associates (23), McNay and Abe (17), and Bay, Stein, Rector, Osgood, and Ferris (4) demonstrated a similar redistribution of renal cortical blood flow in several models associated with renal vasodilation. Since a decrease in renal resistance is also present in aortic constriction (17), the common factor in all these models may be renal vasodilation. In relation to the present studies, a number of investigators have found no change or even a decrease in renal resistance in the first 30 min after the induction of hemorrhagic hypotension (14, 21). Haddy, Scott, and Molnar (14) have noted an initial fall in renal resistance during hemorrhage and have suggested that this is due to the local vasodilatory mechanisms which cause autoregulation. As is shown in Table 4, renal blood flow and mean arterial pressure fell in a parallel fashion, 54 and 52%, respectively, indicating that renal resistance in these studies was essentially unchanged 30 min after the induction of hemorrhagic hypotension. The constancy of renal resistance at this time may be due to a combination of these persistent autoregulatory mechanisms superimposed on the background of the known increased level of circulating vasoconstrictor substances (20, 27).

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