Pressure-Dependent Heterogeneity of Renal Cortical Blood Flow in Dogs

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

ABSTRACT
We determined the effect of perfusion pressure on the distribution of blood flow within the renal cortex of the anesthetized dog. Total blood flow to the denervated kidney was measured by an electromagnetic flowmeter and perfusion pressure was manipulated over the autoregulatory range (136 to 81 mm Hg) by an aortic clamp. Distribution of cortical blood flow was determined by the radioactive microsphere technique. Tissue perfusion rates of four cortical zones of equal thickness differed significantly from each other at normal arterial pressure. In sequence from superficial to deep, perfusion of the cortex zones averaged 4.18, 6.80, 3.07, and 1.68 ml • g⁻¹ • min⁻¹. Aortic constriction significantly reduced perfusion of the outer cortical zone and augmented perfusion of the inner two cortex zones. Twelve percent of total renal blood flow was redistributed by pressure reduction. Atropine, 1 mg/kg, had no effect on cortical perfusion rates at either pressure. The influence of microsphere diameter and density on cortex perfusion rates was systematically studied and found to be minor. This observation implies that the microsphere method is valid for measuring distribution of blood flow within the renal cortex. We conclude that zones of the renal cortex are perfused at different rates and respond differently to changes in arterial pressure.

ADDITIONAL KEY WORDS redistribution of flow autoregulation radioactive microspheres atropine regional blood flow renal medulla renal cortex

It has been demonstrated by a wide variety of methods that tissue perfusion rates within the kidney are heterogenous (1-6). In general, interest has centered on differences in the perfusion rates of the cortex and medulla. Although distribution of blood flow within the renal cortex has received less attention, evidence favoring homogenous cortical perfusion has been obtained by several methods which readily detect differences between cortical and outer medullary perfusion rates (3, 6).

However, evidence obtained by the ⁸⁵Kr method (2) suggests differences in the perfusion rates of outer and inner cortex. In addition, heterogenous cortical perfusion has been observed during hemorrhagic hypotension (7), splanchnic nerve stimulation (8), and infusion of angiotensin (9). The relevance of possible heterogeneity of cortex perfusion has been increased by recent observations of differences between the glomerular filtration rates of superficial and juxtamedullary nephrons (10).

In this investigation, we have specifically analyzed distribution of blood flow within the renal cortex. We approached the problem by the use of radioactive microspheres (11-13). This technique was well suited to our objectives because microsphere emboli of appropriate size are arrested within or adjacent to the first capillary bed they encounter. Since in the kidney, glomerular capillaries are the first to be perfused, the location of microspheres is necessarily cortical. We studied the renal circulation under conditions of normal and reduced perfusion pressure. Pressure reduction within the...
autoregulatory range was a uniquely advantageous maneuver since total renal blood flow remained constant despite large changes in renal vascular resistance.

Materials and Methods

Mongrel dogs ranging in weight from 12 to 20 kg were anesthetized with intravenous pentobarbital, 25 mg/kg. The left kidney was exposed through a retroperitoneal flank incision. All visible nerves entering the renal hilum were divided. In a limited number of experiments, an 18-gauge Angiocath was introduced through the spermatic or ovarian vein and advanced toward the kidney to assure positioning in the renal vein. Total renal nerves entering the renal hilum were divided. In a retroperitoneal flank incision. All visible nerves entering the renal hilum were divided. In a limited number of experiments, an 18-gauge Angiocath was introduced through the spermatic or ovarian vein and advanced toward the kidney to assure positioning in the renal vein. Total renal pressure signifies the lowest RAP at which autoregulation was complete. In one group of experiments (series A2), pressure was reduced below the autoregulatory range.

A no. 6 Lehman end-hole catheter, 20-inches long, was introduced blindly into the left ventricle through the left common carotid artery and its position was confirmed by the recorded pressure tracing. Twenty-milliliter vials containing tracer-labeled microspheres (3M Company, St. Paul, Minn.) suspended in 20% dextran were agitated vigorously by hand for 1 minute before aspiration of 2 ml for injection. The syringe containing the microsphere suspension was rapidly attached to a three-way stopcock on the left ventricular catheter. Injection was performed immediately, followed by rapid duplicate flushing of the injection syringe and catheter by a second syringe previously attached to the stopcock. To minimize retention to labeled microspheres in the injection system, the stopcock was removed, and the catheter allowed to bleed back before replacement by a new stopcock. The injection catheter was then flushed with heparinized saline.

Microspheres of three approximate size ranges were employed. The number of microspheres in a single injection was related to the mean diameter as follows: 35µ, 30,000; 27µ, 26,600; 19µ, 76,000. In most experiments, the microspheres were plastic (carbonized), but where a different density was desired, ceramic microspheres were used. The average density of the two types was 1.5 and 3 g/ml, respectively. The number of microspheres injected was selected according to the following general considerations. For a kidney weighing 40 g, the total number of glomeruli would be approximately 530,000 (14). Given a kidney blood flow equal to 10% of cardiac output and a uniform embolization site in the afferent arteriole, a small proportion (approximately 0.5%) of glomeruli would be occluded by a single injection of the microspheres. Since a proportion of the 36- and 27µ-diameter microspheres embolized afferent arterioles supplying more than one glomerulus (see below), approximately 0.8 and 0.6% of glomeruli, respectively, were occluded per injection. The larger number of 19µ microspheres produced less vascular occlusion, since embolization occurred almost exclusively within the glomerular tuft rather than the afferent arterioles.

The extent of renal trapping of microspheres was measured by counting samples of blood withdrawn at a rate of 38.6 ml/min from the aorta and renal vein during a simultaneous 30-second interval starting immediately before injection. Appropriate matching of samples was assured by the use of identical tubing systems and a dual-syringe withdrawal pump.

After completion of the microsphere injections, the kidney was excised, allowed to drain for 5 minutes, weighed, and measured in three dimensions. A 5-ml thick sagittal section was cut by hand and cortex thickness measured. A series of blocks approximately 5-ml wide was prepared by cuts oriented perpendicularly to the local capsular tangent. The blocks were frozen in a mixture of acetone and dry ice. Six sections diagrammatically represented in Figure 1 were prepared by slicing parallel to the tangent of the capsular surface. There were four cortex zones of equal thickness, an inner and an outer medullary zone. We established that the sectioning process did produce cortex slices of equal average thickness by histological comparison of six sections from each cortex zone of five animals. In this analysis, allowance was made for the slightly convex surface of the outermost slice. The innermost cortical zone necessarily included some outer medullary tissue, due to the scalloped contour of the corticomedullary border. Corresponding slices from approximately 10 blocks were weighed and placed in plastic counting tubes. This pooling process served to reduce variability attributable to slight slicing inaccuracies and local anatomic variation. It was assumed that the
sampled portion of the kidney was representative of the kidney as a whole.

The approximate weight of pooled tissue in each counting tube was 0.6 g. When only two isotopes were used, counting was performed by a Nuclear Chicago dual-channel automatic gamma counting system (model 4233), and individual isotope activity calculated according to the method of Van Herden et al. (15). When three or four isotopes were used, counting was done by a Nuclear Data gamma spectrometer (series 2200) using 128 channels, and individual isotope activity calculated according to Rudolph and Heymann (11).

Total renal blood flow (flowmeter) was equated with cortical blood flow, since the renal medulla contained less than 1.3% of total renal activity (see Results). The weight of each cortex zone was approximated by calculations based on the formula for an ellipsoid. A series of volumes was calculated by sequential reductions in each hemi-axis by an amount equal to one-fourth the cortex thickness. Each calculated volume was expressed as a percent of total renal volume. Subtraction of each percent of renal volume from the immediately larger one yielded a difference equal to the percent of total renal volume in the corresponding tissue zone.

Total cortical volume was calculated to be 78.4% of total renal volume. The volumes of the individual cortex zones expressed as percents of total renal volume were: 1, 27; 2, 21.9; 3, 17.3; 4, 12.2. The slight excess of calculated total cortical volume over the usually cited figure of 70 to 75% (2, 6) may have reflected the inclusion of some outer medullary tissue in zone 4. The mass of each zone, gn, was calculated from equation 1.

\[ g_n = \frac{\text{fraction of total renal volume}_n \times \text{kidney weight}}{1} \]  

The total CPM for each zone, CPM\(_n\), was calculated according to equation 2.

\[ \text{CPM}_n = (\text{CPM}/g)_n \times g_n \]  

The total count for the four zones, CPM\(_N\), was used to calculate flow for each individual zone, flow\(_n\), by equation 3.

\[ \text{flow}_n = \frac{\text{CPM}_n}{\text{CPM}_N} \times \text{RBF} \]  

The data for each cortex zone were expressed as:

(a) tissue perfusion rate (flow per gram tissue weight), and (b) the percent of total renal blood flow perfusing the zone.

Protocol Design.—Our experiments were divided into six series, identified by the letters A to F. We could manipulate two specific factors, renal arterial pressure and the physical character of the microspheres (size and density). Throughout the entire study, we attempted to neutralize the effect of other unrecognized factors by randomization of the order of pressure manipulation and the order in which microspheres of different sizes, densities, and isotope labels were injected. In series A and B, we specifically examined the effect of: (a) the order in which pressure was varied, and (b) prior embolization.

Statistical significance was assessed by analysis of variance, unpaired t-test or paired t-test (16). We used the paired t-test in every case when we compared the effects on individual zone flow rates of such factors as pressure reduction, microsphere size, and microsphere density. The term "significant" is used in the text to indicate a P value of <0.05, except where stated otherwise. Variability was expressed by the standard error, with the single exception of microsphere diameter, for which the standard deviation was used.

Microsphere Data.—A sample of each batch of microspheres was placed in a hemocytometer chamber. The diameter of all spheres in the chamber was measured with an eyepiece micrometer. A histogram of the diameters of each batch was constructed. One batch was considered unsatisfactory because of a bimodal size distribution. The microsphere sizes for each protocol series are presented in Table 1. No clumping of microspheres was noted.

Histological Studies.—The vessel segments at
TABLE 1
Mean Diameter of Microspheres Used in Each Protocol Series

<table>
<thead>
<tr>
<th>Series</th>
<th>Microsphere diameter (μ)</th>
</tr>
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<tbody>
<tr>
<td>A1</td>
<td>34.0(4.2) 34.2(4.2)</td>
</tr>
<tr>
<td>A2</td>
<td>36.5(3.9) 35.8(3.8) 36.0(3.7)</td>
</tr>
<tr>
<td>B</td>
<td>36.5(3.9) 35.8(3.8) 36.0(3.7)</td>
</tr>
<tr>
<td>C</td>
<td>18.5(2.8) 17.9(2.6) 35.8(3.8) 36.0(3.7)</td>
</tr>
<tr>
<td>D1</td>
<td>27.4(4.2) 35.7(3.8)</td>
</tr>
<tr>
<td>D2</td>
<td>26.7(2.5) 36.5(3.9) 36.0(3.7)</td>
</tr>
<tr>
<td>E1</td>
<td>27.4(4.2) 28.3(1.5)*</td>
</tr>
<tr>
<td>E2</td>
<td>27.4(4.2) 28.7(2.5) 28.3(1.5)*</td>
</tr>
<tr>
<td>F</td>
<td>34.0(4.2) 34.2(4.2)</td>
</tr>
</tbody>
</table>

Diameters given are means, with standard deviations in parentheses.

* Ceramic variety; all others, plastic types.

Results

The average kidney weight was 38.6 ± 0.4 g. Average total renal blood flow was 3.33 ± 0.17 ml • g⁻¹ • min⁻¹ at normal pressure and 3.40 ± 0.17 ml • g⁻¹ • min⁻¹ at reduced pressure. There were no significant differences between mean flows of various experimental groups at either pressure and no significant effect of changes in pressure on mean flow of any group of the entire series. The average normal renal arterial pressure was 136.0 ± 1.6 mm Hg, and the average reduced arterial pressure was 81.0 ± 2.3 mm Hg. There was no significant difference between mean pressures of experimental groups at either normal or reduced pressures.

Each size of microsphere was tested in two experiments for completeness of trapping by the kidney. Negligible (less than 0.5%) radioactivity was found in the renal vein, relative to a simultaneously obtained renal arterial specimen. As indicated in Table 2, there were no significant effects of microsphere type or perfusion pressure on medullary content of radioactivity. Accordingly, cortical blood flow was equated with total renal blood flow in calculating the blood flow per cortex zone.

TABLE 2
Influence of Microsphere Diameter and Composition on the Renal Medullary Content of Radioactivity

<table>
<thead>
<tr>
<th>Microsphere diameter (μ)</th>
<th>Percent of total renal radioactivity contained in combined outer and inner medulla</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal pressure</td>
</tr>
<tr>
<td>Mean (μ)</td>
<td>σ (%)</td>
</tr>
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<td>36.0(3.8)</td>
<td>0.77</td>
</tr>
<tr>
<td>27.1(3.4)</td>
<td>1.28</td>
</tr>
<tr>
<td>18.2(2.7)</td>
<td>1.23</td>
</tr>
<tr>
<td>28.3(1.5)*</td>
<td>1.32</td>
</tr>
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</table>

Diameters given are means, with standard deviations in parentheses.

* Ceramic variety; all others, plastic types.
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TABLE 3

Analysis of Variance: Blood Flow per Gram of Cortex Zones 1, 2, 3, and 4

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Sum of squares</th>
<th>D.F.</th>
<th>Mean square</th>
<th>F</th>
<th>P</th>
<th>P</th>
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<td>Animal effect</td>
<td>50.5</td>
<td>18</td>
<td>2.8</td>
<td>0.04</td>
<td>NS*</td>
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<tr>
<td>Pressure effect averaged over zones</td>
<td>28.4</td>
<td>1</td>
<td>28.4</td>
<td>0.44</td>
<td>NS*</td>
<td></td>
</tr>
<tr>
<td>Zone effect averaged over pressures</td>
<td>17,008.6</td>
<td>3</td>
<td>5669.5</td>
<td>87.09</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Pressure effect between zones</td>
<td>2,766.3</td>
<td>3</td>
<td>922.1</td>
<td>14.16</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Sequence of pressure of injection effect</td>
<td>0.0</td>
<td>3</td>
<td>0.0</td>
<td>.00</td>
<td>NS*</td>
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</tr>
<tr>
<td>Error</td>
<td>7,942.3</td>
<td>122</td>
<td>65.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27,796.1</td>
<td>150</td>
<td></td>
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</table>

*Not significant.

results (Table 3) indicated that neither the sequence of pressure variation nor sequence of injection affected the tissue perfusion rates of the cortex zones. The pressure effect averaged over zones was insignificant, consistent with the lack of effect of pressure on total renal blood flow. There was: (1) a significant difference between zones, independent of pressure, and (2) a significant effect of pressure, dependent on zones.

The flow per gram of each cortex zone at normal and reduced pressures is presented in Figure 2. At normal pressure, tissue perfusion rate of each zone differed significantly from that of the other three. The inner zones were characterized by the lower perfusion rates. The responses of tissue perfusion rates to pressure reduction differed among zones; perfusion rate of the outer zone decreased significantly, perfusion rate of zone 2 was unaffected, and perfusion rates of zones 3 and 4 increased significantly. Although the average percent flow increase of zone 4 was larger than that of zone 3, the difference was not significant.

The percents of total renal blood flow perfusing each cortex zone at normal and reduced pressure are presented in Figure 3. This mode of expression incorporates the volume of each zone as well as the tissue perfusion rate. During pressure reduction, the
percent total renal blood flow perfusing zone 3 increased from 15.7 ± 1.2 to 22.5 ± 1.6 and that perfusing zone 4 increased from 5.9 ± 0.7 to 11.5 ± 1.4. There was a reciprocal decrease confined almost entirely to cortex zone 1. Given a mean total renal blood flow of 128.5 ml/min, the average flow redistributed from outer to inner cortex was 15.9 ml/min.

**INFLUENCE OF PRESSURE REDUCTION BELOW THE AUTOREGULATORY RANGE**

*Series A2, Four Experiments.*—In these experiments, we determined the distribution of renal blood flow at three pressures; normal, 130 ± 2.7 mm Hg; lower limit of the autoregulatory range, 77 ± 3.0 mm Hg; and approximately 40% below the autoregulatory limit, 45 ± 2.0 mm Hg. The total renal blood flows at the three pressures were 3.81 ± 0.42, 3.80 ± 0.40, and 2.12 ± 0.21 ml • g⁻¹ • min⁻¹. The flow at the lowest pressure was significantly (P < 0.01) less than at the higher pressures. We have presented the data in terms of percent of total renal blood flow perfusing each cortex zone (Fig. 4). Pressure reduction within the autoregulatory range resulted in a redistribution of flow identical to that seen in group A1 (Fig. 3); i.e., a significant (P < 0.05) decrease in the percent of total flow perfusing zone 1 and significant (P < 0.05) increases in the percents of total renal blood flow perfusing cortex zones 3 and 4. Further pressure reduction produced no change in the distribution of renal blood flow compared to that observed at the lower autoregulatory limit, despite the significant decrease in total renal blood flow.

**INFLUENCE OF PHYSICAL CHARACTERISTICS OF MICROSHERES CONTROL EXPERIMENTS**

*Series B, Five Experiments.*—Four injections of 36μ-diameter plastic microspheres were performed at 15-minute intervals without change in arterial pressure. The hypothetical cumulative embolization in these experiments was 3.2% of total glomeruli. As indicated in Figure 5, the tissue perfusion rate of each cortex zone remained unchanged. These results extended the earlier finding that a single embolization did not affect the results of a subsequent embolization. Also, they demonstrated the stability of the experimental preparation and the reproducibility of the flow measurements.

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**FIGURE 4**

Percent of total renal blood flow perfusing each cortex zone at normal pressure and following pressure reduction: (a) to the lower autoregulatory limit, and (b) below the autoregulatory limit (series A2). Total renal blood flow was significantly reduced at the lowest pressure. Reduction of pressure below the autoregulatory limit did not modify the pattern of flow redistribution caused by pressure reduction within the autoregulatory range.

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FIGURE 5
Control experiments (series B): Tissue perfusion rates of individual cortex zones determined serially with 35M microspheres. Neither time nor prior embolization affected the perfusion rates of any cortex zone.

INFLUENCE OF MICROSPHERE SIZE
Series C, Five Experiments.—Plastic microspheres, 36 and 18μ mean diameter, were injected at both normal and reduced arterial pressures. The flow rates of the individual dogs and cortex zones at both pressures are presented in Table 4. Pressure reduction produced the same pattern of flow redistribution documented in experimental series A1.

We have presented a summary of the paired t-test analysis of the effects of microsphere size on tissue flows of each zone at both pressures in Table 5. In no case was there a significant difference between the flows measured by the microspheres of different diameters. Thus, mean microsphere size (36 vs. 18) was excluded as a factor determining either the

TABLE 4
Influence of Microsphere Diameter on Flow Rates of Individual Cortex Zones at Normal and Reduced Renal Arterial Pressures in Series C

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Microsphere diameter (μ)</th>
<th>RAP* (mm Hg)</th>
<th>Total RBF± min⁻¹</th>
<th>Cortex zone flow rates (ml g⁻¹ min⁻¹)</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
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<tbody>
<tr>
<td>1</td>
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<td>3.87</td>
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<td></td>
<td>36</td>
<td>83</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>(5.5)</td>
<td>(0.28)</td>
<td>(0.22)</td>
<td>(0.47)</td>
<td>(0.40)</td>
<td>(0.49)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Renal arterial pressure. †Renal blood flow.

Circ Res. Vol. XXVII, October 1970
differences between zone perfusion rates at either pressure, or the effect of pressure on the flow distribution between zones.

Since we had available only a single type of tracer labeled plastic microsphere of 21\(\mu\) mean diameter, the comparison with 36\(\mu\)-diameter microspheres was performed in two parts (series D1 and D2). In series D1 (six experiments), tissue perfusion rates were compared only at normal pressure. The results, presented in Figure 6, indicated that microsphere size did not affect calculated zone flow rates. In series D2 (five experiments), the tissue perfusion rates were determined at both normal and reduced pressure. The comparison between 36- and 27\(\mu\)-diameter microspheres was made at the latter pressure (Fig. 7). We observed that pressure reduction produced the usual pattern of flow redistribution, and that microsphere size did not affect the calculated value of tissue perfusion rates at reduced pressure. The combined data from series D1 and D2 are consistent with those from series C.

**Influence of Microsphere Density**

Series E.—In these experiments, we compared the distribution of microspheres of the...
same approximate mean diameter (27 μ) but different densities (1.5 and 3.0 g/ml). As in series D1 and D2, we had available only a single type of tracer labeled dense (ceramic) microsphere and the comparison was performed in two parts. In series E1 (four experiments), cortex zone flow rates were compared only at normal RAP. The results presented in Figure 8 indicate that microsphere density did not affect calculated tissue perfusion rates in cortex zones 2, 3, and 4. However, increased density was associated with a small but significant (P<0.05) reduction in the calculated perfusion rate to cortex zone 1.

In series E2, the cortex zone flow rates were determined at both normal and reduced pressures and the comparison between plastic and ceramic microspheres made at the latter pressure (Fig. 9). Pressure reduction produced the usual pattern of flow redistribution. Microsphere density did not affect the calculated values of cortex perfusion rates at reduced pressure. Taken together, the results of series E1 and E2 indicate only a minor influence of microsphere density (1.5 vs. 3.0) on the calculated cortex tissue perfusion rates and the effect of pressure on the flow distribution between cortical zones.

**ATROPINE ADMINISTRATION**

*Series F, Four Animals.*—Autoregulation of total renal blood flow was tested before and after intravenous administration of atropine, 1 mg/kg. We found that atropine had no effect on total renal blood flow at either normal or reduced pressure. Microspheres, 35 μ, were injected at normal and reduced pressure 10 to 20 minutes after atropine administration (Fig. 10). The tissue perfusion rates at normal and reduced pressure were not significantly different from those of untreated animals (series A to E).

**HISTOLOGICAL STUDIES**

The histological studies indicated that 5% of 37 μ microspheres were located in "preafferent" arterioles (Table 6). All microspheres of 27 or 19 μ diameter were located in afferent arterioles or glomeruli. Reduction in microsphere diameter was associated with a progressively higher frequency of intraglomerular localization.
Cortex zone flow rates at normal and reduced pressures after atropine, 1 mg/kg iv. Atropine produced no effect on cortex tissue perfusion rates at either arterial pressure.

Discussion

Since tracer-labeled microspheres had not been previously utilized to analyze canine intrarenal blood flow distribution, we were obliged to assess the validity of the method. It is apparent that the method may be valid for measuring flow distribution in some organs but not in others. In addition, such factors as optimal microsphere size may vary between organs. For example, Domenech et al. (20) have obtained evidence that distribution of microspheres of greater than 14 \( \mu \) mean diameter is not proportional to the perfusion rate of layers of the left ventricular wall. Such disparity between flow and microsphere distribution might depend on factors such as axial migration of particles in flowing blood, inertial resistance to diversion into branching vessels, or location of the vessel segments at which embolization occurs. Disparities dependent on any of these factors would almost certainly be affected by microsphere diameter or density, or both. Therefore, we evaluated the internal consistency of intrarenal distribution of microspheres with different physical properties. The test of internal consistency was particularly relevant because cortex zones were found to differ in perfusion rates and the perfusion rates were significantly altered by pressure. Thus, evaluation of the method was strengthened by the ability to manipulate the variable under study. This indirect validation was necessary because the methods with which the microsphere technique might be compared either depend on a different circulatory function (e.g., exchange between capillaries and tissue), or are subject to theoretical objections.

The most elementary source of error would have been artifactual distribution based on vascular geometry. It was essential that embolization occur at a uniform terminal vascular site—the afferent arterioles or glomeruli themselves. Our histological studies and the congruence of results obtained from microspheres of different sizes are consistent with this precondition.

Axial migration of microspheres within the interlobular arteries would probably affect their tissue distribution. To arrive at inferences concerning axial migration, it is necessary to apply the findings from simpler experimental systems to the much more complex conditions which exist in vivo. If significant axial migration occurred within the interlobular arteries, blood entering proximal afferent arterioles would contain fewer microspheres than the blood entering more distal vessels due to a lower concentration of microspheres near the orifice of the proximal branches. Another possible consequence of axial migration would be concentration of larger particles with more radioactivity per particle at the peripheral tissue sites. The tendency to axial movement of spherical microspheres may be influenced by factors such as density, inertia, and velocity of blood flow.
particles is a function of the radius of the particle relative to that of the perfused tube (21). The results of our comparisons between microspheres of different diameters do not support significant axial migration of particles. Phibbs et al. (22) have reported that microspheres, 50 μ in diameter, tended to an axial distribution in the rabbit femoral artery. Our failure to obtain evidence of axial migration could be explainable on the basis of the large differences in vessel diameter and blood-flow velocity between the femoral artery and renal interlobular arteries (the ratio of femoral to interlobular artery Reynolds numbers being of the order of 1:0.001).

Our observation that the more dense ceramic microspheres did not show a tendency to peripheral embolic locations is evidence against the operation of centrifugal forces opposing diversion into afferent arterioles. It was reported previously that density of microspheres did not affect their relative distribution between gastric mucosa and muscularis (23).

In addition to the above indirect evidence concerning homogeneous microsphere distribution in blood, we have also shown that alteration of the renal perfusion pressure is not per se a sufficient basis for changes in the intrarenal distribution of microspheres. We studied the distribution of renal blood flow at two pressures where total renal vascular resistance was equal; i.e., at the lower limit of the autoregulatory pressure range and at lower pressures. It is reasonable to propose that given constant overall resistance, resistance of the individual cortex zones would remain constant with the consequence that total renal blood flow would be divided between the zones in identical proportions, independent of perfusion pressure, and necessarily, total renal blood flow. This hypothesis was supported by the observation that blood flow was distributed between cortex zones in identical proportions at the two specified pressures.

We have made similar observations under conditions of renal vasodilation produced by intra-arterial infusion of maximally effective doses of acetylcholine (4 μg·kg⁻¹·min⁻¹) (unpublished observation). Renal blood flow was a function of renal arterial pressure during acetylcholine infusion. The intrarenal distribution of microspheres was identical over a wide range of perfusion pressures (140 mm Hg to 40 mm Hg). Taken as a group, these findings provide very strong evidence against the possibility that changes in either perfusion pressure or total renal blood flow can produce a redistribution of microspheres in the absence of a redistribution of blood flow.

Our results clearly imply that the perfusion of the renal cortex is heterogenous. The tissue perfusion rates differ by at least a factor of 2, based on a comparison of contiguous zones 2 and 3. The range of difference in perfusion rates may be greater, since some degree of overlap between the two adjacent zones is possible. The virtual absence of outer and inner medullary embolization is evidence in favor of the concept that all blood flow to the kidney initially passes through glomeruli. This conclusion is in harmony with most anatomical studies (17-19). Blood flow to the medulla would be expected to arise from cortex zones 3 and 4, and therefore should not exceed their combined value, 21.6% of total renal blood flow. It is interesting in this connection that Edwards found 18% of glomeruli to be juxtamedullary in type (24).

Given that all blood entering the medulla must first pass through glomeruli in the inner cortex, flow through the latter area should be an important factor determining outer medullary blood flow. However, since blood leaving the juxtamedullary glomeruli may flow either through vasa recta or peritubular capillaries of the inner cortex and outer medulla (8), precise definition of outer medullary flow is somewhat elusive. It is apparent the changes in flow rate of juxtamedullary cortex cannot be directly equated with changes in flow through outer medullary peritubular capillaries. The functional significance of potential variations in the proportion of flows through the two parallel postglomerular circuits has been emphasized (19). Despite this limitation, it is of interest to relate our observations concerning flow through inner cortical zones
with the observations of others concerning flow through the outer medulla. The combination of the microsphere technique with one of the methods for local measurement of outer medullary flow (3-5) should provide a workable approach to elucidating the relationship between inner cortical and outer medullary flow rates.

To compare our observations with those obtained by the $^{85}\text{Kr}$ method, we directed our attention to the two most rapid components of the washout curve. In combination, these components contain 95 to 97% of injected radioactivity (2, 7). By autoradiography, the most rapid component has been localized to the “outer cortex” and the slower component to “not only the outer medulla, but also the inner cortex, the region containing the juxtamедullary glomeruli” (2). Since Thorburn et al. concluded that the juxtamедullary region of the cortex and the outer medulla “cleared $^{85}\text{Kr}$ at the same uniform rate, behaving as a single unit” (2), it is reasonable to compare the blood flow to the inner cortex as measured by the microsphere technique with the slow component measured by the $^{85}\text{Kr}$ technique. The comparisons are presented in Table 7. The microsphere data were expressed in terms of a two-compartment model, by pooling the outer two and the inner two zones.

The two methods yield similar figures for the percent of total renal blood flow per compartment. In comparing the relative volumes, it should be recalled that by the $^{85}\text{Kr}$ method the inner cortex and the outer medulla are combined into a single functional unit. Since the flow through the juxtamедullary glomeruli and outer medulla is related to a larger volume by the $^{85}\text{Kr}$ method than by the microsphere method, reciprocal differences in flow per unit mass are observed.

Our results lend weight to the possibility originally raised by Thorburn et al. (2) that the components into which the $^{85}\text{Kr}$ washout curves are analyzed may in actuality represent “the sum of a larger series of exponentials.” Autoradiography would indicate that the flow through cortex zone 1 must be included in the rapid component of the $^{85}\text{Kr}$ washout curve. Quantitative considerations of the microsphere data also lead to this conclusion since summation of zone 1 with zones 3 and 4 would result in a compartment with excessively large values for both fraction of total flow and flow per unit mass. Since the slow component of $^{85}\text{Kr}$ curves probably reflects flow through zones 3 and 4, it seems probable that both components include a range of tissue perfusion rates.

There are relatively few previous studies which bear specifically on the problem of flow rates within the cortex. Methods which permit local detection of indicator dilution curves have been used for this purpose. In the report of Aukland et al. (3), it was noted that within the renal cortex “different electrode positions frequently gave consistently different flow rates.”

| TABLE 7 |
| Comparison between Renal Hemodynamic Data Obtained by the Labeled Microsphere and $^{85}\text{Kr}$ Washout Technique |

<table>
<thead>
<tr>
<th>Labeled microspheres</th>
<th>Cortex zones 1 and 2</th>
<th>Cortex zones 3 and 4</th>
<th>$^{85}\text{Kr}$ washout*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow (k) (ml·g$^{-1}$·min$^{-1}$)</td>
<td>5.3</td>
<td>2.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Percent total renal blood flow</td>
<td>78</td>
<td>22</td>
<td>78</td>
</tr>
<tr>
<td>Relative volume ($%$)</td>
<td>62</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

*Data taken from reference 25.
values." Although the mean flow rates at different cortical depths presented in their Table 1 did not differ, the number of experiments in which multiple cortical positions were studied was small.

The most comprehensive study of this subject was conducted by Wolgast (6). He employed the indicator dilution method using labeled red cells and beta-sensitive detectors. The calculation of local blood flow was based on the relationship: red cell flow equals $V/t$ where $V$ is the volume of the labeled red cells in the detected region of the kidney, and $t$ is the mean transit time. Wolgast found the mean transit time of labeled red cells to be uniform throughout the renal cortex. However, the indicator dilution curves were characterized by an early peak which was large in the inner cortex but absent in the cortical surface. Wolgast attributed this peak to passage of the indicator through the arcuate arteries and proximal interlobular arteries. We contend that this portion of the indicator dilution curve should be excluded from the calculation of mean transit time, since the labeled red cells generating the early peak did not perfuse the local glomeruli, but rather other more superficial glomeruli. The value for $t$ which is calculated from the juxtamedullary curves is significantly affected by the inclusion of the early peak. Using data from Wolgast's Figure 9, we estimate that $t$ would be increased by approximately 26% if the early peak were omitted.

An additional potential source of error is associated with the measurement of local indicator volume. The method of volume measurement was found to present technical difficulties when applied to the cortex (6, p. 50). In particular, the measured volumes near the corticomedullary border were considered to be inaccurately high. It is of particular importance that some of the monitored indicator volume near the corticomedullary junction did not represent blood which actually perfused juxtamedullary glomeruli (i.e., contents of arcuate arteries and veins). Considering these complex difficulties in interpreting the data obtained by the use of labeled red cells, we cannot accept Wolgast's inference that renal cortical perfusion rate is homogeneous.

Our data indicate that the zones of the renal cortex differ not only in relative perfusion rates, but also in the types of responses elicited by changes in perfusion pressure. As pressure was reduced within the autoregulatory range, flow to the superficial cortex decreased, while inner cortical flow increased. Previous work in the field of intrarenal hemodynamics has for the most part been concerned with the influence of perfusion pressure on medullary blood flow, and for methodological reasons discussed earlier, the findings cannot be directly compared with our own. However, to the extent that outer medullary flow is determined at least in part by juxtamedullary cortical flow, our observations would predict an increase in the former during reduction of RAP within the autoregulatory range. Observations have been made by the $^{85}$Kr method which conform with this expectation. The investigations of Stinson et al. (25) include a small series of acute experiments, the results of which may be compared with our own. In each of the two acute experiments which they present in detail (their Table 3), the response to renal artery constriction was a sizable (28% and 38%) increase in flow to the "outer medulla."

There is other experimental work from the same laboratory which can be reasonably interpreted in light of our observations. Carriere et al. (7) studied the effect of hemorrhagic hypotension on the intrarenal distribution of blood flow in dogs. In their experiments, arterial pressure was reduced to 50 mm Hg. The results (their Table 1) indicate that during the first 60 minutes of hypotension, the flow rate of the "outer medulla" increased in nine of ten experiments. Since a renal perfusion pressure of 50 mm Hg is well below the limit of renal autoregulation, the increased outer medullary flow reflected a regional capacity for vasodilation in excess of that characteristic of the kidney as a whole. Our observation of increased inner cortical flow rate at reduced pressure indicates that such disproportionate regional vasodilation...
occurs, and consequently lends support to the inference drawn from the data of Carriere et al. (7).

The techniques which measure intrarenal flow distribution by local detectors have yielded occasional observations consistent with ours. Both Tuttle and Sadler (4) and Grangsjo (5) have observed an increase in outer medullary flow during reduction in renal perfusion pressure. On the other hand, Aukland and Wolgast (26) and Wolgast (6) have observed autoregulation of outer medullary flow, but no augmentation by reduced pressure.

In interpreting the results obtained by the microsphere technique, it should be emphasized that the point of embolization is the initial parallel element (glomerulus or afferent arteriole) of a parallel-series (portal) type circulation. Thus the flow per unit mass of an individual cortex zone may be defined by the following equation:

$$\text{flow per unit mass} = \frac{\text{flow per glomerulus per min} \times \text{glomeruli per g}}{\text{glomeruli per g} \times \text{min}}. \quad (4)$$

This relationship is of interest for several reasons. The possibility exists that the flow per glomerulus is the same throughout all the zones, and the difference in zonal perfusion reflects exclusively differences in the number of glomeruli included in the various zones. To evaluate this possibility, it is necessary to know the number of glomeruli per unit tissue mass for each of the individual cortex zones.

In a separate study (unpublished observation), we have investigated the relative number of glomeruli per unit mass of canine renal cortex, divided into cortex zones by the method described in the present paper. We have indicated in Table 8 the relative number of glomeruli per gram and the relative zonal glomerular perfusion rates. It will be noted that the absence of glomeruli from the subcapsular portion of cortex zone 1 was compensated for in part by a previously described greater frequency of glomeruli in the outer cortex (27), with the result that the relative glomeruli per gram of zones 1 and 2 were not significantly different. However, there were significantly ($P<0.01$) fewer glomeruli per gram in zones 3 and 4 relative to zone 2. The net effect of the differences in relative glomeruli per gram of the cortex zones was that the relative flow per glomerulus of zone 2 significantly ($P<0.01$) exceeded that of the other three zones, none of which differed significantly from the other. Viewed in this perspective, it is apparent that the difference in perfusion rates between cortex zones 1, 3, and 4 may be considered a reflection of differences in the number of glomeruli per unit mass of the tissue zones. However, the perfusion rate of cortex zone 4 differs from that of the other zones in relative flow per glomerulus. It is readily apparent that despite homogeneous perfusion rates of the individual glomeruli of cortex zones 1, 3, and 4, there are qualitative differences between the zonal responses to pressure, as indicated by the changes in zonal perfusion rates presented in Figure 2. The homogeneity of the relative glomerular perfusion rates at normal pressure excludes baseline perfusion,

<p>| TABLE 8 |
| Relative Flow per Glomerulus in the Individual Cortex Zones |</p>
<table>
<thead>
<tr>
<th>Cortex zone</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion rate (ml • g⁻¹ • min⁻¹)</td>
<td>4.13 (.36)</td>
<td>6.80 (.44)</td>
<td>3.07 (.29)</td>
<td>1.68 (.24)</td>
</tr>
<tr>
<td>Relative glomeruli per gram *</td>
<td>0.91 (.09)</td>
<td>1</td>
<td>0.78 (.06)</td>
<td>0.45 (.03)</td>
</tr>
<tr>
<td>Relative flow per glomerulus †</td>
<td>0.67 (.09)</td>
<td>1</td>
<td>0.57 (.08)</td>
<td>0.55 (.12)</td>
</tr>
</tbody>
</table>

All data presented as means ± se.

*Glomeruli per gram zone x / glomeruli per gram zone 2.

†flow • g⁻¹ • min⁻¹ zone x / relative glomeruli/g.
HETEROGENEITY OF RENAL CORTICAL BLOOD FLOW

rate as a factor in the reciprocal flow changes seen in response to pressure reduction.

The observation that portions of the renal cortex respond differently to changes in perfusion pressure carries interesting functional implications. At any given level of postglomerular resistance, hydrostatic pressure in the glomerular capillaries is a function of glomerular perfusion. Changes in regional cortex perfusion rates may therefore affect the distribution of single nephron filtration rates. In this connection, reduction of RAP has been found to decrease superficial single nephron glomerular filtration rates to a greater extent than whole kidney glomerular filtration rates (28). This observation may reflect the difference between outer and inner cortical perfusion rate responses to pressure reduction. We have observed that reduction in RAP to the limit of flow autoregulation results in a decrease in glomerular filtration rate (29). This pressure effect may represent a change in efferent arteriolar resistance throughout all areas of the kidney, or it may alternatively be attributed to a redistribution of blood flow to inner cortical nephrons. If such is the case, the efferent resistance of the inner cortical nephrons would necessarily be less than that of the outer cortical nephrons.

The heterogenous intrarenal flow responses to changes in perfusion pressure are undoubtedly only one example of the complex renal circulatory effects of a variety of physiologic and pharmacologic stimuli. There is evidence that the inner and outer cortex may respond differently to vasoactive drugs and diuretic compounds. Carriere and Friborg (9) have observed that the subcapsular cortex is disproportionately sensitive to intra-arterial angiotensin. In further microsphere experiments, we have observed that intra-arterial acetylcholine increased inner cortical flow by a greater percent than outer cortical flow. On the other hand, the innermost cortex was least responsive to the renal vasodilating effects of ethacrynic acid (unpublished observations). This finding is consistent with earlier observations by Birtch et al. (30).

The mechanisms responsible for the different regional responses to pressure change are not established by our results. However, it is of interest that infusion of maximally effective doses of acetylcholine or bradykinin into the renal artery produces redistribution of flow identical to that produced by pressure reduction (unpublished observation). The similarity of the patterns of renal cortical vascular responses to such different stimuli suggests intrinsic differences in the sensitivity of the cortex zones to vasodilator interventions in general. The failure of atropine to influence the regional flow patterns is evidence against cholinergic mediation of the pressure-induced vasodilation of the inner cortical zones, a possibility suggested by the findings of Stinson et al. (25).

Appendix

USE OF THE ELLIPSOIDAL FORMULA FOR CALCULATION OF KIDNEY VOLUMES

In the following discussion, we assume renal tissue has a specific gravity of 1.0. Accordingly, total renal volume can be equated with kidney weight, and easily obtained by the latter measurement. However, to calculate the proportion of total renal mass contained in each of the cortex zones it is necessary to have an adequate formulation of kidney shape, but a precise formula describing the kidney shape is not presently available. Accordingly, it was necessary to employ an empirical formula which approximately describes the kidney shape. We chose to use a modification of the formula for an ellipsoid for this purpose.

Although the kidney resembles an ellipse in all three projections, the hilar indentation at the internal border causes an obvious deviation from the ellipsoidal shape. The result is that there is asymmetry about the long axis. The net effect of this asymmetry is that the measured length of the axis between the hilus and lateral border is smaller than that required for correspondence of the kidney shape with a true ellipsoid. A necessary consequence of the discrepancy between the actual kidney shape and ellipsoidal shape is that the actual kidney volume does not correspond with the volume calculated by substituting the meas-
ured axis into the formula for the volume of an ellipsoid.

\[
\text{ellipsoid volume} = \frac{4}{3}\pi (a/2 \cdot b/2 \cdot c/2),
\]

where \(a, b, \) and \(c\) are the three axes.

The calculated volume is systematically less than the measured volume. We have defined the ratio of the actual to calculated total renal volume as the “volume correction coefficient,” \(k\).

\[
k = \frac{\text{measured vol}}{\text{calculated vol}} = 1.25 \pm 0.114 \ (n = 20).
\]

For the purpose of calculating the four fractions of cortical volume, it is necessary to bring measured total renal volume into correspondence with calculated total renal volume. To accomplish this, the ellipsoidal formula is modified as follows:

\[
\text{kidney volume} = k\left(\frac{4}{3}\pi (a/2 \cdot b/2 \cdot c/2)\right).
\]

The result of this modification is calculation of the volume of a “virtual” kidney, the volume of which corresponds with measured kidney volume. Since the virtual kidney is based on renal weight, which reflects the absence of parenchymal tissue in the hilar region, the renal pelvis is assumed not to affect the relative proportion of tissue in each zone of the renal cortex; i.e., the pelvis is visualized as resulting from removal of renal parenchyma containing the same proportions of tissue components as the whole kidney. Likewise, the modified formula retains the proportions between the measured kidney axes and cortex thickness. In actual calculations of fractions of renal mass in the individual cortex zones, it is unnecessary to determine \(k\), since the factor \([k \cdot (4/3)\pi]\) is present in both the numerator and denominator of each ratio, volume of cortex zone/total kidney volume.

Acknowledgment

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HETEROGENEITY OF RENAL CORTICAL BLOOD FLOW


Pressure-Dependent Heterogeneity of Renal Cortical Blood Flow in Dogs
JOHN L. MCNAY and YOUICHI ABE

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