Effect of Increased Peritubule Protein Concentration on Proximal Tubule Reabsorption in the Presence and Absence of Extracellular Volume Expansion

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ABSTRACT The effect of increased peritubule capillary oncotic pressure on sodium reabsorption by the proximal tubule of the dog was investigated after extracellular volume expansion (ECVE) with Ringer's solution or during continued hydropenia. Control measurements were made after ECVE or during hydropenia and again during renal arterial infusion with hyperoncotic albumin solution. Absolute reabsorption by the proximal tubule was calculated from fractional reabsorption and single nephron filtration rates as determined by micropuncture. Direct measurements of efferent arteriole protein were used to determine efferent arteriolar oncotic pressure. Albumin infused into the renal artery after ECVE significantly increased efferent oncotic pressure by 17.6±5.3 mm Hg. Fractional and absolute reabsorption by the proximal tubule increased from 20±6 to 37±5% and from 22±6 to 36±7 nl/min, respectively. During hydropenia, the albumin infusion significantly increased efferent oncotic pressure by 15.0 ±4.4 mm Hg. However, in contrast to the effect seen during ECVE, neither fractional nor absolute reabsorption was changed, $\Delta = 0.3 \pm 1.5\%$ and 3±5 nl/min, respectively. Single nephron filtration rates were not significantly different between the groups and were unchanged by the albumin infusion. Peritubule capillary hydrostatic pressures, measured with a null-servo device, were not changed by the albumin infusion in either group. Renal interstitial hydrostatic pressure, measured from chronically implanted polyethylene capsules, was decreased significantly from 7.2±0.9 to 3.4 ±0.6 mm Hg in the hydropenic group and from 9.6±0.6 to 4.8±0.7 mm Hg in the Ringer's expanded group. In the hydropenic group, the increase in efferent oncotic pressure was nearly compensated for by changes in interstitial forces so that the calculated net force for capillary uptake was almost unchanged, 17.8 mm Hg before vs. 21.4 mm Hg during the albumin infusion. The increased efferent oncotic pressure in the Ringer's expanded group was not compensated, so that the calculated net force for uptake was increased, 11.9 mm Hg before to 22.2 mm Hg during the albumin infusion. Thus, while the increase in efferent oncotic pressure during albumin infusion was not significantly different between the groups, absolute and fractional reabsorptions were increased only in the animals in which the extracellular volume was expanded. The results suggest that ECVE alters the effect of increased peritubule oncotic pressure on sodium reabsorption by the proximal tubule.

INTRODUCTION

Several studies indicate that changes in peritubule capillary oncotic pressure are accompanied by changes in sodium reabsorption by the proximal tubule (1–7). For instance, Brenner, Troy, and Daugharty (1) found that capillary microperfusion with hyperoncotic albumin solution increased reabsorption by the proximal tubule in saline-loaded rats, and similarly Knox, Schneider, Willis, Strandhoy, and Ott (2) found that intrarenal infusion of hyperoncotic albumin solution increased proximal sodium reabsorption in saline-loaded dogs. It has been proposed that these changes in peri-

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tubule capillary oncotic pressure influence proximal reabsorption by altering the rate of uptake by peritubule capillaries (6) or by altering interstitial pressures which in turn influence proximal reabsorption (7). Several investigators, however, have failed to find a relationship between peritubule capillary oncotic pressure and reabsorption by the proximal tubule. Capillary microperfusion studies by Conger, Bartoli, and Earley (8) in rats indicate no effect of varying protein concentration on proximal reabsorption. Using similar techniques, Rumrich and Ullrich (9) found no difference in proximal sodium reabsorption between isoncotic perfusate and perfusate containing no protein. Similarly, Györy and Kinne (10), also using microperfusion, found metabolic inhibitors to be 10 times as potent in reducing proximal reabsorption as reductions in peritubular capillary protein concentration to zero.

Since many of the previous studies showing marked effects of oncotic pressure on reabsorption were performed on volume-expanded animals, the present study was undertaken to determine if prior volume expansion was necessary for increased peritubular capillary oncotic pressure to increase reabsorption by the proximal tubule. Clearance and micropuncture techniques were used to evaluate the effect of increased peritubule capillary oncotic pressure in previously volume-expanded dogs and in dogs during continuous hydropenia.

METHODS

Measurements of fractional and absolute reabsorption by superficial proximal tubules, protein concentration in plasma from superficial efferent arterioles, hydrostatic pressures in peritubule capillaries, and renal interstitial hydrostatic pressure were obtained from four groups of six dogs in each of two experimental protocols. In protocol one, measurements were made after extracellular volume expansion with Ringer's solution and again during a renal artery infusion of 25% albumin solution. In protocol two, the measurements were made during hydropenia and repeated during renal arterial infusion of the albumin.

Mongrel dogs of either sex were anesthetized with 30 mg/kg sodium pentobarbital and prepared for micropuncture as previously described (11). A 20-gauge curved needle was inserted against the flow of blood into the left renal artery for infusion of albumin solution. In protocol one, modified Ringer's solution[1] was infused at 1 ml/min per kg of body weight for 20 min and then infused at 0.5 ml/min per kg of body weight for 40 min. At this time the urine flow rate and the rate of infusion were matched and the control measurements taken. Albumin[2] solution containing inulin, magnesium, and ionized calcium, in approximately the same concentration as systemic plasma, was then infused into the left renal artery at 0.45 ml/min per kg, during which the measurements were repeated. This infusion rate of approximately 7.5 ml/min is far in excess of the rate found necessary by Brand and Cohen (12) to ensure adequate mixing with blood and even distribution of isotopes within the kidney. The albumin infusion was limited to 15 min to minimize plasma volume expansion. In protocol two, control measurements were taken during continued hydropenia and repeated during the albumin infusion.

Collections and recollections of tubule fluid were obtained from late proximal segments of superficial proximal tubules for determination of fractional and absolute sodium reabsorption. Pipettes used for the collection were sharpened to an internal diameter of 10 μm. Tubule fluid samples were collected at a rate sufficient to collect all the volume flow at the puncture site, as previously described (11). The volume of the tubule fluid sample was measured with a micropipette calibrated with a radioactive tracer. The concentration of inulin in tubule fluid was determined in duplicate by the microfluorometric method (13). The nephron filtration rate (V_o)[3] was calculated from the expression $V_o = V_e \times (TF/P)_{In}$, where V_e is the volume collected per minute and $(TF/P)_{In}$ is the ratio of inulin concentration in tubular fluid to that in plasma. Proximal tubule absolute reabsorption (V_r) was calculated from the expression $V_r = V_o - V_e$.

Efferent arterioles selected for micropuncture were identified as the main branches of the vascular star. Blood collection pipettes were sharpened to an internal diameter of 15 μm and siliconized. Great care was exercised to avoid contamination of the samples from efferent arterioles with tubule fluid. The criteria used to prevent this contamination have been published in detail (14). Protein concentration in efferent arteriolar blood plasma was determined, usually in duplicate, with an ultramicrocolorimeter (15). The total protein concentration in systemic and renal vein plasma was determined by the biuret method. In a previous study, a comparison of identical samples measured simultaneously with the macro and micro methods for the protein analysis employed in this study indicated no significant difference in measured protein concentration (14). Oncotic pressure was calculated from the empiric relationship between plasma protein concentration and oncotic pressure, as previously detailed (14). Since albumin was the protein infused, the increases in efferent arteriole protein concentrations were considered to be due to increases in albumin concentration alone. Therefore, the increase in oncotic pressure during the albumin infusion was calculated from the relationship between albumin concentration and oncotic pressure. Single nephron filtration fractions were calculated from protein concentration in efferent plasma and protein concentration in simultaneously obtained renal venous plasma. Average single nephron plasma flow (snpf) was determined from these average single nephron filtration fractions (snff) and the average single nephron glomerular filtration

[1] Sodium 138 meq/liter, potassium 3.7 meq/liter, chloride 123 meq/liter, bicarbonate 25 mmol/liter, phosphate 6 mg/100 ml, calcium 6 mg/100 ml, magnesium 2.2 mg/100 ml, dextrose 100 mg/100 ml, bubbled with 6% CO_2-94% O_2 gas mixture.

[2] Salt-poor hyperoncotic human albumin, Parke, Davis and Co., Detroit, Mich.

[3] *Abbreviations used in this paper:* ECVE, extracellular volume expansion; GFR, glomerular filtration rate; Hct, hematocrit; RBF, renal blood flow; RPF, renal plasma flow; sngfr, average single nephron glomerular filtration rate; snff, average single nephron filtration rate; snpf, average single nephron plasma flow; TF/P_{In}, ratio of inulin concentration in tubular fluid to that in plasma; V_e, volume corrected per minute; V_o, nephron filtration rate; V_r, proximal tubule absolute reabsorption average.

TABLE I

Effect of Intrarenal Albumin Infusion on the Superficial Nephron

	Ringer's-expanded dogs				Hydropenic dogs			
	Control	Albumin	Δ	*P*	Control	Albumin	Δ	*P*
Single nephron plasma flow,* *nl/min*	491	542	51		480	486	6	
Single nephron GFR, *nl/min*	108	105	3	NS	96	107	10	NS
	6	9	7		10	4	9	
Single nephron filtration fraction	0.22	0.19	0.02	NS	0.20	0.22	0.02	NS
	0.03	0.05	0.05		0.04	0.05	0.05	
Afferent oncotic pressure,‡ *mm Hg*	16.6	26.5	9.9	<0.001	21.6	30.2	9.1	<0.001
	0.8	1.4	1.1		1.3	1.7	1.0	
Efferent oncotic pressure	24.0	41.6	17.5	<0.025	30.2	45.0	15.0	<0.025
	1.6	5.6	5.3		2.2	4.5	4.4	
Capillary hydrostatic pressure, *mm Hg*	15.7	15.0	0.8	NS	10.8	10.7	0.1	NS
	2.1	1.2	1.1		0.9	1.0	0.3	
Interstitial hydrostatic pressure, *mm Hg*	9.6	4.8	4.8	<0.005	7.2	3.4	3.8	<0.005
	0.6	0.7	0.7		0.9	0.6	0.6	
Absolute reabsorption, *nl/min*	22	36	14	<0.005	42	45	3	NS
	7	7	2		4	2	5	
Fractional reabsorption, %	20	37	18	<0.001	42	42	0.3	NS
	6	5	2		5	4	1.5	

All values presented as mean ±SE, six animals in each group.

* Calculated from mean single nephron GFR from one group and mean single nephron filtration fraction from another group.

‡ Calculated from renal vein protein concentration.

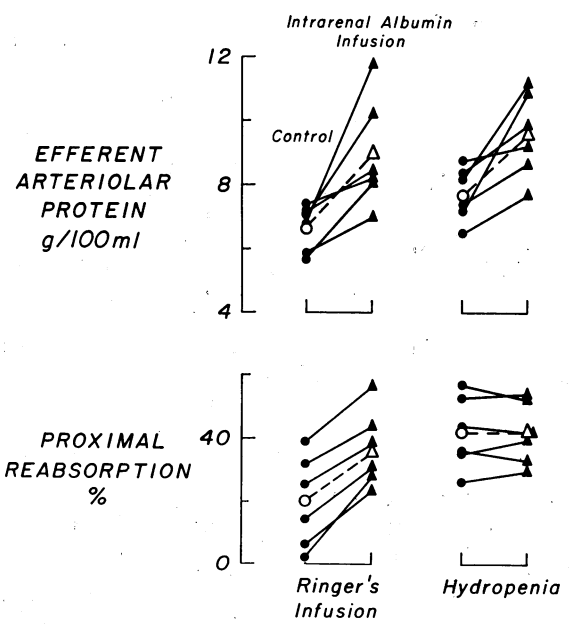

FIGURE 1 Effect of intrarenal albumin infusion on proximal reabsorption in extracellular volume-expanded dogs (left column) and hydropenic dogs (right column).

rate (GFR) (sñgfr) in the groups in which tubule fluid samples were obtained as: sñpf = sñgfr/sñff.

Hydrostatic pressures in 5–8 μm peritubule capillaries were measured by a servo-null device as previously described for use in the dog (16). The identical protocols were used except that the kidney was bathed with isotonic Ringer's solution instead of mineral oil to complete the circuit for recording base-line pressures.

Measurements of renal interstitial hydrostatic pressure were obtained from capsules chronically implanted in the kidney as previously described (17). In brief, the 3 × 5-mm capsules are made of polyethylene matrix material with pores about 60 μm in diameter. Tissue does not grow into the polyethylene and because they are a matrix, they create a permanent fluid-filled space in communication with the interstitium. Measurements were made approximately 4 wk after implantation.

Renal blood flow (RBF) was measured in 26 animals which had sufficient renal artery to allow placement of the renal artery infusion needle and an electromagnetic flow probe. Renal plasma flow (RPF) was calculated from RBF and hematocrit (Hct) as: RPF = RBF × (1 − Hct).

Blood samples were collected at the midpoint of 15-min urine collections. Inulin concentrations in plasma and urine were determined by the anthrone method (18) for determination of GFR. Plasma and urine sodium concentration was determined by flame photometry, while phosphorus was determined by the method of Young (19).

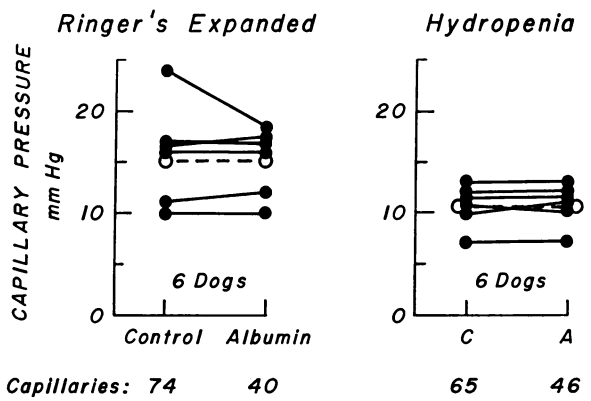

FIGURE 2 Effect of intrarenal albumin infusion on peritubule capillary hydrostatic pressures in extracellular volume-expanded dogs (left) and hydropenic dogs (right).

At the conclusion of the experiment, 5% lissamine green dye was infused into the renal artery at the same rate used for the albumin infusion. Experiments which showed uneven distribution of green dye to the micropunctured area of the kidney were discarded.

Statistical analysis was performed with the Student *t* test for paired data within groups and for unpaired data between groups. Statistical significance was considered to be $P < 0.05$.

RESULTS

The effect of intrarenal albumin infusion on single nephron function is summarized in Table I. Individual efferent arteriolar protein concentration and fractional reabsorption by the proximal tubule before and during albumin infusion into the renal artery of Ringer's-expanded and hydropenic dogs are shown in Fig. 1. In six Ringer's-expanded dogs, infusion of albumin solution significantly increased efferent arteriolar protein concentration from 6.7±0.3 to 9.0±0.7 mg/100 ml, and calculated efferent arteriolar oncotic pressure significantly increased from 24.0±1.6 to 41.6±5.6 mm Hg. Fractional and absolute reabsorption by the proximal tubule significantly increased from 20±6 to 37±5%, and from 22±7 to 36±7 nl/min, respectively. Single nephron filtration rates were not significantly changed, averaging 108±6 and 105±9 nl/min, respectively. Sñgfr were also unchanged and averaged 0.22±0.03 before and 0.19±0.05 during the infusions.

Intrarenal infusion of albumin during continued hydropenia in six dogs significantly increased efferent arteriolar protein concentration from 7.7±0.3 to 9.7± 0.6 mg/100 ml, and calculated efferent arteriolar oncotic pressure significantly increased from 30.2±2.2 to 45.0±4.5 mm Hg. The increases in efferent arteriolar oncotic pressure were not significantly different between volume-expanded and hydropenic dogs. However, in contrast to the effect seen in the volume-expanded animals, there was no significant change in fractional reabsorption by the proximal tubule with values of 42±5% during hydropenia and 42±4% during albumin infusion. Absolute reabsorption by the proximal tubule was also unchanged, 42±4 nl/min and 45±2 nl/min, respectively. Single nephron filtration rate was unchanged, 96±10 nl/min and 107±4 nl/min, respectively. Similarly, single nephron filtration fraction was also unchanged at 0.20±0.04 before and 0.22 ±0.05 during the infusion.

Peritubule capillary hydrostatic pressures measured in six additional animals in each protocol were unchanged (Fig. 2). In Ringer's-loaded dogs, capillary pressures were 15.7±2.1 mm Hg and 15.0±1.2 mm Hg before and during albumin infusion, respectively. In hydropenic dogs, hydrostatic pressures in peritubule capillaries were 10.8±0.9 before and 10.7±1.0 mm Hg during albumin infusion.

The effect of intrarenal albumin infusion on renal interstitial hydrostatic pressure in the two groups is shown in Fig. 3. In the Ringer's-expanded group, renal interstitial hydrostatic pressure was significantly decreased from 9.6±0.6 mm Hg to 4.8±0.7 mm Hg by the albumin infusion, while in the hydropenic group interstitial hydrostatic pressure was significantly decreased from 7.3±0.9 mm Hg to 3.8±0.6 mm Hg.

The effect of intrarenal albumin infusion on whole kidney function is summarized in Table II. Albumin infusion significantly increased RPF in both groups, $\Delta = 37\pm8$ ml/min in the volume-expanded group and $\Delta = 43\pm6$ ml/min in the hydropenic group. GFR was significantly decreased, $\Delta = 7.0\pm2.1$ ml/min in the Ringer's-expanded group, and a similar tendency was seen in the hydropenic group, $\Delta = -3.2\pm1.8$ ml/min. Filtration fraction was significantly decreased in both groups. Albumin infusion decreased filtration fraction 0.10±0.01 in the Ringer's-expanded group and 0.06 ±0.01 in the hydropenic group.

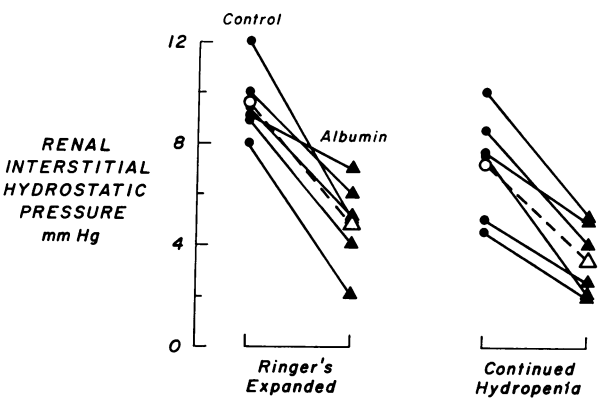

FIGURE 3 Effect of intrarenal albumin infusion on renal interstitial hydrostatic pressure in extracellular volume-expanded dogs (left) and hydropenic dogs (right).

TABLE II

Effect of Intrarenal Albumin Infusion on Whole Kidney Function

	Ringer's-expanded dogs				Hydropenic dogs			
	Control	Albumin	Δ	*P*	Control	Albumin	Δ	*P*
Renal plasma flow, *ml/min*	120	157	37	<0.001	129	172	43	<0.001
	15	20	8	*n* = 12	10	14	6	*n* = 14
Glomerular filtration rate, *ml/min*	27.4	20.4	7.0	<0.005	30.1	27.0	3.2	NS
	3.0	1.5	2.1	*n* = 23	2.1	2.5	1.8	*n* = 22
Filtration fraction	0.22	0.12	0.10	<0.001	0.23	0.16	0.06	<0.005
	0.02	0.02	0.01	*n* = 22	0.01	0.02	0.01	*n* = 22
Renal vein protein, *mg/100 ml*	5.1	6.7	1.6	<0.001	6.3	7.5	1.5	<0.001
	0.1	0.2	0.1	*n* = 24	0.2	0.3	0.2	*n* = 23
Urinary Na excretion, *μeq/min*	115.9	61.8	51.3	<0.005	28.6	22.7	5.9	<0.025
	22.4	11.6	13.6	*n* = 24	6.3	5.6	2.4	*n* = 23
Fractional Na excretion, %	2.8	1.9	0.9	<0.001	0.79	0.67	0.12	<0.05
	0.4	0.3	0.2	*n* = 23	0.19	0.18	0.05	*n* = 22
Fractional phosphate excretion, %	26.4	21.0	5.8	<0.001	17.0	14.8	2.3	NS
	2.4	2.2	1.2	*n* = 23	2.3	2.2	1.2	*n* = 22

All values expressed as mean ±SE. *n*, number of animals in each group.

Albumin infusion increased renal vein protein concentration the same amount in both groups, Δ = 1.6 ±0.1 mg/100 ml in Ringer's vs. 1.5±0.2 mg/100 ml in the hydropenic group. The albumin infusion significantly decreased both absolute and fractional sodium excretions in both groups. However, the decreases were much larger absolutely and relatively in the Ringer's-expanded group. Sodium excretion decreased an average of 51.3±13.6 μeq/min in the Ringer's-expanded animals, compared to a decrease of 5.9±2.4 μeq/min in the hydropenic animals ($P < 0.005$). This represents a decrease in sodium excretion of 44% in Ringer's-expanded dogs compared to 21% in hydropenic dogs. Similarly, fractional sodium excretion was decreased by 0.9±0.2% in Ringer's-expanded dogs compared to 0.12±0.05% in hydropenia ($P < 0.005$). This represents a decrease of 32% in Ringer's-expanded compared to a 15% decrease in the hydropenic group. Fractional phosphate excretion was significantly decreased 3.8±1.2% in the Ringer's-expanded group but unchanged in the hydropenic group.

DISCUSSION

The results show that both absolute and fractional reabsorptions were significantly increased after albumin infusion in the volume-expanded dogs, but were unchanged after albumin infusion in the hydropenic dogs, and therefore indicate that prior volume expansion alters the effect of increased efferent arteriole protein concentration on sodium reabsorption by the proximal tubule. The finding that extracellular volume expansion alters the renal response to changes in intrarenal pressures has also been reported by Wathen and Selkurt (20).

The present findings in hydropenic dogs are consistent with several other studies in the literature. Employing split-drop technique and capillary microperfusion, Rumrich and Ullrich (9) found no effect of peritubule oncotic pressure on reabsorption by the proximal tubule in the rat, while Györy and Kinne (10) found metabolic inhibitors to be much more effective than peritubule protein concentration. Conger et al. (8), using recollection micropuncture and capillary microperfusion with rat plasma, were unable to increase reabsorption by the proximal tubule even though the protein in the perfusate was increased to 13 g/100 ml.

Spitzer and Windhager (4) and Brenner et al. (1), using capillary microperfusion, have found a correlation between peritubule capillary oncotic pressure and reabsorption by the proximal tubule. In the studies of Brenner et al., the peritubular protein concentration was initially lowered by expansion with saline. Our studies and theirs show that after extracellular volume expansion, increased peritubule capillary oncotic pressure results in increased reabsorption by the proximal tubule. In the studies of Spitzer and Windhager, dextran, not protein, was used in the perfusate and a direct assessment of the volume state of the animal cannot be

TABLE III

Effect of Intrarenal Albumin Infusion on Intrarenal Starling Forces and the Net Force for Capillary Uptake in Ringer's-Expanded Dogs and Hydropenic Dogs

	C_u	$\bar{\pi}_c$	P_c	π_i	P_i	K_r	Net
	nl/min	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*nl/min/mm Hg*	*mm Hg*
Ringer's expanded	22	23.3	15.7	5.3	9.6	1.93	11.9
Albumin	36	39.9	15.0	7.5*	4.8	1.93	22.2
Hydropenia	42	28.5	10.8	7.1	7.2	2.46	17.8
Albumin	45	42.4	10.7	13.7*	3.4	2.46	21.4

Cu is the capillary uptake (nl/min), $\bar{\pi}c$ is the integrated average peritubule oncotic pressure (mm Hg), Pc is the average peritubule capillary hydrostatic pressure (mm Hg), πi is the interstitial oncotic pressure (mm Hg), Pi is the interstitial hydrostatic pressure (mm Hg), Kr is the reabsorption coefficient (nl/min/mm Hg), and Net is the net force for capillary uptake calculated as: $(\bar{\pi}_c + P_i) - (\pi_i + P_c)$.

* Calculated value which gave solution to equations in Appendix.

made. However, it was reported that surgical losses were replaced with 1–2 ml infusion of saline in less than 10 min. A study very similar to ours in the dog has also been conducted by Brenner, Falchuk, Keimowitz, and Berliner (15) in the rat. Albumin was infused at high rates for short periods of time into the aorta. Efferent arteriolar protein concentration was determined in one group of animals while tubule fluid collections were made in another group of animals. A correlation was obtained between the increase in efferent arteriolar protein and reabsorption by the proximal tubule. It should be noted, however, that of the 10 control tubules measured in these animals, 8 of them came from previously infused rats, and Ringer's solution was usually the solution infused.

Since the efferent oncotic pressure was increased the same in both groups, but proximal reabsorption was increased only in the Ringer's-expanded group, an estimate of the net force for peritubule capillary uptake was calculated. Although interstitial proteins were not obtained in this study, we have measured lymphatic protein concentrations in hydropenia and after the same volume expansion as used in this study (21). Interstitial oncotic pressure was found to equal 5.3±0.6 mm Hg in hydropenia and 7.1±0.5 mm Hg after volume expansion. These values and the other three forces which determine capillary uptake were subjected to a quantitative analysis with the equations developed by Deen, Robertson, and Brenner (22), which also incorporate peritubule capillary plasma flow. Since all forces which determine capillary uptake were known from control measurements, a net force for capillary uptake and a reabsorption coefficient was obtained for both the Ringer's-expanded and hydropenic groups. For analysis during the albumin infusion, the only unknown variable was the interstitial oncotic pressure. This allowed calculation of a unique value for interstitial oncotic pressure and the net force for capillary uptake. The results are summarized in Table III and the detailed analysis is presented in full in the Appendix. In the previously volume-expanded group, the net force for capillary uptake increased from 11.9 mm Hg to 22.2 mm Hg. In the hydropenic group the net force for reabsorption increased by less than 4 mm Hg, from 17.8 mm Hg to 21.4 mm Hg.

While there was no significant effect of albumin infusion on proximal reabsorption in the hydropenic animals, there was a significant decrease in absolute and fractional sodium excretion in both Ringer's-expanded and hydropenic groups. However, the fractional phosphate excretion was decreased only in the Ringer's-expanded group. Several studies have found a good correlation between proximal sodium reabsorption and fractional phosphate excretion. Although Amiel, Kuntziger, and Richet (23) have evidence for some distal reabsorption of phosphate in the parathyroidectomized animal, Puschett, Agus, Senesky, and Goldberg (24) and Schneider, Strandhoy, Willis, and Knox (25) have shown by micropuncture that changes in superficial proximal reabsorption are correlated with corresponding changes in fractional phosphate excretion under a variety of experimental circumstances. Since parathyroid hormone was one of the factors found to affect both proximal reabsorption and fraction phosphate excretion, changes in parathyroid hormone levels were minimized in this study by including Ca^{++} and Mg^{++} in the Ringer's solution and in the hyperoncotic albumin solution. The clearance data in the Ringer's-expanded group is consistent with an increase in proximal reabsorption of both sodium and phosphate during the albumin infusion and hence a decrease in both sodium and phosphate excretion. The result in the hy-

dropenic animals is less clear-cut. There was a small but not significant decrease in fractional phosphate excretion which might suggest a small increase in proximal reabsorption. Indeed, although not significant, there was a small increase in absolute reabsorption by the proximal tubule of 3 nl/min. The finding of a decreased sodium excretion with no significant change in fractional phosphate excretion might also suggest that deeper nephrons are responding to albumin differently from the superficial nephrons, or that sodium reabsorption is increased by the albumin at some distal portion of the nephron. The present clearance data are consistent with any or all of the above possibilities. However, the micropuncture results clearly show that an increase in peritubule capillary oncotic pressure resulted in a large increase in proximal reabsorption in the previously volume-expanded animals, but the same increase in peritubule capillary oncotic pressure had little effect in hydropenic animals.

The mechanism whereby increased peritubule capillary oncotic pressure significantly increased proximal reabsorption during volume expansion but not during hydropenia is speculative. However, during extracellular volume expansion in the *Necturus,* Boulpaep (26) and Bentzel (27) found passive sodium conductance and backflux of sodium into the proximal tubular lumen increased threefold. Imai and Kokko (28) demonstrated that hyperoncotic serum increased both sodium and volume flux from lumen to bath in isolated proximal tubules. Our results are consistent with a model in which extracellular volume expansion increases passive sodium conductance and backflux into the proximal tubule. Increases in peritubule capillary oncotic pressure might decrease this backflux and thus increase net sodium reabsorption by the proximal tubule. During hydropenia, when both passive sodium conductance and backflux are relatively less, an increase in peritubule oncotic pressure might have little effect on proximal reabsorption.

In addition to the effect on the peritubule microcirculation, albumin infusion also affected whole kidney and superficial nephron hemodynamics. Albumin infusion decreased or tended to decrease whole kidney filtration rate, but single nephron filtration rate was not significantly changed in either group. Blantz, Rector, and Seldin (29) have shown, by direct measurement of superficial glomerular pressures, that an infusion of hyperoncotic albumin resulted in an increase in glomerular capillary permeability, thereby offsetting the increased glomerular capillary oncotic pressure. Changes in both efferent and afferent arteriole resistances have been demonstrated as determinants of single nephron filtration rate (30). Thus afferent dilatation and efferent constriction may have increased glomerular capillary pressure sufficient to offset the increased glomerular capillary oncotic pressure and hence autoregulated both sniff and single nephron plasma flow. Whatever the mechanism, the data are consistent with other studies which indicate a strong tendency for superficial nephrons to autoregulate single nephron filtration rate under a variety of conditions (14, 17, 31). The finding that whole kidney filtration fraction was decreased while single nephron filtration fraction was unchanged during a large increase in RPF is in close agreement with a previous study by Stein, et al. (31). When RPF was increased by direct intrarenal infusion of bradykinin, single nephron filtration fraction and single nephron GFR were unchanged while whole kidney filtration fraction significantly decreased.

In conclusion, it has been found that prior volume expansion alters the response of the proximal tubule to increased efferent arteriolar protein concentration. After extracellular volume expansion, increased efferent arteriolar protein concentration increased sodium reabsorption by the proximal tubule, while in the hydropenic animal, increased efferent arteriolar protein concentration had no significant effect on proximal sodium reabsorption.

APPENDIX

Quantitative analysis for the relationship between peritubule capillary uptake and intrarenal Starling forces

Deen and associates (22) have developed equations which relate peritubule capillary uptake and peritubule capillary plasma protein concentration to peritubule capillary plasma flow and distance along an idealized peritubule capillary.

$$\frac{dc^*}{dx^*} = (Hc^{*2})\cdot[A - B(x^* - 0.5) - (D_1c^* + D_2c^{*2})] \quad (1)$$

$$Cu = (Qea)\cdot\left(\frac{1}{c^*(L)} - 1\right) \quad (2)$$

In eq. 1, c* is the peritubule plasma protein concentration (C) relative to efferent arteriolar protein concentration (Cea) : ($c^* = C/C_{ea}$). At capillary distance = O, c* = 1.0, x* is the distance along the capillary relative to total distance–at total capillary length L, x* = 1.0.

In eq. 2, capillary uptake (C_u) over the entire length is calculated as a function of efferent arteriolar plasma flow (Q_{ea}) and the relative protein concentration at the end of the capillary c* (L).

Relative protein concentration as a function of capillary distance can be computed by integration of eq. 1. The integrated average relative protein concentration ($\bar{C}^*$) along the capillary can be computed as:

$$\frac{\int_0^{x^*} c^* dx^*}{\int_0^{x^*} dx^*}.$$

The integrated average absolute protein concentration ($\bar{C}$) can be calculated from $\bar{C}^*$ and efferent arteriolar protein concentration (C_{ea}) as: $\bar{C} = C_{ea} \cdot \bar{C}^*$. The integrated average peritubule capillary oncotic pressure ($\bar{\pi}_c$) can be calculated from the relationship between plasma protein concentration and oncotic pressure (14).

While any number of solutions may be determined for any number of theoretical parameters in the equation, a unique solution for a specific physiological condition can be determined when all the parameters have been experimentally measured. Parameters which must be determined are: H, A, B, D_1, and D_2, H, $(K_r \cdot \pi_{ea})/Q_{ea}$, A, $(P_c + \pi_i - P_i)/\pi_{ea}$, B, $\Delta P_c/\pi_{ea}$, D_1, $(1.629 \cdot C_{ea})/\pi_{ea}$, D_2, $(0.2935 \cdot C^2_{ea})/\pi_{ea}$.

The physiological values necessary to determine these parameters are: K_r, reabsorption coefficient (nl/min/mm Hg), π_{ea}, oncotic pressure at efferent arteriole (mm Hg), Q_{ea}, postglomerular plasma flow (nl/min), P_c, average capillary hydrostatic pressure (mm Hg), π_i, interstitial hydrostatic pressure (mm Hg), P_i, interstitial hydrostatic pressure (mm Hg), ΔP_c, pressure drop from beginning to end of capillary (set at 2 mm Hg), C_{ea}, efferent arteriole plasma protein concentration (g/100 ml).

C_{ea}, P_i, P_c, and π_i were determined experimentally. π_{ea} was calculated from C_{ea} as $\pi_{ea} = 2.1\ C_{ea} + 0.19\ C^2_{ea} + 0.009\ C^3_{ea}$. Q_{ea} was determined from single nephron filtration fraction (snff) and single nephron glomerular filtration rate (sngfr). Snff was calculated from renal vein protein concentration (Cv) and efferent arteriole protein concentration (Cea): $\text{snff} = (1 - C_v/C_{ea})$ and $Q_{ea} = \text{sngfr} \cdot (1/\text{snff} - 1)$.

In steady-state conditions, capillary uptake must equal tubule reabsorption. A unique K_r was determined for each group by trial solutions with various values of K_r until capillary uptake was equal to tubule reabsorption in control conditions. Once K_r had been uniquely determined, the net force for capillary uptake could be determined during the albumin infusion. Since interstitial oncotic pressure (π_i) was not determined during albumin infusion in either the hydropenic or Ringer's-expanded groups, capillary permeability was held constant and a unique π_i was determined by trial solutions with various values of π_i until calculated capillary uptake was equal to measured proximal reabsorption.

The determination of a unique π_i during albumin infusion assumes steady-state conditions. It is possible that this was not achieved during the short albumin infusion. However, identical time protocols were followed in each group. Thus, even if complete equilibrium was not achieved, it should have been relatively the same in both groups.

The net force for capillary uptake was determined as: $\text{net force} = \text{forces in} - \text{forces out} = (\bar{\pi}_c + P_i) - (\pi_i + P_c)$. The results of the computer analysis are summarized in Table III. The computer analysis calculated the net force for peritubule capillary uptake to be 17.8 mm Hg during hydropenia and 21.4 mm Hg during the albumin infusion. The net force for capillary uptake was calculated to increase from 11.9 mm Hg in Ringer's-expanded group to 22.2 mm Hg during albumin infusion.

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