The present study is concerned with the renal mechanisms of salt and water retention during the formation of experimental ascites. In animals exhibiting chronic fluid retention, the extracellular fluid volume expands as a result of more complete reabsorption of sodium by the kidney tubules. In this important respect, dogs with experimental ascites are similar to patients with cardiac failure and decompensated hepatic cirrhosis. Study of the mechanisms involved in such animals may provide information pertinent to the retention of fluid and electrolytes in clinical states.

Previous study of acute and chronic experimental pericarditis failed to suggest a direct effect of venous hypertension on the kidney or to indicate a correlation between the rate of glomerular filtration and electrolyte excretion. Alterations in electrolyte balances and the low Na and high K pattern of fecal electrolyte excretion during acute and chronic pericarditis suggested altered adrenocortical function.

In addition to the factors studied in experimental pericarditis, the present report includes data on the relation of cardiac output and postprandial glomerular filtration rate (GFR) to salt retention during ascites formation. Measurements of glomerular filtration rate were made after the meal to determine whether the increase from the postabsorptive to the postprandial level is as great and lasts as long in dogs accumulating ascites as in the normal dog. These data are important because the daily peak of salt excretion occurs during the postprandial increase in GFR in the normal dog whereas Na excretion is very low in the postprandial state. Eosinophil counts were made in an attempt to further the evaluation of adrenocortical function. Water exchange and the response to a water load have also been measured.

Methods

Ascites was produced in trained female mongrel dogs by constriction of the thoracic inferior vena cava to one-third to two-thirds its original diameter. Cardiac output was measured by the direct Fick procedure in unanesthetized dogs in the postabsorptive state. Oxygen consumption was determined with a Blalock dog mask attached to a Tissot spirometer. Expired air was collected for a four-minute period and analyzed in duplicate for the percentage of oxygen and carbon dioxide with a Haldane apparatus. Mixed venous blood was obtained from the right ventricle by passing a polythene catheter through a no. 15 needle via the external jugular vein. Arterial blood samples were obtained by direct puncture of the femoral artery. Blood samples were drawn under oil into heparinized syringes, and oxygen content was determined in duplicate by the manometric method of Van Slyke and Neill. External jugular and femoral venous pressures were measured with a saline manometer; all other pressure measurements were made with a Statham strain gauge and a D'Arsonval galvanometer.

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Total peripheral resistance was calculated from the formula,
\[ T = \frac{P_m \times 980 \times 13.6}{V_t} \]
where \( P_m \) denotes mean arterial pressure in mm Hg and \( V_t \) = cardiac output in cubic centimeters per second.

The dogs were kept in metabolic cages except at the end of each hour when urine and blood samples were obtained; water was allowed ad libitum.

The three-hour renal excretory response to a gastric or intravenous water load was determined in the postabsorptive state. Water (40 cc. per kilogram) was given by stomach tube; gastric drainage was performed 40 minutes after water administration to determine the completeness of absorption. The volume of unabsorbed water was measured and the fluid was replaced immediately. For the intravenous water test 25 cc. per kilogram of water were infused during a 40-minute period.

For the eosinophil counts, a mixture of propylene glycol and phloxine was used in the proportions suggested by Speirs and Meyer. All other experimental procedures and chemical methods have been described elsewhere.
The dogs were fed a synthetic diet containing 50 Cal. per kilogram per day, 0.2 Gm, per kilogram per day of nitrogen, and 4 mEq. per kilogram per day of Na during the control interval and during the experimental period until protein depletion was established. A high protein and a low salt diet was given to effect protein repletion.

Different dogs were used for different aspects of the study. In dogs 1 to 5, postabsorptive measurements of GFR, RPF, plasma Na, and plasma protein were made. GFR and Na excretion were determined in the postprandial state in dogs 4 and 5. Determinations of cardiac output and intracardiac pressures were made in dogs 4 and 5; femoral venous and arterial pressures were measured in dogs 1, 2, 3, 5, and 6. Studies of metabolic balances, plasma K and chloride (Cl), hematocrit, and T-1824 dye space were conducted in dogs 1 to 3. Eosinophils were counted in dogs 2 to 6. Water exchange and the response to a water load were determined in a group of normal dogs as well as in dogs 1 to 10.

Fig. 2. The effect of thoracic inferior vena cava constriction on renal function, protein metabolism, and cardiovascular pressures. Values for Cr, CPAH, FF, and plasma protein are plotted as solid columns above or below a line which represents the average control value. See figure 4 for the convention used in plotting N balance. The stippled areas indicate the variation in systolic and diastolic arterial pressures with respiration. E. J. and V. P. represent external jugular and venous pressure respectively. Ascitic fluid N is not included in the plot of N balance but total N removed by paracentesis is shown above the columns for ascitic fluid.

RESULTS

Cardiovascular Hemodynamics. Following constriction of the thoracic inferior vena cava, femoral venous pressure increased 10 to 15 cm. of water above the control level and ascites developed (figs. 1 and 2). External jugular, right auricular, and right ventricular pressures were not appreciably altered. A reduction in systolic and pulse pressures occurred in two
of the six animals (see fig. 2), but mean femoral arterial pressure remained unchanged or increased slightly. Cardiac output remained at the control level after caval constriction in dog 5 (fig. 1) whereas a marked reduction occurred in dog 6. In this animal, a second operation was performed and the ligature loosened to reduce the degree of constriction. Subsequently, cardiac output and total peripheral resistance returned to the control level, arterial pressure remained unchanged, and of the average control value; FF remained elevated. This fall in renal function occurred concurrently with protein depletion which resulted from removal of large quantities of protein by abdominal paracentesis (figs. 1 and 2).

In order to test the hypothesis that reduced renal function was the result of protein depletion, a low salt and a high protein diet was fed (figs. 1 to 3). On this regimen, protein repletion was rapidly effected; $C_{CR}$ returned.

![Graph](https://via.placeholder.com/150)

**Fig. 3.** Relation of postabsorptive and postprandial GFR to renal Na excretion ($E_{Na}$) before and during ascites formation. Values for postabsorptive $C_{CR}$ are shown as adjacent black columns which are plotted above and below the horizontal line representing the average of nine control periods. Hourly measurements of postprandial $C_{CR}$ are shown by the open areas plotted from the same horizontal line; Na excretion during corresponding periods is plotted as adjacent black columns. The vertical arrows which precede experimental values for $E_{Na}$ and postprandial $C_{CR}$ indicate the time of feeding. After protein repletion, Na intake was increased from 9 to 60 mEq. per day so that plasma Na and, consequently, the filtered load of Na returned to the control level or above.

femoral venous pressure fell. However, venous tension below the constriction remained sufficiently high (10 cm. of water above the control level) for the continued formation of ascites.

**Postabsorptive Renal Clearances.** During the first 7 to 10 days following caval constriction, GFR remained at the control level or increased slightly while RPF fell (figs. 1 to 3); consequently, filtration fraction (FF) was elevated. After the initial phase, GFR fell 20 to 30 per cent below the control level and RPF showed a further decline of 25 to 50 per cent to the control level (dogs 1, 2, and 4) or above (dog 3), and $C_{PAB}$ returned to the level observed before the onset of protein depletion. In dog 5 (fig. 1), protein repletion was not completely accomplished, and renal function failed to reach the control level. The results suggest a causal relationship between protein depletion and reduced renal function.

**Relation of Postprandial GFR to Na Excretion.** In addition to the postabsorptive measurements of renal function, GFR was estimated for 8 to 12 hours after feeding in
dogs 4 (fig. 3) and 5. To establish the preprandial level of renal function, postabsorptive measurements were made within a few days of each group of postprandial determinations. Before caval constriction, GFR increased between 20 and 40 per cent after ingestion of food and remained elevated for several hours in GFR which was similar in magnitude and duration to that observed during the control period; however, postprandial Na excretion was never greater than 5 μEq. per minute. In dog 4, protein depletion was accompanied by a fall in postprandial as well as postabsorptive GFR and subsequent repletion resulted in a rise in GFR both before and after feeding. In dog 5, both postabsorptive and postprandial values for GFR decreased during protein depletion and Na excretion following the meal was as low as in dog 4. As in the case of the postabsorptive measurements, postprandial GFR failed to return to the control level.

Fig. 4. Changes in CCR, metabolic balances, and body weight following constriction of the thoracic inferior vena cava. The convention for the plot of the balance data is as follows: (1) intake was plotted downward from the zero line, (2) output was plotted upward from intake line, (3) solid black areas represent total balance, and (4) cross hatched areas indicate fecal electrolyte excretion. Consequently, solid black area above the zero line indicates negative balance and black area below the zero line represents positive balance. Fecal Na excretion was too low to plot during ascites formation and ascitic fluid electrolytes are not included in plots of balance data.
level in dog 5 because protein repletion was not complete.

Metabolic Balances, Plasma Electrolytes, Water Metabolism, Hemoglobin, Hematocrit, T-1824 Dye Space, and Eosinophil Counts. Na, Cl, and water balances were markedly positive following caval constriction (fig. 4). Since surgical trauma results in alterations in electrolyte and nitrogen (N) balances, changes seen before the appearance of ascites may have been partially related to the effect of the surgical procedure. After ascites appeared, the peritoneal cavity served as the principal depot for retained fluid and electrolytes (fig. 4), and renal tubular reabsorption of Na was almost complete throughout the experimental period.

Although the principal reduction in Na excretion was renal, fecal Na output was also decreased (fig. 4). Control values for fecal Na excretion ranged from 4.5 to 8.5 mEq. per day; during ascites formation fecal Na output was never above 2.0 mEq. per day (dogs 1 to 3). Urinary K excretion was reduced whereas a marked elevation in fecal K output occurred (fig. 4); total K balance was positive. Plasma K was slightly elevated throughout the experimental period. Calculations showed no evidence for movement of Na into the intracellular compartment and K into the extracellular space. Changes in Cl balance occurred at the same time and in the same direction as alterations in Na balance.

Water exchange was increased following caval constriction (fig. 5) although water balance was always positive and isotonicity of body fluids was maintained during normal Na intake. (4 mEq. per kilogram per day) On a low Na diet (.5 mEq. per kilogram per day), plasma Na consistently declined to levels of 130 to 135 mEq. per liter. The three-hour renal excretory response to a gastric

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**URINE OUTPUT**

**RESPONSE TO WATER LOAD (%)**

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**Fig. 5.** Daily urine output and the three-hour renal excretory response to a water load administered by stomach tube in normal dogs and in dogs with ascites. The values for urine output are the average for several weeks. Solid symbols represent values obtained in normal dogs while open circles show results during ascites formation. The broken horizontal lines have been drawn to emphasize the lack of overlapping between open and solid symbols.
water load of 40 cc. per kilogram was impaired (fig. 5). Normal dogs excreted 80 to 95 per cent of administered water but dogs with ascites excreted only 40 to 65 per cent of the water load. Part of this delay in excretion may be related to incomplete absorption since 17 to 37 per cent of the water load was recovered by gastric drainage performed 40 minutes after water administration. However, a defect in excretion was present since only 28 to 62 per cent of the intravenous water load was excreted.

Hemodilution occurred during the early postoperative period; hemoglobin and hematocrit fell while an elevation in T-1824 dye space occurred. Later in the course of the experimental period, protein depletion resulted; hemoglobin and hematocrit continued to decline while T-1824 dye space remained unchanged in dog 1 and increased 15 to 20 per cent in dogs 2 and 3.

Since the low Na and high K pattern of fecal electrolyte excretion suggested an alteration in adrenocortical function, circulating eosinophils were enumerated and N balance was measured. A postoperative drop in eosinophils occurred, but the number of circulating eosinophils returned to the control level and remained within normal range throughout the period of ascites formation. The response to epinephrine and adrenocorticotropic hormone (ACTH) was not detectably altered during the experimental period. N balance was positive in the presence of adequate protein intake and ascites accumulated regardless of the state of protein metabolism (fig. 2).

**DISCUSSION**

Hepatic venous congestion appears to be essential to the formation of ascitic fluid with a high protein concentration. This type of ascites is permanent unless hepatic venous pressure declines. The necessity of a congested liver or splanchnic area for ascites formation is indicated by the finding that partial ligation of the inferior vena cava below the hepatic venous outflow produces hind leg edema but no ascites. These data and personal observations that a transient ascites with a low protein concentration follows constriction of the hepatic portal vein implicate the liver rather than the splanchnic area.

Of vital importance in the pathogenesis of ascites is the retention of salt and water by the kidney. The extracellular fluid volume expands as a result of more complete renal tubular reabsorption of Na and water. The factors effecting this alteration in renal tubular transport of Na have not been defined. A direct effect of elevated venous pressure on the kidney has been ruled out by the results of Volwiler and co-workers and Hwang and associates who failed to obtain chronic fluid retention following constriction of the abdominal inferior vena cava superior to the renal veins. The possible influence of adrenal venous congestion has also been excluded by placing an abdominal caval ligature superior to the adrenal venous tributaries (personal observations).

The observations reported show that the formation of ascites is not related to a drop in cardiac output. Ascitic fluid formed in dog 5 in which cardiac output remained unchanged. In case 6 in which cardiac output was initially reduced, ascites continued to accumulate after the ligature was loosened although cardiac output returned to the control level.

Extensive measurements of GFR demonstrate that a reduction in GFR is not the primary factor leading to salt retention. Values for postabsorptive and postprandial GFR were observed at the control level or above in the presence of almost complete Na retention. It should be emphasized that under the present circumstance of alterations in protein metabolism, measurements of postabsorptive GFR provided a satisfactory index to changes in postprandial GFR.

In an attempt to further the evaluation of adrenocortical activity, circulating eosinophils were counted. While an eosinopenic response is no longer considered definitive evidence of adrenocorticotropic activity, the negative findings failed to indicate increased adrenocortical hormone secretion from stimulation of the adrenal cortex by ACTH. Additional observations are needed to clarify the relation of the adrenal cortex to the pathogenesis of ascites.
SUMMARY AND CONCLUSIONS

1. Following constriction of the thoracic inferior vena cava, femoral venous pressure became elevated and ascites appeared. Cardiac output remained at the control level or decreased but no correlation between the level of cardiac output and salt retention was observed.

2. During the early part of the experimental period, both the postabsorptive and postprandial rate of glomerular filtration remained unchanged or increased whereas RPF decreased. Later, during protein depletion, postabsorptive and postprandial GFR fell below the control levels and RPF showed a further decline. Renal function was restored during protein repletion. These findings suggest a causal relationship between protein depletion and reduced renal function.

3. Marked Na retention occurred while postabsorptive and postprandial GFR was at the control level or above. This evidence demonstrates that a mechanism other than a low GFR was operative.

4. A striking reduction in fecal Na and urinary K excretion occurred; fecal K output was elevated.

5. The number of circulating eosinophils was not detectably altered.

6. Water exchange was increased whereas the renal excretory response to a water load was reduced.

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