Redistribution of Cortical Blood Flow during Renal Vasodilatation in Dogs

By John L. McNay, M.D., and Youichi Abe, M.D.

ABSTRACT

We studied the distribution of cortical blood flow during renal vasodilation induced by four maneuvers; reduction of perfusion pressure, intraarterial infusion of acetylcholine, and diuresis induced by ethacrynic acid or mannitol. Dogs were anesthetized with pentobarbital and urinary losses replaced. Blood flow of the denervated kidney was measured by an electromagnetic flowmeter, and distribution of renal cortical blood flow analyzed by the radioactive microsphere technique. Acetylcholine caused progressively greater proportional vasodilation from superficial to deep cortex. The resulting pattern of flow redistribution was nearly identical to that observed in response to reduced perfusion pressure (autoregulation). Since the same pattern of heterogeneous cortical response was elicited by two qualitatively different stimuli, we propose that it reflects differential responsiveness of individual cortex zones. Ethacrynic acid redistributed flow in a different pattern, augmenting the proportion to the middle, but not the juxtamedullary cortex. High urine flow was excluded as a nonspecific basis for this difference, since acetylcholine produced its usual pattern of redistribution during the ethacrynic acid-induced diuresis. Additionally, ethacrynic acid-induced flow redistribution was not secondary to high urine flow per se, since mannitol diuresis did not significantly alter distribution of flow.

ADDITIONAL KEY WORDS

acetylcholine, mannitol, ethacrynic acid, radioactive microspheres, vascular responsiveness, autoregulation, blood viscosity.

We have recently shown that the renal cortex is perfused at heterogeneous rates. In addition, reduction of renal arterial pressure over the autoregulatory range results in redistribution of renal cortical flow from the outer to inner cortex (1). We designed the present study as a first step in defining the mechanisms underlying the differential vascular responses of the renal cortical zones. Our objective was to determine whether the heterogeneous vascular response pattern was specific for vasodilation due to pressure reduction (autoregulation) or whether it also occurred in response to other vasodilating interventions. We selected acetylcholine as a standard vasodilating substance which acts directly to inhibit arteriolar smooth muscle tone in general. Ethacrynic acid contrasts with acetylcholine since its vasodilating properties are selective for the kidney (2). In addition, we studied the distributional effects of mannitol which shares with ethacrynic acid the ability to augment renal blood flow (3, 4), but which might possibly do so by a different mechanism.

Materials and Methods

Mongrel dogs ranging in weight from 12 to 20 kg were anesthetized with intravenous pentobarbital, 25 mg/kg. The urinary bladder was catheterized. The left kidney was exposed via a retroperitoneal flank incision and all visible nerves entering the renal hilum were divided. The ureter was cannulated and urine flow was measured by a drop counter or timed collections depending on flow rate. Total renal blood flow (RBF) was measured by an electromagnetic flowmeter (Medicon X-4000). Zero flow baseline was determined...
by brief occlusion of the renal artery distal to the flow probe. Flow probes were calibrated by saline perfusion of excised vessels. Renal arterial pressure was considered equal to aortic pressure measured at the level of the renal artery via a left femoral arterial cannulation. RBF and renal arterial pressure were recorded continuously by a Beckman RC Dynograph.

The distribution of cortical blood flow was determined using radioactive microspheres (3M Company, St. Paul, Minn.) according to a technique described in an earlier publication (1). Briefly, a suspension of plastic microspheres 19 μm in diameter was injected into the left ventricle through a catheter introduced via the left common artery. Each injection contained 0.5 mg bead mass, representing approximately 95,000 microspheres. Sequential injections were performed using microspheres labeled with different gamma emitting isotopes. Four cortex zones of equal thickness were analyzed for individual isotope content (5) and perfusion rate of each zone calculated.

The following properties of 19 μm plastic microspheres are pertinent to studies of intrarenal blood flow distribution (from ref. 1): (1) trapping of microspheres by the kidney is more than 99.95% complete; (2) virtually all embolization occurs in the renal cortex, since only 1.2 ± 0.3% of radioactivity is found in the renal medulla; (3) of microspheres arrested in the cortex, 97% are in glomerular capillaries and 3% in afferent arterioles; (4) time (up to 1 hour) and repeated embolization (up to four times) have no effect on the cortical distribution of microspheres; (5) there is good evidence that microspheres are distributed in the renal cortex in proportion to the distribution of blood flow through the initial capillary bed, i.e., that of the glomeruli.

In interpreting the results obtained by the microsphere technique, it should be emphasized that the loci of embolization are in the initial parallel elements (glomerular capillaries) of a parallel-series (portal) type circulation. The measured flow per unit mass of individual cortex zones may be represented by the product: (flow per glomerulus) × (glomeruli per gram). In a separate publication (1), we have discussed the implications of differences in the number of glomeruli per gram of different cortex zones. It should be emphasized that the microsphere method of measuring the effects of vasoactive stimuli on renal flow rates depends on measurement of the activities of different isotopes detectable in the same tissue sample. Consequently, proportional changes in flow rates are independent of differences in the number of glomeruli per gram. We use the terms "cortex zone perfusion rate" or "cortex zone flow rate" with the understanding that the microsphere method gives no information on the course of post-glomerular blood flow. For example, the perfusion rates of the subcapsular glomerular cortex and of the renal medulla cannot be inferred from microsphere data.

**EXPERIMENTAL PROTOCOLS**

**Renal Arterial Acetylcholine Infusion.**—In nine experiments (acetylcholine series A), microsphere injections were performed before and 5 minutes after starting infusion of a solution of acetylcholine hydrobromide (Eastman, Rochester, N. Y.) into the left renal artery. The solution was infused through a 23-gauge needle at a rate of 0.4 ml/min. The acetylcholine concentration was individualized to produce a standard administration rate of 4 μg/kg body weight. In five of the animals, the effects on RBF and urine flow of serial two-fold increments in the infusion rate of acetylcholine were studied.

In an additional five experiments (acetylcholine series B), the circulatory effects of pressure reduction were compared with those of acetylcholine infusion. The first microsphere injection was performed at normal renal arterial pressure (134.0 ± 3.3 mm Hg se) in the absence of acetylcholine administration. Pressure was then reduced to the lower autoregulatory limit (77.0 ± 3.7 mm Hg se) and a second injection of the microspheres performed. The aortic pressure was then returned to control level. We have previously demonstrated that the flow rates of the individual cortex zones are not affected by a prior temporary reduction in pressure (1). A third injection of microspheres was made during subsequent intraarterial infusion of acetylcholine at a rate of 4 μg/kg body weight.

**Ethacrynic Acid Administration.**—(Ten experiments). The initial microsphere injection was performed before diuretic administration (control observation). Ethacrynic acid (Edecrin, Merck) was then administered intravenously as a loading dose (2 mg/kg body wt) followed by a maintenance infusion of 2 μg/kg per hour. To maintain approximate overall fluid and electrolyte equilibrium, normal saline was infused intravenously at a rate continuously matched to total urine flow. This method of ethacrynic acid administration produced stable plateaus of urine flow and RBF within 30 minutes after the loading dose. A second microsphere injection was made at this time. In five experiments, we determined whether the dosage schedule described above produced a maximal effect on RBF and urine flow. We administered a second loading dose (2 mg/kg) and doubled the rate of maintenance infusion one-half hour after initial ethacrynic acid administration. One-half hour subsequently, we adminis-
tered a third loading dose (4 mg/kg) and increased the maintenance infusion to four times its initial value.

**Concurrent Administration of Acetylcholine and Ethacrynic Acid.**—In five experiments the following protocol was followed. After initial control observations (control 1), acetylcholine was infused for 5 minutes and microspheres injected. Acetylcholine infusion was discontinued and one-half hour allowed for kidney function to recover (control 2). Ethacrynic acid was then administered and microsphere injection performed in the usual manner. During continuation of ethacrynic acid maintenance infusion, acetylcholine infusion was reinstated, and microspheres injected after 5 minutes. Since we had available a maximum of four varieties of gamma-labeled microspheres, only a single control observation could be made in each experiment; control 1 was used in three experiments and control 2 in two experiments.

**Hypertonic Mannitol Administration—Mannitol** (Fisher Scientific Co.) was dissolved in normal saline to produce a solution containing 15 g/100 ml final volume. In seven experiments (mannitol series A), an initial control injection of microspheres was performed, following which mannitol solution was infused intravenously at a constant rate of 0.7 ml/kg body weight per minute. We elected to perform the second injection of microspheres at a time when urine flow and RBF had increased to levels comparable to those seen during ethacrynic acid diuretics.

**Concurrent Administration of Acetylcholine and Mannitol.**—In a separate series of five experiments (mannitol series B), we followed a protocol analogous to that used in the concurrent acetylcholine and ethacrynic acid series described above; i.e., the microsphere injection periods were identified as: control 1, acetylcholine infusion; control 2, mannitol infusion, and acetylcholine infusion during mannitol.

**Analysis of Results**

All perfusion rates, whether of the kidney as a whole or of individual zones, were expressed as ml/g • min⁻¹. The perfusion rate before vasodilating intervention was termed "control." Statistical significance was assessed by ′-test or paired ′-test as appropriate (6). Variability was expressed by the standard error (se).

Analysis of the effects of the vasodilating interventions on the four cortex zones was based on three modes of expressing circulatory responses.

1. The absolute tissue perfusion rates during various periods of a single experimental series were compared by paired ′-tests. Differences between the changes in perfusion rates produced in separate experimental series were analyzed by the ′-test of differences between sample means.

2. We divided the perfusion rate during vasodilation by the central perfusion rate to obtain the "perfusion response ratio." This ratio was calculated for the kidney as a whole and for each cortex zone.

3. We calculated the percent of total renal flow perfusing each individual zone under control conditions and during each intervention. This expression took into account both the perfusion rate of each cortex zone and its mass as a percent of the total kidney cortex. Changes in total flow distribution reflect changes in relative flow rates of the individual cortex zones, since the tissue masses to which the flows were referred were constant for a given kidney under all experimental conditions.

**Correction for Changes in Blood Viscosity**

In interpreting the flow effects of mannitol it was important in some parts of the analysis to consider the effects of whole blood viscosity. It has been shown that the whole blood viscosity can be estimated from the hematocrit (7). Neither acetylcholine nor ethacrynic acid affected whole blood hematocrit, but mannitol significantly decreased it. Since changes in vascular geometry were of primary interest, we took the changes in blood viscosity into account according to Poiseuille's law, which may be expressed in the following manner:

\[ \pi = \frac{8L}{\pi r^4} u_c, \quad \pi' \]  

where \( \pi \) denotes pressure; \( L \), vessel length; \( r \), vessel radius; \( u \), the absolute viscosity of blood under control conditions; and \( \pi' \), flow. The flow effects of mannitol were analyzed independently of the viscosity components. We chose to express the vascular geometric factors in terms of conductance, since it is convenient to think interchangeably in terms of increased perfusion (flow) and increased conductance.

\[ C_c = \frac{1}{(8L/\pi r^4) u_c} = \frac{\pi'}{\pi}, \]  

where \( C_c \) indicates conductance under conditions of control blood viscosity, \( u_c \).

We modified the conductance expression during mannitol as follows to obtain a value for \( C_c' \):

\[ C_c' = \frac{1}{(8L/\pi r^4) u_m} \frac{u_c}{u_m}, \]  

where \( u_m \) designates blood viscosity during mannitol infusion. The ratio, \( u_c/u_m \), was termed the viscosity correction factor (\( n \)), and calculated from the nomogram of blood viscosity presented.
Effects of Acetylcholine, Ethacrynic Acid and Mannitol on Renal Arterial Pressure, Renal Blood Flow and Urine Flow

<table>
<thead>
<tr>
<th>Intervention</th>
<th>N</th>
<th>Renal arterial pressure (mm Hg)</th>
<th>Renal blood flow (ml • g⁻¹ • min⁻¹)</th>
<th>Urine flow (ml • g⁻¹ • min⁻¹ • 10⁻⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9</td>
<td>125.3 ± 5.7</td>
<td>126.4 ± 5.6</td>
<td>116.0 ± 3.6</td>
</tr>
<tr>
<td>Acetylcholine*</td>
<td>10</td>
<td>122.9 ± 1.8</td>
<td>12.5 ± 1.8</td>
<td>117.5 ± 3.8</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>7</td>
<td>102.5 ± 1.9</td>
<td>4.77 ± 0.69</td>
<td>132.5 ± 1.9</td>
</tr>
</tbody>
</table>

All values are means ± SE.

*Acetylcholine, series A. tMannitol, series A.

in reference 7. Under control conditions, n = u/uc < 1, while during mannitol, n = um/uc < 1.

The final equation used to calculate conductance was:

\[ C_v = \frac{F}{n} \cdot \Delta - \] (4)

Results

Table 1 presents the values for renal arterial pressure, RBF and urine flow before and during each vasodilating intervention. Only mannitol affected renal arterial pressure (P < 0.01). All three interventions caused significant (P < 0.001) changes in both RBF and urine flow. The augmentation of RBF by acetylcholine significantly exceeded that caused by both ethacrynic acid (P < 0.001) and mannitol (P < 0.05). The increments of RBF and urine flow produced by ethacrynic acid and mannitol did not differ significantly. Acetylcholine and ethacrynic acid were administered in maximally effective doses, since increments in the standard dose of both agents by factors of 2 or 4 produced no significant increase in their effects on either RBF or urine flow.

Responses to Experimental Interventions by Individual Cortical Zones

Table 2 presents the perfusion rates of the individual cortex zones before and during acetylcholine, ethacrynic acid, and mannitol. Before intervention (control), tissue perfusion varied according to zone in the characteristic pattern described in our previous publication (1), i.e., perfusion of zone 2 exceeded zone 1, and there was a progressive decrease in perfusion rate from zone 2 to zone 4. Each intervention resulted in significant increase in the perfusion of each zone, with a single exception; ethacrynic acid did not significantly affect perfusion of zone 1. The increases

Table 2: Perfusion Rates of Individual Cortical Zones before and during Vasodilating Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Zone</th>
<th>N</th>
<th>Perfusion rate zone 1 (ml • g⁻¹ • min⁻¹)</th>
<th>Perfusion rate zone 2 (ml • g⁻¹ • min⁻¹)</th>
<th>Perfusion rate zone 3 (ml • g⁻¹ • min⁻¹)</th>
<th>Perfusion rate zone 4 (ml • g⁻¹ • min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1</td>
<td>9</td>
<td>3.77 ± 0.58</td>
<td>5.93 ± 0.33</td>
<td>3.56 ± 0.21</td>
<td>3.28 ± 0.30</td>
</tr>
<tr>
<td>Acetylcholine*</td>
<td>2</td>
<td>9</td>
<td>4.09 ± 0.63</td>
<td>11.74 ± 0.84</td>
<td>7.71 ± 0.74</td>
<td>6.68 ± 0.56</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>3</td>
<td>10</td>
<td>3.39 ± 0.21</td>
<td>5.75 ± 0.17</td>
<td>3.01 ± 0.29</td>
<td>2.04 ± 0.21</td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
<td>10</td>
<td>3.89 ± 0.43t</td>
<td>8.99 ± 0.40</td>
<td>5.43 ± 0.41</td>
<td>3.09 ± 0.32</td>
</tr>
<tr>
<td>Mannitol†</td>
<td>5</td>
<td>7</td>
<td>4.50 ± 0.63</td>
<td>10.33 ± 0.65</td>
<td>5.89 ± 0.29</td>
<td>3.73 ± 0.61</td>
</tr>
</tbody>
</table>

All values are means ± SE. The perfusion of all zones was significantly (paired t-test) increased by each intervention, with one exception (designated†).

*Acetylcholine, series A. †Mannitol, series A.

Circulation Research, Vol. XXVII, December 1970
during ethacrynic acid and mannitol were smaller than during acetylcholine as expected from the lesser effects on RBF (Table 1). The differences were significant in the case of ethacrynic acid for zone 2 (P<0.01), and both ethacrynic acid and mannitol for zone 3 (P<0.05). The greatest differences between the responses to acetylcholine and those to ethacrynic acid and mannitol occurred in zone 4 (P<0.001). During acetylcholine, perfusion of zone 4 significantly (P<0.02) exceeded that of zone 1, while during both ethacrynic acid and mannitol it did not differ significantly from that of zone 1.

Perfusion Response Ratio during Vasodilation by Acetylcholine, Ethacrynic Acid and Mannitol (Figure 1).—This mode of analysis clearly revealed two prominent features of the renal circulatory responses to various vasodilators: (1) the zones differed from one another in their capacity to respond to acetylcholine, and (2) the pattern of zonal responses depended on the particular vasodilating intervention. The response to acetylcholine was characterized by progressively greater percent flow increases in sequence from outer to inner cortex. The percent increase of zone 1 during acetylcholine was 28 ± 10, compared to an increase of 305 ± 32 for zone 4.

Neither ethacrynic acid nor mannitol produced a similar pattern. While the responses to ethacrynic acid did increase progressively from zone 1 to zone 3, the response of zone 4 was significantly (P<0.05) less than zone 3. The response pattern to mannitol was characterized by an almost uniform increase in perfusion in all four cortex zones. Since zone 4 was relatively most responsive to acetylcholine, it was most sensitive in reflecting differences between the effects of the three

Effects of acetylcholine (series A), ethacrynic acid and hypertonic mannitol (series A) on perfusion response ratios of the kidney as a whole and individual cortical zones. The response ratio of acetylcholine increased progressively from the superficial to the deep cortex. Cortical zone 4 responded significantly less to ethacrynic acid than to acetylcholine. The response of the outer three cortex zones to ethacrynic acid was progressively greater from superficial to deep cortex, but such a trend was not definitely present during hypertonic mannitol diuresis.

RBF = renal blood flow.
Changes from control in the percent of total renal blood flow perfusing each cortical zone during acetylcholine (A), ethacrynic acid (E) and hypertonic mannitol (M). Both acetylcholine and ethacrynic acid caused significant redistribution of blood flow from the outer cortex (zone 1) to the inner cortex (zone 3). Only acetylcholine significantly increased the percent of total renal blood flow perfusing zone 4. None of the effects of mannitol was significantly different from either zero or from the effect of ethacrynic acid.

Percent of Total Renal Blood Flow Per Zone.—There was no significant difference among the three experimental groups in the percent of total RBF perfusing the four cortex zones under control conditions. In Figure 2, we present the change from control in percent of total RBF perfusing each zone during the vasodilating interventions. It is evident that acetylcholine and ethacrynic acid caused significant redistribution of total RBF, while mannitol did not. The distributional effects of acetylcholine and ethacrynic acid differed in that acetylcholine caused a significantly (P < 0.025) greater increase in percent of flow to zone 4.

Comparison between Pressure Reduction and Acetylcholine Infusion.—Table 3 summarizes the overall renal hemodynamic status during the control period, pressure reduction, and acetylcholine infusion. Paired t-tests indicated that overall renal vascular resistance was significantly (P < 0.05) less during acetylcholine than during pressure reduction and that renal vascular resistance during pressure

### Table 3
Comparison of Overall Renal Hemodynamic Effects of Pressure Reduction and Intra-arterial Acetylcholine Infusion (Series B, N = 5)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Renal blood flow (ml/g/min)</th>
<th>Renal arterial pressure (mm Hg)</th>
<th>Renal resistance (mm Hg·g⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.26 ± 0.21</td>
<td>134.0 ± 3.32</td>
<td>42.1 ± 3.0</td>
</tr>
<tr>
<td>Pressure reduction</td>
<td>3.12 ± 0.20</td>
<td>77.0 ± 3.74</td>
<td>25.1 ± 1.3</td>
</tr>
<tr>
<td>Acetylcholine infusion</td>
<td>6.93 ± 0.62</td>
<td>133.0 ± 4.64</td>
<td>19.7 ± 1.7</td>
</tr>
</tbody>
</table>

All values are means ± se.
redistribution was significantly \( P < 0.01 \) less than during the control period. This pattern is consistent with previous observations from our laboratory (8) and reflects the effects of acetylcholine on resistance of the efferent arterioles.

In Table 4, we present a comparison of the effects of pressure reduction and intra-arterial acetylcholine infusion on the distribution of blood flow to the four cortical zones. Both interventions caused significant changes from control in the percent distribution to cortical zones 1, 3, and 4. In addition, the zonal flow distributions during the two interventions were not significantly different one from the other.

**Table 4**

<table>
<thead>
<tr>
<th>Effect of Intra-arterial Acetylcholine Infusion and Pressure Reduction on the Distribution of Cortical Blood Flow (Series B, ( n = 5 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of renal blood flow to cortical zones</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Acetylcholine infusion</td>
</tr>
<tr>
<td>Pressure reduction</td>
</tr>
</tbody>
</table>

All values are means ± se. Values in parentheses are significance of difference from control; ns indicates not significant.

In Table 5, we present the distributional effects of acetylcholine and ethacrynic acid, administered to the same animals, alone and in combination. Given singly, each drug produced effects typical of those presented previously (Fig. 2). Distribution of flow during ethacrynic acid differed significantly from that during acetylcholine alone (cortical zones 2 and 4) and from that during concurrent administration of both agents (cortical zones 3 and 4). However, there were no significant differences between the effects of acetylcholine infusion alone and acetylcholine infusion during ethacrynic acid diuresis.

In Table 6, we present the distributional effects of acetylcholine and mannitol administration to the same animals alone and in combination (mannitol series B). The distributional effects of each intervention were typical of those presented previously (Fig. 2). Distribution of flow during mannitol differed significantly from that during acetylcholine alone (cortex zones 1, 3 and 4) and from that during control, 307 (8) and ethacrynic acid alone, 423 (18).

### Table 5

<table>
<thead>
<tr>
<th>Effects of Acetylcholine and Ethacrynic Acid, Alone and in Combination, on the Distribution of Cortical Blood Flow (( n = 5 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of renal blood flow to cortical zones</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Acetylcholine infusion</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
</tr>
<tr>
<td>Acetylcholine during ethacrynic acid</td>
</tr>
</tbody>
</table>

All values are means ± se. Values in parentheses are significance of difference from control; ns indicates not significant.

Circulation Research, Vol. XXVII, December 1970
Effects of Acetylcholine and Mannitol, Alone and in Combination, on the Distribution of Cortical Blood Flow
(Mannitol Series B, n = 5)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent of renal blood flow to cortical zones</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>25.1 ± 0.8</td>
</tr>
<tr>
<td>Acetylcholine infusion</td>
<td>15.9 ± 1.1 (.001)</td>
</tr>
<tr>
<td>Mannitol</td>
<td>24.5 ± 1.8 (ns)</td>
</tr>
<tr>
<td>Acetylcholine during mannitol</td>
<td>15.4 ± 1.4 (.001)</td>
</tr>
</tbody>
</table>

All values are means ± SE. Values in parentheses are significance of difference from control; ns indicates not significant.

during concurrent administration of both agents (cortical zones 1, 3 and 4). However, the effects of acetylcholine infusion were not significantly different when given alone or during mannitol diuresis.

The effects of mannitol on total renal conductance, with and without correction for changes in blood viscosity, are presented in Table 7. The increase in uncorrected conductance during mannitol diuresis was significant (P < 0.01). As a result of the highly significant (P < 0.001) decrease in n, the corrected conductance increased by a lesser, although still significant (P < 0.05) amount.

Discussion

Our results clearly indicate that acetylcholine caused a redistribution of renal cortical blood flow from the outer to the inner cortex. Although perfusion of all renal cortical zones increased during acetylcholine administration, the percent increase in perfusion rate was progressively greater from outer to inner cortex. It is of particular interest to compare the response to intra-arterial acetylcholine infusion with that produced by decreased renal arterial pressure (1). A prerequisite for rigorous comparison of the effects of acetylcholine and pressure reduction was that the comparison be made under conditions of maximal effectiveness of each intervention. This condition was met, since intensification of neither stimulus produced further reduction in total renal vascular resistance. The two interventions were found to produce virtually indistinguishable effects on the percent of total renal blood flow perfusing the individual cortex zones (Table 4).

It is notable that this similarity of response pattern obtained despite major differences in both pressure and flow due to the modes of experimental intervention. Our intent is not to suggest an exact equality of the responses to the two maneuvers, but rather to emphasize that there is a general tendency toward equivalence between two interventions of completely different types. This similarity clearly indicates that flow redistribution seen with pressure reduction is not specific for the autoregulatory process, but is a more general

Table 7

Effect of Mannitol on Total Renal Conductance, with and without Correction for Change in Calculated Blood Viscosity (n = 7)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control</th>
<th>Mannitol</th>
<th>Mannitol X n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>mm Hg x g min x 10^-2</td>
<td>mm Hg x g min x 10^-2</td>
<td>mm Hg x g min x 10^-2</td>
</tr>
<tr>
<td>Mean</td>
<td>2.59</td>
<td>3.61</td>
<td>0.808</td>
</tr>
<tr>
<td>Se</td>
<td>0.15</td>
<td>0.26</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*n signifies "viscosity correction factor" = whole blood viscosity during mannitol diuresis/viscosity during control conditions.


* indicates not significant.
pattern that may depend not on the stimulus to vasodilation but rather on intrinsic differences in the responsiveness of the individual cortex zones. If responsiveness is defined as the ratio of perfusion during response to that during control period, the cortical zones did differ since there were significant ($P<0.01$) serial zone to zone differences in the perfusion response ratios (Fig. 1).

To make valid comparisons between the circulatory effects of acetylcholine, mannitol and ethacrynic acid, it was necessary to exclude the possibility that increase of urine flow or changes in blood viscosity which accompany the latter maneuvers had an intrinsic effect on microsphere distribution, either by heterogeneous intrarenal passive effects on vascular caliber or by rheological effects secondary to hemodilution. This problem was approached by determining whether ethacrynic acid or mannitol modified the effect of acetylcholine on the intrarenal distribution of blood flow. The maximum effective dose of acetylcholine was employed before and during the diuretic interventions. In both experimental series, acetylcholine produced the typical pattern of flow redistribution under control conditions. This characteristic pattern of flow redistribution was unaffected by concurrent diuresis induced by either ethacrynic acid or mannitol. These data strengthened previous evidence that distribution of microspheres reflects distribution of blood flow under a variety of conditions of RBF and renal arterial pressure (1), and extended the validation to conditions of altered urine flow and hematocrit. We have obtained analogous data validating the microsphere method under conditions of high urine flow and hemodilution induced by saline infusion (McNay and Abe, unpublished observations).

The renal circulatory effects of ethacrynic acid differed from those produced by either acetylcholine or pressure reduction. The observation that ethacrynic acid increases RBF (10). The lesser vasodilating effect of ethacrynic acid than acetylcholine was not secondary to an effect of high urine flow, since the combination of acetylcholine and ethacrynic acid increased total renal blood flow to the same extent as acetylcholine alone. In addition, the ethacrynic acid diuresis was associated with a highly specific pattern of flow distribution characterized by absence of an effect on the perfusion response ratio of zone 4. Redistribution of RBF during ethacrynic acid diuresis was first recognized by Birtch et al. on the basis of $^{85}$Kr experiments (10). On the basis of autoradiographs, it was inferred that blood flow to the juxtamedullary cortex and outer medullary peritubular capillaries was reduced. Our results clearly indicate that flow to the juxtamedullary cortex is actually augmented in exact proportion to the increase in RBF. Close analysis of their Table 1 (10) suggests that the basis for their conclusion may have been difficulty in making sufficiently accurate correlations between the calculated washout "compartments" and actual anatomical locations. Under control circumstances, flow to the "outer medulla" probably represented flow to cortex zones 3 and 4 (1). So defined, this "compartment" received 19% of RBF by the $^{85}$Kr method (ref. 10, Table 1) and 22% by the microsphere method (1). However, following ethacrynic acid, external counting could no longer be expected to separate flow to cortical zone 3 from that to more superficial cortical zones, since we observed that zone 3 actually exceeded zone 1 in perfusion rate (Table 2). We infer that the compartment designated "cortex B" after ethacrynic acid or furosemide was probably zone 4, because it corresponded with that zone in two regards: (1) It had a lower perfusion rate than any other cortical zone and (2) it comprised an average of 7.6% of RBF (Table 1, ref. 10) compared to 7% measured by the microsphere method.

The circulatory effects of ethacrynic acid on the outer three cortical zones remain unexplained. We studied the effects of mannitol diuresis to determine whether high urine flow
per se would produce the same pattern of cortical blood flow redistribution. As indicated in the analysis of the changes in percent total renal blood flow perfusing each zone (Fig. 2), the effects of ethacryninc acid on zones 1 to 3 closely resembled those of acetylcholine, while the effects of mannitol were insignificant and differed from those of acetylcholine. This evidence tends to exclude the presence of high urine flow with its associated changes in renal interstitial pressure and arteriolar transmural pressure as the basis for the ethacryninc acid effect.

The effect of mannitol to reduce the renal extraction of para amino hippurate (PAH) has been attributed to a redistribution of blood flow to the medulla. While mannitol and acetylcholine produce virtually equal effects on the extraction of PAH (11), we found that their effects on cortical flow distribution were different. Mannitol did not redistribute blood flow to the inner cortex while acetylcholine did. This disparity suggests that if mannitol causes a redistribution of flow, it probably occurs secondary to mechanisms operating at the level of the postglomerular circulation. Our data offer support to the observations and conclusions of Velasquez et al. (12) that redistribution of renal blood flow secondary to mannitol is minimal, and that a mechanism other than flow redistribution may be responsible for its effect on PAH extraction. Although the effect of mannitol to reduce hematocrit and blood viscosity is considered an unlikely mechanism for increasing renal blood flow (3), we infer that decrease in viscosity may make a substantial contribution. As indicated in Table 7, changes in whole blood viscosity were sufficient to account for 45% of the increase in renal conductance during mannitol diuresis.

References

Redistribution of Cortical Blood Flow during Renal Vasodilation in Dogs
JOHN L. MCNAY and YOICHI ABE

Circ Res. 1970;27:1023-1032
doi: 10.1161/01.RES.27.6.1023

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1970 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/27/6/1023

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/