INFLUENCE OF GRADED ARTERIAL PRESSURE DECREMENT ON RENAL CLEARANCE OF CREATININE, P-AMINOhippurate AND SODIUM

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In a previous study designed to establish the relationship of renal blood flow to arterial perfusion pressure in the intact kidney of the dog, it was demonstrated that due to apparent renal autonomy, blood flow was maintained despite considerable decrease in perfusion pressure (1). This resulted in a curvilinear pressure-flow relationship convex toward the pressure axis. Since direct blood flow measurements only were made in this study, no conclusion could be drawn with regard to the behavior of the renal arterioles in this mechanism. Forster and Maes (2) studied the effects of elevation of mean arterial blood pressure on the clearance of creatinine and p-aminohippurate (PAH) in rabbits whose kidneys had been denervated and whose adrenal glands had been demedullated. They found that when blood pressure was elevated by neurogenic mechanisms resulting from clamping of the carotid arteries that these clearances remained remarkably constant. This apparent constancy of glomerular filtration rate and effective plasma flow appeared to result from increase in afferent arteriolar resistance.

In the present study, the effect of graded decrease in arterial blood pressure on the clearance of PAH, taken to measure effective plasma flow, and on creatinine clearance, measuring glomerular filtration rate, was studied in dogs. In addition, the reduction in glomerular filtration which accompanied the decrease in arterial pressure afforded an opportunity to examine the effect of reduced sodium load on the renal mechanism for sodium excretion. This was of particular interest because of the phenomenon of sodium retention accompanying the reduction in glomerular filtration rate and effective plasma flow noted in congestive heart failure (3, 4).

METHODS

Female dogs averaging 16.5 kg. in weight (range, 11.5 to 23.5) were used. They were anesthetized with 30 mg/kg. of pentobarbital sodium administered intravenously. The left kidney and dorsal aorta were exposed by a dorsal retroperitoneal approach. The left ureter was catheterized so that the tip of the catheter lay within the renal pelvis; the length of the catheter was kept to a minimum so that the dead space of the collecting system was kept to a negligible volume. With the exception of several of the earlier experiments, the right kidney served as a control. Its urine was collected by means of an indwelling bladder catheter.
Arterial pressure decrement to the left kidney was produced by a tourniquet around the dorsal aorta just between the right and left renal arteries, made possible by the higher origin of the right renal artery. Gradual occlusion of the aorta by the tourniquet thus decreased arterial inflow pressure to the left kidney but kept the blood supply to the right kidney reasonably constant. Carotid mean blood pressure was taken as the index of arterial pressure to the right (control) kidney, and the femoral mean blood pressure was taken as the index of arterial pressure to the left (experimental) kidney. The validity of the latter procedure was tested in 3 dogs by introduction of a long cannula into the abdominal aorta via the femoral artery, ligated in position just behind the axis of the left renal artery. The results of these experiments were in accord with those in which renal arterial inflow pressure was measured via the femoral artery.

The plan of each experiment was to follow a pair of control periods with four stages of graded arterial pressure decrement, with two consecutive urine collection periods at each level, followed by return of arterial pressure to control levels with two final recovery urine periods. Adequate discard periods were observed between each level of arterial pressure, with longer periods during stages of low urine flow. To insure adequate urine volumes, all animals were hydrated with 200 to 300 cc. of 0.9 per cent saline prior to the initial urine period, and a moderate amount of mannitol was included in the infusion fluid containing creatinine and PAH so that about 12 mg/min/kg. of body weight were given following a 5-gm. priming dose. Constant infusion was obtained by use of a mercury pump. Control urine flow averaged 2.0 cc/min. for the left kidney. Bloods were taken before and after each pair of urine periods, and interpolated values corrected for emptying time were used for calculation of the clearances.

The method of Smith et al. (5) was used for PAH analysis. Plasma PAH determinations were done on CdSO₄ filtrates. Creatinine was measured by the alkaline picrate method (6). Sodium tungstate filtrates were used for plasma creatinine determinations. All analyses were made in duplicate. Sodium was analyzed with a Perkin-Elmer model 18-A flame photometer on diluted urines and plasmas; in some cases, trichloroacetic acid filtrates were used for plasma sodium analysis. No difference from direct plasma analysis was noted. When sodium clearances were calculated, a plasma sodium correction for the Donnan effect was made by the factor: KP/W, in which KNa = 0.925, and W (percentage of water in the plasma) was taken as 0.94.

RESULTS

Effect of Graded Arterial Pressure Decrement on Clearance of PAH and Creatinine.

Ten animals are included in this series. In three earlier experiments control clearances on the right kidney were not made simultaneously with the experimental changes produced in the left kidney by decreased arterial pressure, hence systemic factors which might alter clearances could not be detected. Although these three experiments are in approximate agreement with those done later, the emphasis of this section will

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2 We are indebted to Dr. Viola Startzman, Dept. of Pediatrics, for use of the Perkin-Elmer flame photometer.
be placed on seven experiments in which both right and left kidney clearances were followed simultaneously.

A representative experiment is illustrated in figure 1. This experiment is particularly instructive because systemic factors which might influence renal blood flow appear to be absent during the 3-hour duration of the experiment, as evidenced by the constancy of the control clearances. Thus it can be concluded that alterations noted in the experimental kidney clearances must be specifically due to intrarenal changes resulting from the influence of decreased arterial pressure. The control clearances of PAH and creatinine, together with the filtration fraction, appear in the lower part of the figure in relation to the control arterial pressure.

In the upper part of figure 1 it is seen that as arterial pressure is progressively decreased from a mean of 162 mm. Hg through stages averaging 127 mm. and 104 mm. respectively, there are no significant changes in PAH and creatinine clearance, and the filtration fraction remains constant. At the level of 73 mm. Hg, however, clearances begin to decrease noticeably, and are significantly lower at a level averaging...
50 mm. Hg. During the latter stages, the clearance of creatinine falls somewhat more rapidly than that of PAH, with the result that the filtration fraction decreases, a finding typical of all experiments. With release of the tourniquet, clearances recover to 78 per cent of the control kidney values. (In all experiments, average recovery for PAH clearance was to 89 per cent of the control kidney, and to 81 per cent of control for creatinine clearance.)

Systemic factors were frequently found to be operative which tended to decrease clearances somewhat during long experiments. In order to correct for this trend the experimental (left) kidney clearances are presented as a ratio to the control (right) kidney in figure 2 for all experiments. Each symbol in the figure represents the average of two consecutive urine collection periods. It is evident that the PAH clearance is well maintained as pressure is decreased to about 100 mm. Hg, then decreases rapidly with further decreases in pressure. Creatinine clearance is maintained to about 120 mm. Hg, then decreases somewhat more rapidly than the PAH clearance, resulting in decrease in the filtration fraction. At about 60 mm. Hg, all clearances rapidly approach zero.

**Fig. 2. Effect of decreased arterial pressure on PAH and creatinine clearance expressed as a ratio to the control kidney. Each point is the average of 2 consecutive urine periods. Data are from 7 experiments.**

**Changes in Regional Renal Vascular Resistance Resulting From Graded Arterial Pressure Decrease.** Changes in afferent arteriolar resistance (R_A), efferent arteriolar resistance (R_E), post-arteriolar resistance (R_V), and total renal resistance were analyzed by means of Lamport’s equations (7). The same experiment graphically presented in figure 1 is used to exemplify the trend of resistance changes in figure 3.

In the upper half of the figure PAH and creatinine clearance are given in cc/min/gm.

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9 Calculation of regional renal vascular resistance in mm. Hg/cc/min. was made according to the following original equations of Lamport (7), with minor modifications cited below:

\[
R_A = \frac{(P_M - P_o - 23 Hc - 20)/HD}{HD}; \\
R_E = \frac{(1 - 0.47F)(P'_o - P_o - 23 Hc + 10)/HD}{HD}; \\
R_V = \frac{P_V - P_v + 20}{HD}. \\
\]

Total Renal Resistance = \( R_A + R_E + R_V \).

\( P_M \) = mean arterial blood pressure; \( P_o \) = osmotic pressure of plasma protein, with protein concentration of plasma taken as 6 gm/100 cc.; \( P'_o \) = osmotic pressure of plasma protein after glomerular filtration; \( P_V \) = renal vein pressure; \( Hc \) = hematocrit; \( HD \) = effective blood flow; \( F \) = filtration fraction.

The minor modifications employed in our calculations were to circumvent the spurious negative resistance values observed by Lamport (7) at substantially decreased arterial pressures. One modification substituted a yield pressure of 14 mm. Hg (1) for the value of 20 mm. Hg employed by Lamport, with an adjustment for nonlinearity for values below 80 mm. Hg arterial pressure. A second minor modification was to make intracapsular pressure proportional to glomerular filtration rate, instead of utilizing a constant value of 10 mm. Hg.
of kidney as related to arterial pressure. Here each point is the average of two consecutive clearance periods, and the trend of results is indicated by curves of best fit for the experimental points. The maintenance of clearance during early stages of pressure decrement is obvious.

In the lower half of the figure appear the trends of resistance changes in the kidney. Total renal vascular resistance shows a gradual decrease through the range 162 to 104 mm. Hg, then remains constant to 73 mm. Hg. The decrease in total
resistance appears to be entirely attributable to decrease in afferent arteriolar resistance ($R_a$). $R_e$ and $R_v$ show no significant changes, although $R_v$ may increase a bit at lower pressures. (The data for the lowest clearance figures are omitted in the resistance calculations because small absolute errors in the clearance data give large percentile errors in calculation.)

The conclusion that the constancy of plasma flow and glomerular filtration rate in the earlier stages of arterial pressure decrement is due to decrease in afferent arteriolar resistance is confirmed in the combined data shown in figure 4. Note here again the general downward trend of $R_a$ and the relative constancy of $R_e$ and $R_v$.

**Effect of Reduced Glomerular Filtration Rate on Renal Clearance of Sodium.** In 5 animals gradual reduction in glomerular filtration rate by aortic occlusion was employed to study the effects of reduced sodium load to the renal tubules. Table I illustrates a typical experiment. During the control periods the average sodium load is 5.7 mM/min/kidney. Urinary excretion averages 0.115 mM/min. and the plasma clearance of sodium averages 0.85 cc/min. With reduction of load to 4.83 mM/min. urinary excretion decreases to 0.10 mM/min. and clearance to 0.70 cc/min. During the next stage in reduction of glomerular filtration rate, load is diminished

### Table I. Representative Experiment Showing Effect of Decrease in Glomerular Filtration on Renal Clearance of Sodium

(All data for one kidney only: weight 43 gm. Female dog, 13 kgm. body weight.)

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>MAP</th>
<th>FILL. RATE</th>
<th>SODIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mm. Hg</td>
<td>cc/min.</td>
<td>Plasma conc.(1)</td>
</tr>
<tr>
<td>1</td>
<td>141</td>
<td>30.4</td>
<td>134</td>
</tr>
<tr>
<td>2</td>
<td>146</td>
<td>45.3</td>
<td>136</td>
</tr>
<tr>
<td>Av.</td>
<td></td>
<td></td>
<td>5.70</td>
</tr>
<tr>
<td>3</td>
<td>124</td>
<td>35.9</td>
<td>140</td>
</tr>
<tr>
<td>4</td>
<td>121</td>
<td>32.2</td>
<td>142</td>
</tr>
<tr>
<td>Av.</td>
<td></td>
<td></td>
<td>4.83</td>
</tr>
<tr>
<td>5</td>
<td>99</td>
<td>23.3</td>
<td>138</td>
</tr>
<tr>
<td>6</td>
<td>98</td>
<td>33.3</td>
<td>133</td>
</tr>
<tr>
<td>Av.</td>
<td></td>
<td></td>
<td>3.90</td>
</tr>
<tr>
<td>7</td>
<td>81</td>
<td>30.5</td>
<td>133</td>
</tr>
<tr>
<td>8</td>
<td>74</td>
<td>21.8</td>
<td>136</td>
</tr>
<tr>
<td>Av.</td>
<td></td>
<td></td>
<td>3.50</td>
</tr>
<tr>
<td>9</td>
<td>66</td>
<td>8.3</td>
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</tr>
<tr>
<td>10</td>
<td>55</td>
<td>4.0</td>
<td>142</td>
</tr>
<tr>
<td>Av.</td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>11</td>
<td>145</td>
<td>33.0</td>
<td>142</td>
</tr>
<tr>
<td>12</td>
<td>138</td>
<td>35.7</td>
<td>142</td>
</tr>
<tr>
<td>Av.</td>
<td></td>
<td></td>
<td>4.89</td>
</tr>
</tbody>
</table>

\(1\) Plasma Na is corrected for the Donnan effect by the factor $K_P/W$, in which $K_{Na} = 0.925$, and $W$ (% of water in plasma) is taken as 0.94.
to 3.90 mM/min., urinary excretion is markedly reduced to 0.014 mM/min. and clearance decreases to 0.10 cc/min. as tubular reabsorption of filtered sodium becomes almost complete. This trend is continued in the remaining stages of reduced filtration rate. With restoration of arterial blood pressure and a return of filtration rate toward control values, urinary sodium excretion returns to 0.057 mm/min. and clearance 0.40 cc/min. during the last period when load is 5.07 mm/min.

The relationship of glomerular filtration rate to sodium excretion for all experiments is summarized in figure 5. This shows that sodium excretion diminishes as glomerular filtration rate is decreased from the control average of 40 cc/min/kidney, and that in a range 20 to 30 cc/min. urinary excretion is almost entirely abolished as tubular reabsorption of sodium becomes almost complete at reduced loads.

Fig. 5. RELATIONSHIP OF SODIUM EXCRETION to glomerular filtration rate (5 experiments). Open circles: values obtained after return of arterial pressure to normal after experimental changes. It is observed that these data are in the range of normal. Data are for one kidney only.

The relationship of sodium load to urinary excretion and tubular reabsorption is summarized for all experiments in table 2. Here it is revealed that the most pronounced decrease in excretion occurs at the second level of reduced glomerular filtration rate (average, 32 cc/min.), where average excretion is only 0.0173 mm/min. at a load of 4.3 mm/min. At this stage, reabsorption of filtered sodium is 99.5 per cent complete, as compared with 97.3 per cent during the control periods.

DISCUSSION

In connection with the previous work (1) employing direct blood flow measurement in analysis of pressure-flow relationship of the kidney, speculation was raised concerning the possibility that changes in blood viscosity resulting from changes in glomerular filtration might be the basis for the apparent renal autonomy of flow. The hypothesis put forward suggested that as arterial pressure was increased, increased filtration of fluid from the plasma at the glomeruli would increase protein and cell concentration of the blood passing through the glomeruli, increasing its...
viscosity and thus buffering effects of increased pressure. With reduction in arterial pressure, the reverse effect might be expected to occur. This hypothesis necessarily assumed a linear relationship of glomerular filtration rate to arterial pressure, increases in filtration rate paralleling increase in arterial pressure, and vice versa.

The present investigation has revealed that the above hypothesis is not tenable. Apparently, autonomous renal arteriolar changes are basic to an adjustment of glomerular filtration rate whereby this is kept constant as arterial pressure is decreased, thus precluding changes in blood viscosity. Analysis of the clearance data by the method of Lamport reveals that this maintenance of glomerular filtration rate (and effective plasma flow) is by afferent arteriolar dilatation. It is interesting to note that Forster’s data on the rabbit (2) suggest that the constancy of renal blood flow in the face of increased arterial pressure is by afferent arteriolar constriction. These findings together identify the role of the afferent arterioles as a buffering mechanism which counteracts the effects of changes in systemic arterial blood pressure. Beyond the conclusion that this regulation is definitely intrarenal, no further information can be supplied at present as to the exact nature of this buffering mechanism.

### Table 2. Summary of relationship of sodium load to urinary excretion and tubular absorption

<table>
<thead>
<tr>
<th>SODIUM</th>
<th>LOAD</th>
<th>EXCRETED</th>
<th>REABSORBED</th>
<th>% REABSORBED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mM/min.</td>
<td>mM/min.</td>
<td>mM/min.</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.77</td>
<td>0.160</td>
<td>5.61</td>
<td>97.3</td>
</tr>
<tr>
<td>Experimental</td>
<td>5.8</td>
<td>0.074</td>
<td>5.31</td>
<td>98.7</td>
</tr>
<tr>
<td>Recovery</td>
<td>5.10</td>
<td>0.026</td>
<td>4.07</td>
<td>99.3</td>
</tr>
</tbody>
</table>

Data taken from 5 animals, for one kidney only. Kidney wt., range 41-43 gm. Each level represents the average of 10 urine collection periods. Figures in parentheses are the range of variations.
The findings in connection with the alterations in the renal clearance mechanism of sodium during graded arterial pressure decrement throw some light on the problem of sodium retention in congestive heart failure. In this condition, due to reduction in cardiac output, glomerular filtration rate and effective plasma flow are decreased, the latter more so than the former (3, 4). Decreased filtration rate is associated with decrease in urinary excretion of sodium.

Our findings lead to the conclusion that as glomerular filtration rate is decreased, the load of sodium to the tubular cells is decreased, with the result that tubular reabsorption becomes more complete at lower filtration rates. In fact, the present data suggest that an actual ‘threshold’ for sodium exists, below which sodium re-absorption is complete. The normal kidney offers a load which is above this ‘threshold’ with the result that small amounts of sodium are normally excreted in the urine. This threshold has been computed for the present series and tentatively set at a value of 3.9 mm. of sodium per minute per kidney (average weight 42 gm.). The load at which sodium excretion begins is delivered to the tubules at a filtration rate of about 25 cc/min., 63 per cent of the control average. This is in no wise to be interpreted as meaning that a ‘Tm’ (tubular maximum) for sodium exists here, for in the range of the present data tubular reabsorption continues to increase as load is increased, even though accompanied by increased urinary excretion. Higher sodium loads to the tubular cells would be required than attained in the present series to establish the presence of a Tm such as exists, for example, for glucose.

The implication of these findings to the renal mechanism in congestive heart failure is apparent, notwithstanding. Because of reduction of glomerular filtration rate in congestive failure, a smaller load than normal is offered to the tubular cells whose reabsorptive capacity does not appear to be altered. This load is less than the ‘threshold’ for sodium, and as a result all filtered sodium is reabsorbed and hence retained in the blood by the kidneys. Sodium retention supplies the osmotically active substance needed for the fluid retention which leads to edema formation.

It is interesting to note that when glomerular filtration rate is improved in patients by the use of xanthine diuretics (4) that sodium excretion increases noticeably. This may be assumed to mean that the increase in sodium load resulting from increased filtration exceeds a threshold such as exists in dogs. Likewise, when glomerular filtration rate in patients normally edema-free is reduced by exercise below a critical level of 70 cc/min., sodium retention and edema formation begin (8), also supporting the concept that a threshold exists below which sodium reabsorption is complete.

**SUMMARY AND CONCLUSIONS**

When arterial infusion pressure to the kidney is gradually reduced by gradual aortic occlusion, clearances of p-aminohippurate and creatinine are well maintained.
near control values through a range of about 150 mm. Hg to 100 mm. Hg. Subsequently, clearances decrease as glomerular filtration rate and urine flow cease at about 60 mm. Hg. During this latter phase, creatinine clearances fall more rapidly than the PAH clearances, so that the filtration fraction decreases.

Calculation of renal resistance changes by the method of Lamport indicates that maintenance of renal clearances is due to afferent arteriolar dilatation; efferent arteriolar resistance and post-arteriolar resistance remain essentially constant. This emphasizes the role of the afferent arterioles as a buffering mechanism to maintain blood flow and glomerular filtration in opposition to systemic arterial blood pressure changes.

Renal excretion of sodium decreases as glomerular filtration rate is decreased by aortic occlusion. This is because as filtration is reduced, the sodium load to the tubular reabsorptive mechanism is decreased with the result that tubular reabsorption becomes more complete. The data suggest that a 'threshold' for sodium reabsorption exists at a load of about 3.0 mm/min/kidney below which reabsorption is complete. The normal kidney offers a load somewhat above this threshold so that small amounts of sodium are normally excreted. The significance of these findings as they bear on the problem of renal sodium retention in congestive heart failure is discussed.

REFERENCES