Lack of Nonexcretory Renal Influences on Hemodynamics and Fluid Volume Distribution after the Volume Loading of Conscious Dogs

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SUMMARY I studied the nonexcretory influences of the kidney on hemodynamics and fluid volume distribution in six conscious dogs post-splenectomy. The dogs with intact kidneys were volume loaded with 100 ml/kg of lactated Ringer's solution in 1 hour; the left kidney was removed 2 days later. The volume infusion was repeated 12 days later, within 1 day after the sole remaining kidney was removed. Arterial pressure was elevated to hypertensive levels immediately after the infusion in the intact and anephric groups, but pressure in the intact group returned to control within 5 hours after infusion. Fluid volume expansion was evidenced by a sustained increase in blood volume and sodium space in the anephric group. Blood volume and sodium space of the intact group increased after the infusion but then decreased toward control. Total circulating protein mass increased only in the anephric group and reached a value of 107.5 ± 1.3% of control by 24 hours after infusion. Central venous pressure was elevated in both groups throughout the entire 25-hour period of measurements subsequent to infusion, with the greater elevations occurring in the anephric group. The regression lines relating blood volume to central venous pressure, and blood volume to mean arterial pressure, were not significantly different for the anephric and intact groups. Also, the ratio of blood volume to sodium space was not significantly different for the two groups during the control and postinfusion periods. Thus, the increase in central venous pressure and mean arterial pressure after volume loading appears to be related to the increase in blood volume and not to a change in vascular compliance. I found no evidence indicating that removal of the kidney influences hemodynamics or fluid volume distribution.

Several investigators have suggested that the kidney exerts nonexcretory influences on hemodynamics and fluid volume distribution (Bianchi et al., 1978; Grollman et al., 1949; Kolff et al., 1954; Lucas and Floyer, 1973). Anephric dogs have been shown to develop hypertension when they are overhydrated; however, when dogs are overhydrated after the ureter of their sole remaining kidney is anastomosed into either the vena cava (Kolff et al., 1954) or the small intestine (Grollman et al., 1949), no hypertension occurs. These investigators have proposed that a substance secreted by the kidney prevented hypertension from developing. Also, Lucas and Floyer (1973) proposed that the compliance of the interstitium may be influenced by a substance present in the kidney. Their studies in rats suggest that removal of the kidney causes the compliance of the interstitium to decrease and also results in a decrease in venous compliance. In contrast, a recent study showed that the effective vascular compliance increases in anephric dogs (Liard, 1976).

Although a number of studies have described the nonexcretory influences of the kidney on hemodynamics and fluid volume distribution, these renal influences have not yet been elucidated. The results of many of the previous studies have been complicated by the strong probability that urinary products which are returned to the circulation through an ureterocaval anastomosis are not usually found in the blood. These unknown substances could have profound hemodynamic effects. Two of the above studies measured arterial pressure by femoral artery puncture (Grollman et al., 1949; Kolff et al., 1954), and one was performed on lightly anesthetized animals (Lucas and Floyer, 1973).

The present experiments were designed to study the nonexcretory influences of the kidney on hemodynamics and fluid distribution between the interstitium and the blood by volume-loading intact dogs and then later repeating the volume load in the same dogs after their kidneys had been removed. Thus, the effects of urine entering the circulation were eliminated. This study was performed on conscious, trained dogs, and arterial pressure was measured 24 hours a day through an indwelling catheter. The effects of the kidney on fluid distribution were determined by making serial measurements of blood volume, sodium space, and plasma protein in intact and anephric dogs for 25 hours subsequent to an intravenous infusion of lactated Ringer's solution. Also, the effects of volume load-
ing on central venous pressure and plasma electrolytes were determined.

Methods

Animal Preparation

Anesthesia was induced on six dogs with intact kidneys with sodium thiopental (Pentothal, 25 mg/kg, iv, Abbott Labs) and was maintained with an inspired mixture of methoxyflurane (Penthrane, Abbott Labs) and oxygen. The gas mixture was delivered from an Ohio Medical Products anesthesia machine to the animal through an endotracheal tube. Hydromorphone sulfate (Dilaudid, 1 mg in 0.5 ml, im, Knoll Pharamaceutical Company) was given 30 minutes after the administration of methoxyflurane was stopped. A splenectomy then was performed through a midabdominal incision. Also, at this time, indwelling Tygon (Norton) catheters were implanted in the thoracic aorta and the thoracic vena cava through the femoral artery and vein. The catheters were tunneled subcutaneously and exteriorized at the cephalad portion of the dog's back for protection. After blood samples were withdrawn, the catheters were filled with a solution containing heparin (Upjohn), 1,000 USP U/ml. The dogs were allowed to recover from surgery for 10 days. During this time, they were familiarized with the laboratory and were trained to lie quietly in their cages. The dogs were maintained on a dietary intake of 30 mEq sodium/day (prescription diet K/d, Riviana Foods) and water ad libitum throughout the control and experimental periods. On the day of the infusion, the dogs were fed just after the 5th hour of the postinfusion period.

A 7-day control period immediately followed the post-splenectomy recovery period. During this time, the arterial pressure was measured 24 hours a day. On the day after the end of the control period, control measurements were made for 3 hours, then 100 ml of warmed lactated Ringer’s solution per/kg were infused intravenously. The same measurements that were made on the intact group were repeated on this anephric group.

Experimental Measurements and Statistics

The dogs were fitted with a backpack which housed a Statham P23AC transducer at the level of the heart. The transducer wires were connected to a Grass model 7D recorder which was used to record arterial pressure 24 hours a day. Central venous pressure was measured while the dogs lay quietly in their cages with a Statham P23BC transducer that was attached to a permanent laboratory fixture. Both arterial and venous transducers were zeroed to the level of the right atrium.

Measurements of blood volume, sodium space, and iothalamate space were made using the dilution principle. Blood volume was measured by the dilution of $^{51}$Cr (New England Nuclear) tagged red blood cells (Swan and Nelson, 1971). The dog’s red cells were tagged with 100 $\mu$Ci of $^{51}$Cr the day before the infusion (Wennesland et al., 1962). Samples of blood in the amount of 7 ml were withdrawn through the arterial catheter before injection of the isotopes to determine radioactive background. Then, at the beginning of the 3-hour control period on the morning of the infusion, 10 ml of radiochromated red cells, 2 ml (5 $\mu$Ci) of $^{22}$Na (New England Nuclear) and 20 ml (25 $\mu$Ci) of $^{125}$I-labeled iothalamate (Glofil, Abbott Labs) were injected through the venous catheter. Seven-milliliter blood samples were drawn through the arterial catheter 20 minutes and 3 hours after injection and at 2 minutes, 5 minutes, 20 minutes, 40 minutes, 1 hour, 2 hours, 3 hours, 4 hours, and 5 hours after the infusion of lactated Ringer’s for determination of dilution volumes. A 20-ml blood sample was withdrawn through the arterial catheter just after the 2-hour postinfusion sample, and the blood was labeled with 200 $\mu$Ci of $^{51}$Cr. Just after the 24-hour postinfusion sample, 10 ml of the radiochromate-labeled cells were injected intravenously. Seven-milliliter arterial blood samples were drawn 20 minutes and 1 hour later for the determination of blood volume. A Searle (model 1185) solid crystal scintillation counter was used for radioactive counting, and appropriate corrections for overlapping energy spectrums and for $^{22}$Na lost in the urine were used. The control values for blood volume (Swan and Nelson, 1971), sodium space (Manning et al., 1979a; Manning et al., 1979b), and iothalamate space (Hall et al., 1978) were determined from the blood samples drawn 3 hours subsequent to isotope injection. Iothalamate space was determined only for the anephric group. Plasma volume was calculated using blood volume and hematocrit (Swan and Nelson, 1971).

Plasma protein concentration was determined
with an American Optical refractometer. Total intravascular protein mass was calculated by multiplying plasma protein concentration and plasma volume. An Instrumentation Laboratory flame photometer was used to determine plasma sodium and plasma potassium concentrations.

Statistical analysis of arterial pressure, blood volume, sodium space, plasma protein, total intravascular protein, central venous pressure, plasma volume, plasma sodium, and plasma potassium data was performed using Dunnett's test for multiple comparisons (Dunnett, 1964). The overall mean data from the postinfusion period of the anephric group were compared statistically to the overall mean data of the intact group over the same time period. The regression of blood volume on sodium space, central venous pressure on blood volume, and mean arterial pressure on blood volume are first-order equations determined by the least-squares method. The predicted regression lines for the intact and anephric groups were statistically compared by joint consideration of the slope and intercept (Draper and Smith, 1966; Scheffe, 1959).

The level of statistical significance was \( P < 0.05 \). All data are expressed as mean ± 1 SEM. The measurements of fluid volume, plasma protein, plasma electrolytes, and central venous pressure which were made 3 hours after the beginning of the control period on the infusion day were considered to be the control values. Subsequent data were calculated as percent of control. The control value of arterial pressure for the intact and anephric groups was the average value over the 3-hour control period on the infusion day.

**Results**

The nonexcretory influences of the kidney on hemodynamics and fluid distribution were studied by first infusing lactated Ringer's solution into six conscious dogs post-splenectomy but with kidneys intact and repeating the infusion 2 weeks later, after the kidneys had been removed. Arterial pressure, fluid volumes, plasma proteins, plasma electrolytes, and central venous pressure were measured during a control period and for 25 hours after the infusion. Control values for the intact and anephric groups are shown in Table 1. The values during the control period are all within the physiological range, and the only significant difference between the groups is the ratio of plasma volume to sodium space and the hematocrit. At least part of the increase in the ratio of plasma volume to sodium space in the anephric group was due to fluid transfer into the circulation which compensated for a decrease in red cell mass. This decrease in red cells resulted primarily because of the amount of blood withdrawn for samples during the series of measurements while the dogs had intact kidneys. Nevertheless, the total blood volume and the blood volume-to-sodium space ratio were not different in the two groups.

**Arterial Pressure Responses to Volume Loading**

Arterial pressure was measured during the 7-day control period for the intact and anephric groups. The arterial pressure was measured 24 hours a day, and the values represent the average over the entire 24-hour period. The arterial pressure was consistent in each group during the control period, and the maximum deviation was 5.1% from its control value in the anephric group and 4.6% in the intact group. On the 7th day of the control period, the remaining kidney was surgically removed. The dogs were placed back in their pens immediately after surgery, and the arterial pressure measurement resumed at that time. Very little change in arterial pressure was observed after surgery.

The effects on mean arterial pressure of intravenous infusion of 100 ml of lactated Ringer's solution per/kg into the intact and anephric groups are shown in Figure 1. An immediate increase in arterial pressure to hypertensive levels was observed in both groups. The pressure increased to a maximum value of 138.2 ± 3.4% of control in the intact group and 142.1 ± 4.0% of control in the anephric group at 2 minutes postinfusion. Hypertension persisted...

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**Table 1 Summary of Control Values**

<table>
<thead>
<tr>
<th></th>
<th>Intact</th>
<th>Anephric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>96.8 ± 1.6</td>
<td>94.8 ± 1.2</td>
</tr>
<tr>
<td>Blood volume (ml/kg)</td>
<td>68.1 ± 2.0</td>
<td>67.0 ± 2.6</td>
</tr>
<tr>
<td>Na space (ml/kg)</td>
<td>355.2 ± 14.3</td>
<td>342.7 ± 12.9</td>
</tr>
<tr>
<td>Blood volume/Na space</td>
<td>0.192 ± 0.007</td>
<td>0.196 ± 0.005</td>
</tr>
<tr>
<td>Plasma volume (ml/kg)</td>
<td>39.6 ± 2.2</td>
<td>46.1 ± 3.6</td>
</tr>
<tr>
<td>Plasma volume/Na space</td>
<td>0.112 ± 0.004</td>
<td>0.134 ± 0.007*</td>
</tr>
<tr>
<td>Total circulating protein (g/kg)</td>
<td>2.53 ± 0.12</td>
<td>2.79 ± 0.19</td>
</tr>
<tr>
<td>Plasmas protein concentration (g/100 ml)</td>
<td>6.4 ± 0.25</td>
<td>6.1 ± 0.17</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>22.9 ± 1.2</td>
<td>22.2 ± 1.1</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>-0.5 ± 0.5</td>
<td>-1.6 ± 0.7</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>44 ± 2</td>
<td>35 ± 2*</td>
</tr>
</tbody>
</table>

No. of animals | 6 | 6

Control values were determined on the morning of the infusion of lactated Ringer's solution.

* \( P < 0.05 \) compared to intact.
in the anephric group, but arterial pressure decreased to its control value in the intact group by the 5th postinfusion hour.

Blood Volume Responses to Volume Loading

The effects of intravenous infusion of lactated Ringer's solution on the blood volume of the anephric and intact groups are shown in Figure 2. Fluid retention during the infusion period was evidenced by an increase in blood volume to a value of 127.0 ± 4.2% of control in the anephric group and an increase to a value of 119.4 ± 2.1% of control in the intact group by 2 minutes postinfusion. Blood volume remained elevated in the anephric group during the entire postinfusion period, but blood volume of the intact group decreased back to its control value as expected.

Sodium Space and Iothalamate Space Responses to Volume Loading

Fluid retention after volume loading was also evidenced by a considerable increase in sodium space, as is shown in Figure 3. Sodium space of the anephric group remained near a plateau of 140% of control throughout the post-infusion period. In contrast, the sodium space of the intact group increased by 30% immediately after the infusion and then decreased toward its control value. Iothalamate space was determined for the anephric group to obtain another index of the changes in extracellular fluid volume. Iothalamate space increased from a control value of 309.6 ± 12.7 ml/kg to a value of 145.9 ± 1.4% of control by 2 minutes postinfusion and remained very close to this value for the subsequent 5 hours of measurement. Thus, the percentage changes in sodium space and iothalamate space after volume loading were nearly equal.

Plasma Protein Concentration and Total Intravascular Protein Responses to Volume Loading

Figure 4 illustrates the effects of intravenous infusion of lactated Ringer's solution on the plasma protein concentration of the intact and anephric groups. Protein concentration decreased immediately after infusion in both groups with the greater decrease occurring in the anephric group. Plasma protein concentration of the intact group returned nearly to control by the next day. However, the protein concentration of the anephric group remained below its control value throughout the post-infusion period.

The effects of volume loading on the total intra-
vascular protein were calculated for both groups. The total intravascular protein of the intact group remained close to its control value until the 24th hour of the postinfusion period when a small decrease was observed. In contrast, a moderate increase in intravascular protein to 107.5 ± 1.3% of control was observed in the anephric group by 24 hours postinfusion.

Responses of Central Venous Pressure to Volume Loading

The effects of intravenous infusion of lactated Ringer's solution on central venous pressure are shown in Figure 5. A sustained increase in central venous pressure was seen in the anephric group. The maximum increase in central venous pressure was 6.0 ± 1.5 mm Hg by 2 minutes postinfusion. Central venous pressure increased 3.3 ± 1.6 mm Hg by 2 minutes postinfusion in the intact group, but then decreased toward its control value.

Responses to Plasma Sodium and Plasma Potassium Concentrations to Volume Loading

The effects of volume loading on the plasma sodium concentration of the intact and anephric groups were measured throughout the postinfusion period. Very little change in sodium concentration was observed in the anephric group. The maximum increase in plasma sodium concentration in the intact group was to a value of 102.1 ± 0.4% of control by 60 minutes postinfusion. Thereafter, the sodium concentration decreased toward its control value.

The effects of volume loading on the plasma potassium concentration of the intact and anephric groups are shown in Figure 6. The potassium concentration of the intact group decreased to a minimum value of 90.0 ± 3.8% of its control value of 4.3 ± 0.1 mEq/liter by 60 minutes postinfusion, but then the plasma potassium increased back toward its control value. The potassium concentration of the anephric group increased above its control value of 5.1 ± 0.3 mEq/liter by the 4th postinfusion hour and reached a maximum value of 119.2 ± 3.5% of control by 25 hours postinfusion.

The Relationship between Sodium Space and Blood Volume

The linear regression equation for the blood volume and sodium space of the intact group is illustrated in Figure 7. The individual points in this figure represent the values for sodium space and blood volume of the intact and anephric groups during the control and postinfusion periods which have been illustrated in Figures 2 and 3. The population of data points of the anephric group lies
very close to the regression line of the intact group. The blood volume-to-sodium space ratio decreased from its control value to an average value during the postinfusion period of 0.174 ± 0.003 in the intact group and 0.173 ± 0.002 in the anephric group. There is no significant difference in these values. Therefore, we found no evidence which would indicate that removal of the kidney or some unknown renal substance causes a shift in fluid from the extracellular space to the blood.

The Relationship between Blood Volume (BV) and Central Venous Pressure (CVP)

Linear regressions describing the relationship between blood volume and central venous pressure were calculated for the intact and anephric groups. The data for the regressions are the values of blood volume and central venous pressure during the control and postinfusion periods which have been illustrated in Figures 2 and 5. The equation for the intact group is CVP = 0.099BV - 9.39, \( r = 0.749 \), and the equation for the anephric group is CVP = 0.222BV - 22.5, \( r = 0.897 \). When the slopes and intercepts of the regression equations were jointly compared no significant difference was found.

The Relationship between Blood Volume (BV) and Mean Arterial Pressure (MAP)

The linear regressions describing the relationship between blood volume and mean arterial pressure were calculated for the intact and anephric groups. The data for the regressions are the values of blood volume and mean arterial pressure during the control and postinfusion periods which have been illustrated in Figures 1 and 2. The equation for the intact group is MAP = 1.90BV - 91.6, \( r = 0.936 \), and the equation for the anephric group is MAP = 1.18BV - 8.84, \( r = 0.946 \). No significant difference in the regressions were found when the slopes and intercepts were jointly compared.

Discussion

The nonexcretory influences of the kidney have been studied in anephric and intact dogs that were volume loaded with lactated Ringer’s solution. We found no evidence to indicate that the kidney or some renal substance causes changes in either hemodynamics or body fluid distribution. Earlier studies on the nonexcretory renal influences compared anephric animals to animals with their ureters anastomosed either to the vena cava (Kolff et al., 1954; Lucas and Floyer, 1973) or to the small intestine (Grollman et al., 1949). There is a possibility that substances enter the circulation of these animals from the recirculated urine which would not be present in the blood under normal physiological conditions. These urinary substances could have profound effects on the heart, vasculature, and interstitium. In the present study, I compared the hemodynamic responses of intact and anephric dogs to volume loading and thus eliminated the effects of the urine entering the circulation. The plasma potassium concentration was higher in the anephric group, and the plasma levels of urea and of creatinine, although not measured, were certain to be higher in this group. However, the data in Table 1 show that the effects of these changes had minimal influence on the physiological status of the dogs.

Because blood volume and extracellular fluid volume began to decrease in the intact dogs immediately after volume infusion in the present study, serial measurements of blood volume and sodium space were made, and the effects of changes of blood volume on mean arterial pressure and central venous pressure were compared for the intact and anephric groups. There was no significant difference in the regressions of mean arterial pressure on blood volume for the two groups. This indicates that arterial pressure increases by the same amount for a given change in blood volume whether the kidneys are present or not. In addition, the regression of central venous pressure on blood volume, which has been referred to as the effective vascular compliance, was not significantly different in the intact and anephric groups. Thus, the higher venous pressure in the anephric group was due primarily to the sustained hypervolemia.

The population of data points relating blood volume to sodium space for the anephric group lies close to the regression line of the intact group as is seen in Figure 7. Also, the ratio of blood volume to sodium space of the two groups was not significantly different in either the control or postinfusion periods. Thus, we found no evidence to indicate that removal of the kidney causes a redistribution of fluid from the interstitium to the blood. Lucas and Floyer (1973) found that the blood volume-to-extracellular fluid volume ratio increased after bilateral nephrectomy in rats when daily injections of saline and blood were given to one group of rats, although the blood volume did not increase in another group.
which received no supplementary blood injections. They also found a decrease in venous compliance of rats after bilateral nephrectomy. The difference between the present study and Lucas and Floyer's work may be due to the daily injections of blood, species differences, or their use of anesthesia, which may have affected fluid distribution during overhydration (Schad and Brechtelsbauer, 1978). Also, the present study was performed 1 day after nephrectomy, whereas the study by Lucas and Floyer was made 4 days after nephrectomy. However, an earlier study (Manning and Guyton, unpublished observation) showed that blood volume and arterial pressure were stable in anephric dogs for at least 72 hours after nephrectomy. The anephric dogs had a blood volume of 108.4% of control at 2 days after nephrectomy and a blood volume of 109.1% of control 3 days after nephrectomy. Mean arterial pressure increased slightly from 102% of control 2 days after nephrectomy to 104.6% of control by 3 days after nephrectomy. Control measurements were made 1 day subsequent to nephrectomy. These data testify to the stability of the hemodynamic measurements on the infusion day of the anephric group in the present experiment despite their lack of renal function.

The increase in total circulating protein in the present study in the anephric group agrees with results of previous volume loading studies in conscious patients (Harroun et al., 1950; Stewart and Rourke, 1942) and conscious dogs (Schad and Brechtelsbauer, 1978). This excess protein could help maintain the elevated blood volume in the anephric group in the present study. The reason for the difference in the total protein in the anephric groups is not clear, but several possibilities exist. The increase in extracellular fluid volume in the anephric group probably causes an increase in lymphatic return of protein to the circulation; thus, the total protein in the blood would increase. There also is a possibility that in the anephric group capillary permeability to protein decreased.

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