# Effect of Renal Arterial Infusion of Albumin on Saline Diuresis in the Dog.* (29219)

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It has been suggested that the protein concentration of peritubular plasma may be an important determinant of sodium and water reabsorption by the renal tubule(1,2,3). The effect of protein on excretion of water and electrolyte has been the subject of several investigations(4,5,6,7). Infusions of hyperoncotic albumin reduce excretion of sodium in normal man(4,5,7). In the dog, infusion of hyperoncotic albumin may not result in increased excretion of sodium(6), whereas the infusion of iso-oncotic "plasma-like" solutions is associated with a natriuresis similar to that resulting from the infusion of equal volumes of saline(8). Since the excretion of sodium must be the difference between total filtered load and *net* tubular reabsorption, changes in filtration rate could mask changes in tubular reabsorption when plasma volume is expanded during the infusion of solutions containing protein. Thus, an increase in filtration rate associated with infusions of protein solutions may result in a natriuresis which could be independent of any effect that plasma protein concentration may have on tubular reabsorption. Despite the demonstration by micropuncture that active reabsorption by the proximal tubule of Necturus is not grossly influenced by the transtubular gradient of oncotic pressure(9), the possibility cannot be excluded that overall net tubular reabsorption by the mammalian kidney is in some way affected by the protein concentration of peritubular plasma. Even though the osmotic gradient for water produced by the protein concentration gradient between tubular lumen and capillary is too small to account for a major fraction of tubular reabsorption(9), changes in protein concentration could conceivably influence net reabsorption indirectly through such mechanisms as a change in interstitial volume or a redistribution of blood within the kidney. The present studies were designed to determine whether increasing the protein concentration of renal arterial blood during the natriuresis of saline loading results in any major change in sodium excretion. It was anticipated that this procedure would permit local changes in plasma protein concentration without systemic effects which might result in an increased filtered load of sodium.

*Material and methods.* Mongrel dogs of either sex, ranging in weight from 14.5 to 16 kg, were studied. Each animal received 10 mg of desoxycorticosterone acetate (DOCA) by intramuscular injection 12-15 hours prior to experiment, and an additional 5 mg 2 hours prior to experiment. Under pentobartital anesthesia, the right ureter was exposed retroperitoneally through a flank incision and cannulated with polyethylene tubing. The left kidney and ureter were exposed retroperitoneally through a subcostal incision. The ureter was similarly cannulated, and a 23-gauge needle connected to plastic tubing was inserted in the direction of flow into the left renal artery. The surgical wounds were closed, and a minimum of 60 minutes was allowed between completion of the surgical procedure and the beginning of collections. Prior to the surgical procedure a constant intravenous infusion of isotonic saline was begun at a rate of 0.75 ml per minute. This infusate contained creatinine and p-aminohippurate in concentrations sufficient to maintain plasma levels of 10-25 and 1-2 mg %, respectively. The renal arterial needle was maintained patent by infusion of isotonic saline at 0.50 ml per minute, and all arterial infusates were maintained at 37°C by a water bath. Blood samples were withdrawn into heparinized syringes from a plastic cannula inserted into the right atrium by way of an external jugular vein, or from a superficial vein of the forelimb. Urine was allowed to flow freely into graduated cylinders.

* Supported in part by grant from U.S.P.H.S.

After collecting a minimum of 3 control periods each animal received an intravenous infusion of 800 ml "saline" (Na 142, K 3.5, Cl 125.5, $HCO_3$ 20 mEq per liter) over a 20-minute period. Thereafter this infusion was maintained at 10 ml per minute. At the same time, the renal arterial infusion of saline was increased to 5.0 ml per minute. When the urine flow from both kidneys had increased and remained relatively stable for at least 2 collection periods, the renal arterial infusion was changed to 25 g % human albumin† (sodium concentration, 142-150 mEq per liter). This arterial infusion of hyperoncotic albumin was continued for 20-40 minutes at a rate of 5.0 ml per minute. During infusion of protein, collection periods were shortened to 5-10 minute intervals to allow a minimum of 4 collections during this phase of the experiment. Afterwards, the renal arterial infusion was changed to saline at 5.0 ml per minute, and collection periods were continued. All infusates, including the albumin, contained creatinine and p-aminohippurate in amounts equal to estimated plasma concentrations. By subsequent analysis it was found that the concentrations of these substances in the infusates differed from those in plasma by no more than 20%.

Total protein in plasma was determined by a biuret method(10). Creatinine was determined by a modification of the method of Folin(11). P-aminohippurate was measured by the method of Smith *et al*(12), and sodium was measured by internal standard flame photometry.

*Results.* During the pre-loading control periods excretion of sodium ranged from 11-84 $\mu$Eq per minute per kidney. After saline loading, excretion of sodium during the period immediately preceding the arterial infusion of albumin ranged from 119-480 $\mu$Eq per minute per kidney. When comparison was made with the lowest value during control periods, glomerular filtration rate during the saline-induced natriuresis was unchanged in 6 kidneys, decreased in 3, and increased in only one. Thus, in a total of 10 observations in the 5 experiments, no relationship existed between the natriuresis of saline loading and a change in glomerular filtration rate. When hyperoncotic albumin was infused into the left renal artery during the maintained saline load, sodium excretion decreased in 4 of the 5 experiments. During the last period of protein infusion, sodium excretion by the experimental kidneys ranged from 44-105% of the rates of sodium excretion observed immediately preceding the protein infusion. Sodium excretion from the non-infused control kidney decreased 34% in one experiment, was essentially unchanged in one experiment and increased in the remaining 3 experiments. In all 5 of the infused kidneys glomerular filtration rate decreased during the protein infusion to values less than those present prior to the saline infusion (range of decrease, 13-31%). A decrease in glomerular filtration rate of 19% was associated with the decreased sodium excretion which occurred in one noninfused control kidney. Serum sodium concentration during the infusion of protein differed from control values by $-3$ to $+5$ mEq per liter. Thus, despite relatively large decreases in the filtered load of sodium and an increased arterial plasma protein concentration, the excretion of sodium induced by the saline infusion was not abolished.

The clearance of p-aminohippurate during the saline infusion ranged from 67-97 ml per minute. If a minimal extraction of p-aminohippurate of 80% is assumed, then the infusion of 1.25 g of albumin per minute would have increased the renal arterial plasma protein concentration to values ranging from 86-96% (average 92%) of the value which preceded the saline infusion.

Following infusion of protein, glomerular filtration rate and sodium excretion by the infused kidney increased to values similar to those observed prior to the arterial infusion of protein. Sodium excretion by the control kidneys increased further following the arterial infusion. At this time systemic plasma protein concentration was increased from an average of 63% to an average of 82% of the control value which preceded the infusion of saline. In 8 of the 10 kidneys glomerular filtration rate was equal to or lower than the

† Normal "salt poor" human albumin supplied by American Red Cross.

TABLE I. Effects of Renal Arterial Albumin Infusion on Saline Diuresis.

| Time, min | Urine vol, ml/min R | Urine vol, ml/min L | GFR,* ml/min R | GFR,* ml/min L | $C_{PAH}$, ml/min R | $C_{PAH}$, ml/min L | Sodium excretion, μEq/min R | Sodium excretion, μEq/min L | Plasma Protein, g % | Plasma Sodium, mEq/l |
|---|---|---|---|---|---|---|---|---|---|---|
| 0-20 | .14 | .22 | 27 | 24 | 80 | 66 | 21 | 37 | 5.7 | 150 |
| 20-40 | .15 | .19 | 30 | 27 | 88 | 82 | 24 | 30 | | |
| 40-60 | .13 | .18 | 27 | 25 | 82 | 70 | 23 | 30 | 5.5 | 148 |
| | 800 ml Ringer solution I.V. 60-80 min; then 10 ml per min Ringer solution left renal artery 5 ml per min | | | | | | | | | |
| 60-100 | .59 | 1.02 | 33 | 24 | 100 | 73 | 101 | 172 | 3.0 | 150 |
| 100-130 | 1.07 | 1.53 | 28 | 23 | 84 | 74 | 195 | 214 | 3.2 | 150 |
| 130-140 | 1.10 | 1.56 | 22 | 21 | 75 | 64 | 178 | 201 | | |
| 140-150 | 1.70 | 2.12 | 29 | 24 | 87 | 77 | 264 | 265 | 3.2 | 147 |
| | 25% albumin 5 ml per min left renal artery 150-187 min | | | | | | | | | |
| 150-160 | 1.55 | 1.28 | 24 | 17 | 70 | 41 | 234 | 156 | 3.6 | 149 |
| 160-170 | 1.26 | 1.36 | 23 | 17 | 60 | 41 | 203 | 193 | 4.3 | 145 |
| 170-180 | 1.22 | 1.25 | 25 | 19 | 69 | 44 | 195 | 154 | 4.9 | 145 |
| 180-187 | 1.08 | 1.07 | 24 | 18 | 64 | 44 | 150 | 117 | | |
| | End albumin infusion 187 min; Ringer 5 ml per min left renal artery | | | | | | | | | |
| 187-195 | 1.21 | 1.12 | 25 | 21 | 70 | 54 | 146 | 104 | 5.1 | 145 |
| 195-205 | 1.50 | 1.50 | 24 | 23 | 71 | 65 | 148 | 145 | | |
| 205-220 | 1.90 | 2.12 | 25 | 23 | 62 | 60 | 180 | 211 | 4.8 | 150 |
| 220-235 | 2.28 | 2.50 | 23 | 22 | 64 | 61 | 241 | 259 | 4.6 | 150 |

* Exogenous creatinine clearance.

values prior to protein infusion. Thus a clear elevation of plasma protein and no rise in glomerular filtration rate (and filtered sodium) was associated with no fall or an increase in sodium excretion.

The results of all 5 experiments are summarized in Fig. 1. Details of a single representative experiment are given in Table I.

*Discussion and summary.* The present studies provide 10 observations on the relationship between glomerular filtration rate and sodium excretion during saline loading in the dog. De Wardener *et al*(13) reported that saline loading may increase sodium excretion without increasing filtration rate. In the present study, a clear increase in filtration rate during the natriuresis of saline loading was observed in only 2 of 10 kidneys. Other authors have recently reported that controlled reductions of filtration rate (and the filtered load of sodium) do not abolish the natriuresis of saline loading(14,15). Thus, contrary to previous suggestions, it now appears clear that, in the dog, increases in sodium excretion without increases in amount of sodium filtered may be produced by saline loading. The necessary conclusion, therefore, is that saline loading results in a decrease in *net reabsorption* of the total filtered load of sodium. In addition, this apparent decrease in tubular reabsorption takes place in the presence of exogenous mineralocorticoid(13, 14), making it unlikely that a suppression of endogenous aldosterone is responsible for the decreased reabsorption.

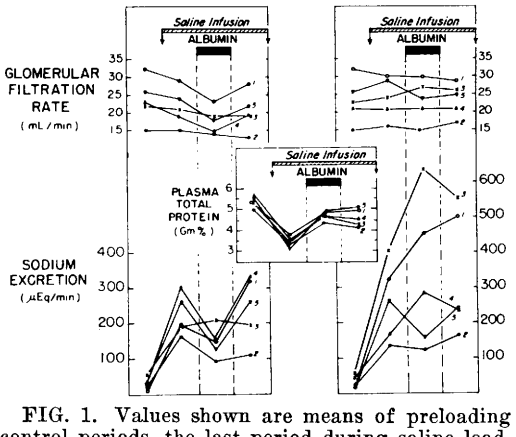


FIG. 1. Values shown are means of preloading control periods, the last period during saline loading prior to renal arterial infusion of albumin, the last period during infusion of albumin, and last collection period of each study.

These results demonstrate that restoring the protein concentration of renal arterial blood approximately to control values also

does not abolish the natriuresis induced by saline loading. Sodium excretion continued above control levels despite a local increase in protein concentration and a decrease in the filtered load of sodium. The decreases in filtered sodium which occurred during the protein infusion exceeded the associated decreases in excreted sodium, so that *net tubular reabsorption* was even further reduced during the protein infusion. Thus, it appears unlikely that the apparent decrease in tubular reabsorption of sodium observed in these studies resulted from the dilution of plasma protein associated with the saline infusion. This conclusion is in agreement with that of Levinsky and Lalone, who found that the natriuresis resulting from infusions of "plasma" continued in the presence of a hemodynamically induced decrease in filtration rate (14). The present studies do not exclude the possibility that once induced, the natriuresis of extracellular volume expansion may continue despite normal plasma oncotic pressure and a decreased filtered load of sodium, even though these factors may be of importance in initiating the natriuresis.

The observation that renal arterial infusions of hyperoncotic albumin uniformly reduced glomerular filtration rate is consistent with the premise that the oncotic pressure of glomerular capillary blood may be a significant factor determining rate of filtration. Increasing the concentration of impermeant solute would increase resistance to filtration, and if other factors (hydrostatic pressure, permeability) were unchanged, filtration rate should decrease. However, the possibility cannot be excluded that the presence of alien protein or unrecognized constituents of the albumin solution produced a fall in glomerular filtration rate by some non-specific mechanism.

The author is grateful to Miss Deborah Lufkin for her assistance with these studies.

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Received January 31, 1964. P.S.E.B.M., 1964, v116.

## Slow Elimination of Urethan in Relation to its High Carcinogenicity in Newborn Mice.* (29220)

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It now seems well established that newborn mice are more sensitive to urethan carcinogenesis than adults. This has been most strikingly demonstrated for leukemogenesis, which is very pronounced when urethan is given soon after birth(1,2,3), but weak or absent when adults are treated, unless very

* This work was supported in part by research grants from Nat. Cancer Inst., U.S.P.H.S. The authors thank Miss R. Plager for technical assistance.