Intrarenal Distribution of Blood Flow during Elevation of Ureteral Pressure in Dogs

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ABSTRACT

The $^{85}$Kr method was used to determine the effect of elevated ureteral pressure on total cortical and outer medullary nutrient renal blood flow of pentobarbital-anesthetized dogs. Increased ureteral pressure during mild saline diuresis resulted in increased total nutrient blood flow from 316 to 402 ml/100 g/min. Autoradiographs demonstrated that the increased blood flow is confined to the renal cortex and that juxtamedullary cortical and outer medullary flow is unchanged. Elevated ureteral pressure decreased total renal blood flow from 473 to 381 ml/g/min during copious mannitol diuresis. This is due at least partly to decreased cortical blood flow; we were unable to measure juxtamedullary cortical plus outer medullary blood flow during mannitol diuresis. Isolated renal arteries relaxed when placed in a physiologic salt solution containing 70 mM mannitol. Renin release is increased during elevation of ureteral pressure. We concluded that the mechanism for increased renal blood flow during ureteral occlusion selectively involves the nutrient circulation of the renal cortex.

ADDITIONAL KEY WORDS

renal mannitol diuresis

Elevation of ureteral pressure in dogs usually results in an increased total renal blood flow, although under some experimental conditions total renal blood flow may be decreased or unchanged (1-4). Knowledge of the location of these changes in blood flow within the kidney may help to elucidate the mechanism by which the changes are brought about. For this reason, we studied the effect of elevating ureteral pressure on the intrarenal distribution of blood flow under conditions in which the increased ureteral pressure resulted in an increased (during mild saline diuresis) or decreased (during mannitol diuresis) total renal blood flow.

Methods

Renal Blood Flow Preparation.—Eighteen fasted male mongrel dogs (14 to 25 kg) were anesthetized with sodium pentobarbital (30 mg/kg). The left kidney (in some cases both kidneys) was exposed retroperitoneally and a polyvinyl catheter (0.015 inches i.d., 0.025 inches o.d., Wrenco Co., Boston, Mass.) was placed in the renal artery. The ureter was cannulated. In four experiments a polyethylene catheter (PE 160) was placed in the renal vein via the femoral vein. Femoral arterial pressure and ureteral pressure were measured with Statham pressure transducers and recorded on a Grass polygraph. One-half to one hour elapsed between completion of the preparation and the first experimental measurements.

An infusion of 0.85% saline, 5 ml/min, was begun after administration of the pentobarbital. After the surgical preparation was complete, one of two protocols was followed. Ten dogs continued to receive saline until the urine flow was greater than 0.1 ml/min. The other eight dogs received 200 ml of 20% mannitol in 0.85% saline given over 5 to 10 minutes, and then an infusion of the same mannitol solution at 5 to 10 ml/min. As soon as blood pressure and urine flow became relatively constant, less than 1 ml of $^{85}$Kr dissolved in saline was injected into the renal artery catheter. The clearance of the radioactive inert gas was monitored by an external scintillation detector coupled with a digital rate meter. Counting intervals ranged from 2 seconds immediately after
the injection to 60 seconds later on, depending on
the clearance rate.

After a control curve was obtained, ureteral
pressure was elevated to approximately 70% of
mean arterial pressure by means of a pressure
bottle. When blood pressure and ureteral pressure
were stable (15 to 30 minutes), the clearance of
\( ^{85}\text{Kr} \) was again determined. Then ureteral
pressure was lowered and in most dogs \( ^{85}\text{Kr} \)
clearance was measured again.

The amount of \( ^{85}\text{Kr} \) in the kidney was
monitored for 20 minutes and plotted on
semilogarithmic graph paper against time. The
best straight-line fit of the terminal portion of the
curve was obtained; this line was then extrapolated
to time 0 and subtracted from the clearance
curve. The monoeponential portion of the
remainder was designated as component II. This
component was then subtracted from the remain-
ing points and the resulting monoeponential line
was designated as component I as outlined by
Thorburn et al. (5). Pomeranz has validated the
use of short time periods for determining
components I and II (6).

 Autoradiograms of kidneys removed at various
times after injection of \( ^{85}\text{Kr} \) were obtained to
determine the anatomic representation of compo-
nents I and II. The renal pedicle was tied and the
kidney quickly removed and placed in acetone
and dry ice. Transverse slices of the frozen kidney
were then used to expose Kodak AA industrial x-
ray film. As in previous studies (5), under control
conditions component I of the washout curve
represents outer cortical blood flow rate and
component II represents clearance of \( ^{85}\text{Kr} \) from
the juxtamedullary cortex and the outer medulla.

 Analysis of the data involves several assump-
tions: (1) steady state with respect to flow and
volume, (2) no recirculation of \( ^{85}\text{Kr} \), (3)
complete transcapillary equilibration of \( ^{85}\text{Kr} \), (4)
a blood-tissue partition coefficient of approximate-
ly 1.0, (5) components I and II represent
components I and II (6).

 Autoradiography helps to determine whether these
conditions exist.

 Since components I and II represent clearance from
parallel compartments, the distribution of
renal blood flow to the compartments determines
the relative values of \( \frac{A_i}{D_i} \) and \( \frac{A_n}{D_n} \). Dobson and
Warner (7) pointed out that the relative volumes
of the compartments can be calculated by the
following equation:

\[
\frac{V'}{V} = \frac{A_i}{D_i/k} + \frac{A_n}{D_n/k}
\]

and

\[
\frac{V''}{V'} = \frac{A_i}{D_i/k} + \frac{A_n}{D_n/k}
\]

where \( V' \) and \( V'' \) are the volumes of the compart-
ments and \( V' \) equals \( V' + V'' \).

The relative volumes then allow calculation of the
total renal blood flow in ml/min/100 g:

\[
\left( \frac{F}{V} \right) = \frac{100}{\frac{V}{V'} + \frac{V''}{V'}}
\]

To determine whether a steady state was
reached, we observed the time course of changes
in flow by measuring renal blood flow directly in
six experiments, using the two experimental proto-
cols. A siliconized tube was inserted into the renal
vein, and the renal venous effluent returning
through a cannula in the jugular vein was
measured at intervals with a graduated cylinder
and stopwatch. The time at which total renal
blood flow
blood flow became stabilized after each maneuver was determined, and this information was used to ensure that \(^{85}\)Kr clearance curves were obtained at times when flow was not changing. When \((F/V)_r\), calculated as outlined above, was plotted against total venous effluent corrected for kidney weight, the regression coefficient was 0.04 and the intercept was on the \((F/V)_r\) coordinate at 17 ml/100 g/min. This intercept does not equal 0 because the relationship is slightly nonlinear at low flow values. The correlation coefficient was 0.97. This supports the study of Ladefoged (8), who found a favorable correlation between \(^{85}\)Kr clearance and electromagnetic flow-meter values.

In preliminary experiments we noted that if urine flow was less than 0.1 ml/min, the elevation of ureteral pressure did not produce an increase in total renal blood flow. In each of nine animals with a urine flow below 0.1 ml/min, elevation of ureteral pressure resulted in a decrease in total renal blood flow. Of ten animals with a urine flow above 0.1 ml/min, eight had an increase in renal blood flow with elevation of ureteral pressure. Also, our preliminary experiments confirmed Gilmore's observation (3) that during mannitol diuresis elevation of ureteral pressure caused a decrease in total renal blood flow only if total renal blood flow had been elevated by the mannitol infusion.

Renin Determination.—Renal venous renin determinations were made in four experiments. Renin activity of the venous blood obtained from a catheter placed in the renal vein via the femoral vein was determined in the laboratory of Dr. A. J. Vander (9).

Isolated Artery Experiments.—Four dog interlobular renal arteries (0.6 to 1.0 mm o.d.) were isolated and helically cut strips 1 to 1.5 cm long and 1 mm wide were prepared. After overnight storage at 4°C, a strip was suspended in a constant temperature (37°C) bath containing physiologic salt solution of the following composition in mM: NaCl, 119; KCl, 4.7; KH$_2$PO$_4$, 1.18; MgSO$_4$, 1.17; NaHCO$_3$, 14.9; dextrose, 5.5; sucrose, 50; CaCl$_2$, 1.6; CaNa$_2$ versenate, 0.026. The bath was aerated with a mixture of 95% O$_2$ and 5% CO$_2$ and exposed to light of constant intensity. One end of the strip was tied to a rigid support and the other end to an isometric tension transducer (Grass FT 03) which led to a Grass polygraph. Strips were stretched so that rest tension was 100 to 200 mg. The preparations were allowed to equilibrate for 2 hours before experimental procedures were begun. "Pins" was established by adding norepinephrine, 10⁻⁸ g/ml, to the bath.

**Results**

**Elevation of Ureteral Pressure during Saline Diuresis.**—When ureteral pressure was elevated during mild saline diuresis, total renal blood flow and outer cortical blood flow increased, but juxtamedullary cortical plus outer medullary blood flow was unchanged. Figure 1 is a series of autoradiographs taken during saline infusion with and without the elevation of ureteral pressure. The cortex of a kidney removed and frozen during the injection of \(^{85}\)Kr at time 0 filled evenly in both


states. Fifteen seconds after injection, the cortex of the control kidney exposed the film uniformly, but the outer cortex of the kidney with elevated ureteral pressure had less activity than the juxtamedullary cortex plus the outer medulla. Subsequent autoradiographs show that the outer cortex of a kidney with elevated ureteral pressure had relatively less activity than did the outer cortex of control kidneys. Relatively little $^{85}$Kr remained in the outer cortex of control kidneys after 60 seconds, whereas the outer cortex of the kidney with elevated ureteral pressure was devoid of $^{85}$Kr between 30 and 60 seconds. At
120 seconds, $^{85}$Kr remained in the outer medullary region of both kidneys. We conclude that the faster clearance of $^{85}$Kr (component I) was from the outer cortex and slower clearance (component II) from the juxtamedullary cortex plus the outer medulla in both experimental situations.

Table 1 gives the flow values calculated from the clearance curves for 10 experiments and the mean values. In 8 experiments total renal blood flow increased during elevated ureteral pressure, whereas in one experiment (5) total renal blood flow and outer cortical blood flow decreased, and in another (9) variable results were obtained. Urine flow ranged from 0.13 to 2.6 ml/min, and blood pressure averaged 130 mm Hg during infusion and 138 mm Hg during elevation of ureteral pressure. Total renal blood flow rate increased from 316 during the control periods to 402 during elevation of ureteral pressure. This can be accounted for by the increase in outer cortical blood flow rate from 462 to 567, whereas juxtamedullary cortical plus outer medullary blood flow rate did not change.

**Elevation of Ureteral Pressure during Mannitol Diuresis.**—When ureteral pressure was elevated during a copious mannitol diuresis, total renal blood flow and outer cortical blood flow decreased and component II of the clearance curve was unchanged. Figure 2 shows a series of autoradiographs of kidneys with normal and elevated ureteral pressure during mannitol infusion. In both cases the cortex has dark radial stripes which represent areas with more $^{85}$Kr than the surrounding parts. The dark stripes radiate from the arcuate arteries in the autoradiographs of kidneys taken during the injection of $^{85}$Kr and so may represent areas of greater nutrient blood supply. The outer cortex was cleared of $^{85}$Kr within 30 seconds after the injection of mannitol; the comparable value for mild saline diuresis was 60 seconds, $^{85}$Kr was still present in outer cortex after 120 seconds when ureteral pressure was elevated. With normal ureteral pressure the outer medulla and papilla contained the highest concentration of $^{85}$Kr at 60 and 120 seconds, whereas during elevated ureteral pressure the activity was primarily in the juxtamedullary cortex plus the outer medulla. We conclude that component I of the $^{85}$Kr clearance curves represents outer cortical blood flow, whereas component II represents clearance from the juxtamedullary cortex, outer medulla, and inner medulla during mannitol diuresis and juxtamedullary cortex plus outer medulla during elevated ureteral pressure. Total renal blood flow decreased during the elevated ureteral pressure in seven of eight dogs and increased slightly in one dog (13).
### TABLE 2
Renal Blood Flow Values during Copious Mannitol Diuresis with Zero and Elevated Ureteral Pressure

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Ureteral pressure (mm Hg)</th>
<th>Flow rate (ml/100 g/min)</th>
<th>Distribution of flow (%)</th>
<th>Relative volumes (F/V)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outer cortex</td>
<td>JG + OM</td>
<td>Outer cortex</td>
<td>JG + OM</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>494</td>
<td>132</td>
<td>96</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>892</td>
<td>197</td>
<td>88</td>
</tr>
<tr>
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<td>90</td>
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<td>0</td>
<td>712</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>823</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>793</td>
<td>83</td>
<td>91</td>
</tr>
<tr>
<td>17</td>
<td>0</td>
<td>855</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>MEANS</td>
<td>0</td>
<td>858</td>
<td>89</td>
<td>92</td>
</tr>
</tbody>
</table>

P = <0.01, <0.2, <0.4, <0.4, <0.025

*ml/100 g/min.
See footnote to Table 1.

### TABLE 3
Comparison of Renal Blood Flow Values during Mild Saline and Copious Mannitol Diuresis

<table>
<thead>
<tr>
<th></th>
<th>Flow rate (ml/100 g/min)</th>
<th>Distribution of flow (%)</th>
<th>Relative volumes (F/V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>Outer cortex</td>
<td>JG + OM</td>
<td>Outer cortex</td>
</tr>
<tr>
<td></td>
<td>Compartment II</td>
<td>456 ± 38</td>
<td>98 ± 34</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Outer cortex</td>
<td>503 ± 65</td>
<td>89 ± 14</td>
</tr>
<tr>
<td>diuresis</td>
<td>Compartment II</td>
<td>85 ± 13</td>
<td>85 ± 13</td>
</tr>
<tr>
<td>(8)</td>
<td>&lt;0.001</td>
<td>&gt;0.5</td>
<td>&lt;0.2</td>
</tr>
</tbody>
</table>

Number in parenthesis is number of experiments. (F/V) = total renal blood flow. Values are means ± 1 SD. P values were calculated using unpaired, pooled values and Student's t-test.

Table 2 shows the results of the eight experiments and the mean values. During mannitol diuresis, urine flow was 7 to 12 ml/min and blood pressure averaged 141 mm Hg before and 147 mm Hg during elevated ureteral pressure. Total renal blood flow rate decreased, on the average, from 473 to 381 ml/100 g/min. This was accompanied by a decrease in outer cortical blood flow from 808 to 574 ml/100 g/min. We cannot ascertain the effect of elevated ureteral pressure on juxta-medullary cortical plus outer medullary blood flow.
flow because the autoradiographs indicate that component II does not solely represent blood flow through this area when ureteral pressure is normal.

Average values for renal blood flow during mild saline and copious mannitol diuresis are found in Table 3. These values are calculated from the control data in Tables 1 and 2. It should be emphasized that more mannitol must be administered to elicit the increased blood flow rates observed here than is necessary to raise urine flow. The average total renal blood flow of the animals receiving mannitol was 473 ml/100 g/min as compared with 329 ml/100 g/min for dogs receiving saline. This was at least partly due to the increased outer cortical blood flow: 456 during saline diuresis as compared with 803 ml/100 g/min during mannitol diuresis. The increase in relative volume during mannitol infusion may reflect the fact that component II represents inner medulla as well as juxtamedullary cortex and outer medulla during mannitol diuresis.

Renal Venous Renin.—Because renal venous renin has not been measured when ureteral pressure is elevated during mild saline diuresis, we collected renal venous blood in four experiments: before, during, and after elevation of ureteral pressure. These results are presented in Table 4. Both cortical blood flow and renal venous renin were elevated during increased ureteral pressure in each experiment.

Mannitol and Isolated Renal Arteries.—Figure 3 is a reproduction of a polygraph tracing showing the response of a helically cut strip of interlobular renal artery to mannitol, 70 mM, after baseline active tension was established with norepinephrine, 10^{-6} g/ml. Adding the control volume of physiologic salt solution with no mannitol caused no response, but this same volume of physiologic salt solution plus enough mannitol to make the bath concentration 70 mM caused relaxation of the vascular smooth muscle. This experiment was repeated several times on each of four strips.

Discussion

We have demonstrated that the change in total renal blood flow associated with elevation of ureteral pressure can be explained by the changes in outer cortical blood flow. When ureteral pressure is raised during mild saline diuresis, outer cortical blood flow is increased and juxtamedullary cortical plus outer medullary blood flow is unchanged. If mannitol is infused until there is an increase in total renal

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Renal Venous Renin and Cortical Blood Flow Rate with Zero and Elevated Ureteral Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cortical blood flow rate (ml/100 g/min)</td>
</tr>
<tr>
<td>Expt no.</td>
<td>Control</td>
</tr>
<tr>
<td>7</td>
<td>455</td>
</tr>
<tr>
<td>6</td>
<td>450</td>
</tr>
<tr>
<td>8</td>
<td>450</td>
</tr>
</tbody>
</table>

FIGURE 3

Response of interlobular renal artery to 70 mM mannitol. Baseline tension established by norepinephrine, 10^{-6} g/ml.
blood flow, elevation of ureteral pressure causes decreased total renal blood flow and outer cortical blood flow.

The results of the experiments using mannitol indicate the importance of autoradiography when using externally monitored clearance of $^{85}$Kr to estimate intrarenal distribution of blood flow. Whereas component I seems to be a reliable index of outer cortical flow under a variety of circumstances (5, 7, 10, 11), component II may or may not represent juxtamedullary cortical plus outer medullary blood flow, depending on the experimental conditions. Whenever urine flows from the cortex to the medulla there is the possibility that $^{85}$Kr will be transported to the medulla by urine and trapped by the countercurrent arrangement. The autoradiographs we obtained during mild saline diuresis (Fig. 1) are very similar to those obtained during oliguria by Thorburn et al. (5), and so we conclude that it is probable that this urine flow rate is not high enough to seriously affect the estimate of juxtamedullary cortical plus outer medullary blood flow. This is supported by the observation that no $^{85}$Kr is detectable in urine at flow rates below 2 ml/min (5); in most experiments the urine flow was below 2 ml/min during mild saline diuresis. Further support is provided by the similarity of the autoradiographs at 60 and 120 seconds (Fig. 1) during elevated ureteral pressure, when tubular urine flow must be decreased. On the other hand, it is clear that during mannitol diuresis a relatively large amount of $^{85}$Kr is in the inner medulla at 60 and 120 seconds (Fig. 2). This is probably because of the high urine flow rate, since elevation of ureteral pressure greatly reduces the $^{85}$Kr in this area. Thus during mannitol diuresis component II does not represent juxtamedullary cortical plus outer medullary blood flow but, instead, clearance of $^{85}$Kr from the juxtamedullary cortex, outer medulla, and inner medulla by blood and urine.

Our results do not agree with those of previous studies on the changes in intrarenal distribution of blood flow with elevated ureteral pressure. Harsing et al. (12) used $^{88}$Rb to estimate cortical and medullary blood flow when the ureter was occluded during mild mannitol diuresis. Directly measured total renal blood flow increased, whereas according to $^{88}$Rb extraction measurements, both cortical and medullary blood flow decreased. These authors suggest that the increased total blood flow may be through non-nutrient channels. Our results obtained during mild saline diuresis probably can be compared to their results obtained during mild mannitol diuresis, since total renal blood flow increased in both cases. We cannot support the idea that the increase in total renal blood flow is via non-nutrient channels, since the inert gas method measures only nutrient blood flow and we found increased total renal blood flow using this method. In addition, we found an increase in cortical blood flow and no change in outer medullary blood flow.

An alternative explanation of the results of Harsing et al. rests on the fact that extraction of $^{86}$Rb from blood perfusing a tissue usually decreases as blood flow increases (13). The increased cortical blood flow associated with ureteral occlusion could result in decreased deposition of $^{88}$Rb in the kidney cortex because of the decreased extraction.

The observation that extraction of PAH decreases during ureteral occlusion has led to the proposal that there is a relative increase in medullary blood flow (1), which is contrary to our observation that cortical blood flow is increased and outer medullary blood flow is unchanged. This disparity may result from the fact that PAH extraction is, at best, a poor indicator of distribution of blood flow, since it is not completely extracted from blood perfusing cortical nephrons at normal blood flow rates and the extraction by cortical nephrons is further decreased by ureteral occlusion (14).

Any mechanism we propose to explain the increase in total renal blood flow after elevation of ureteral pressure must be consistent with our findings that (1) the increased blood flow is through nutrient channels, and (2) the increased flow is confined to the
cortex. The most popular explanation of the decrease in renal resistance in the presence of elevated ureteral pressure is that afferent arterioles relax in response to the decrease in transmural pressure resulting from increased tissue pressure (1). Our results in no way contradict this hypothesis, but the lack of change in outer medullary blood flow must be explained. One explanation would be that the resistance vessels determining outer medullary flow are maximally relaxed during the control period and can relax no further when transmural pressure is reduced. This seems unlikely because, when perfusion pressure is lowered by renal constriction, outer medullary blood flow remains constant, indicating decreased resistance, i.e., relaxation of outer medullary resistance vessels (12).

Any increase in blood flow with elevated ureteral pressure must represent a large decrease in resistance of those vessels with a high distending pressure, i.e., afferent arterioles, which overwhelms the compression of vessels with lesser distending pressures, i.e., the postglomerular vessels. Winton has shown that medullary tissue pressure is higher than cortical pressure when ureteral pressure is raised (15). If this is the case, outer medullary flow may not increase, because any decrease in preglomerular resistance is completely balanced by increased postglomerular resistance, whereas the decrease in resistance of the afferent arterioles of the cortex is not balanced by the compression of low-pressure vessels because tissue pressure is lower.

It may be that the increased cortical blood flow is unrelated to the Bayliss phenomenon and, instead, depends on some other local regulatory device. Since the concentration of renin is highest in this area and Thurau (16) has suggested release of renin as a local control mechanism, we measured renin release during ureteral occlusion simultaneously with measurement of cortical blood flow. Since renin release increases with cortical blood flow during ureteral occlusion (Table 4), it seems unlikely that the renin-angiotensin system can be linked in a direct way to the decreased cortical vascular resistance during ureteral occlusion.

The results obtained during copious mannitol diuresis seem easier to interpret. It is true that there is increased renin release when ureteral pressure is elevated during mannitol diuresis (17), but since renin release is also increased when outer cortical blood flow is increased, we do not favor this as a mechanism for the decrease of renal cortical blood flow.

Elevation of the osmolarity of the blood with various substances, including mannitol, abolishes the autoregulation of renal blood flow when renal arterial pressure is varied (18). We have shown (Fig. 3) that mannitol causes relaxation of vascular smooth muscle of interlobular renal arteries. Thus, elevating plasma osmolarity by infusing mannitol may abolish the myogenic tone of the cortical resistance vessels and result in increased renal blood flow. Since the vessels are relaxed, the unopposed effect of the elevated tissue pressure during occlusion of the ureter is collapse of the postglomerular vessels, and renal blood flow decreases. Further support for this view is the finding that elevation of ureteral pressure does not cause decreased total renal blood flow unless blood flow has first been elevated by the mannitol infusion (3).

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References

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