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Research Article

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Demonstration of a Role of Physical Factors as Determinants of the Natriuretic Response to Volume Expansion *

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Abstract. The importance of plasma protein concentration, renal vascular resistance, and arterial pressure as mediators of the natriuretic response to volume expansion was investigated in anesthetized dogs.

Saline loading depressed plasma protein concentration and increased arterial pressure but did not decrease renal vascular resistance. Restoring plasma protein concentration by infusing hyperoncotic albumin increased sodium reabsorption and decreased sodium excretion during saline loading despite simultaneous decreases in renal vascular resistance and increases in arterial pressure.

Infusion of "plasma" did not depress plasma protein concentration and produced natriuresis associated with increased arterial pressure and marked decreases in renal vascular resistance. Unilateral hemodynamic natriuresis was produced before "plasma" loading by the renal arterial infusion of acetylcholine, and the subsequent infusion of "plasma" resulted in much smaller increases in sodium excretion by the vasodilated kidney than by the control kidney. If perfusion pressure to both kidneys was then reduced by aortic constriction sodium excretion by the vasodilated kidney could be reduced to preloading (vasodilated) levels without reduced glomerular filtration, despite continued natriuresis in control kidneys which underwent vasodilatation in response to the infusion of plasma.

Infusion of equilibrated whole blood did not alter plasma protein concentration or the hematocrit, and renal vascular resistance did not decrease. Sodium excretion was increased minimally or not at all by the infusion of blood despite increased arterial pressure and glomerular filtration. However, in kidneys vasodilated before infusing blood sodium excretion increased in response to the infusion in association with increased arterial pressure. This increased excretion of sodium by vasodilated kidneys during infusion of blood could be abolished by reducing perfusion pressure to the preloading level.

These observations indicate that changes in plasma oncotic pressure, renal vascular resistance, and arterial pressure either alone or in combination are important variables determining the natriuretic response to volume expansion, and that the relative importance of each of these factors depends on the manner in which volume is expanded (viz., the infusion of saline, plasma, or blood).

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Introduction

A series of studies from this laboratory has demonstrated that over-all tubular reabsorption and excretion of sodium can be influenced by intrarenal physical factors (1–4). Thus, (*a*) renal vasodilatation alone may result in diminished reabsorption and increased excretion of sodium (2), (*b*) the reabsorption of sodium relates inversely and the excretion of sodium relates directly to renal perfusion pressure if the pressure changes are transmitted along the intrarenal circulation (1, 3, 4), and (*c*) apparent proximal tubular reabsorption of sodium during saline infusion increases in response to increases in plasma oncotic pressure (4). We suggested that changes in the renal interstitial volume and/or pressure could be the common pathway through which these physical factors affect sodium reabsorption and excretion (3, 4). Since causal roles for these physical factors as determinants of the natriuretic response to volume expansion have not beeen demonstrated, it was the purpose of the present studies to examine the extent to which natriuresis during volume expansion is dependent upon changes in renal vascular resistance, perfusion pressure, and plasma oncotic pressure, either alone or in combination.

The present experiments in the dog were designed to control or alter one or more of these physical variables (renal vascular resistance, perfusion pressure, plasma oncotic pressure) during volume expansion in order to assess the importance of these factors in the natriuretic response to volume expansion. Evidence for a role of reduced plasma oncotic pressure as a mediator of natriuresis during saline infusion was afforded by demonstrating reduced sodium excretion and increased sodium reabsorption when plasma protein concentration was restored to presaline loading values by infusion of hyperoncotic albumin. Infusion of an isooncotic Ringer's solution ("plasma") did not lower plasma protein concentration but resulted in natriuresis associated with profound reductions in renal vascular resistance and usually increases in arterial pressure. The importance of this reduced renal vascular resistance as a determinent of the natriuretic response to "plasma" infusion was assessed by vasodilatating one kidney before infusing the plasma load, and thereby minimizing the vascular effect of the infusion. During loading with plasma the additional increase in excretion of sodium by vasodilated kidneys was always less than the increase by control kidneys. When increases in arterial pressure produced by the infusion of plasma were abolished by constricting the aorta above both kidneys sodium excretion by vasodilated kidneys could be returned to the preloading (vasodilated) rates despite no reduction in glomerular filtration and a continued natriuretic response to the load by control kidneys, which underwent vasodilatation in response to the infusion of "plasma." These observations indicate that reduced renal vascular resistance and increased arterial pressure may be important determinants of the extent to which sodium excretion increases in response to infusion of "plasma."

The infusion of equilibrated whole blood permitted selective expansion of the vascular volume with no compositional changes in blood. This loading procedure usually resulted in increased rather than decreased renal vascular resistance, and despite increases in arterial pressure sodium excretion was changed only minimally by the infusion of blood. However, if one kidney was vasodilated before infusing blood, sodium excretion by the vasodilated kidney increased in association with increased arterial pressure during the loading procedure, which demonstrated the interdependency of vascular resistance and perfusion pressure as natriuretic factors.

Taken together these observations demonstrate that changes in plasma protein concentration, renal vascular resistance, and arterial pressure may be important determinants of the natriuretic response to volume expansion, and the relative importance of each of these factors appears to relate to the effects of the solution (viz., saline, plasma, or blood) to alter these physical variables.

Methods

Studies were carried out in 38 mongrel dogs of either sex, ranging in weight from 12 to 32 kg. The animals were not given water for 12 hr before experiments, anesthetized with pentobarbital, and ventilated through an endotracheal tube connected to a Harvard respirator.[1] Through flank incisions each ureter was cannulated with polyethylene tubing, and each renal vein was cannulated with plastic tubing inserted in the direction of the kidney. A 23 gauge needle connected to plastic tubing was

[1] Harvard Apparatus Company, Dover, Mass.

inserted in the direction of flow into one renal artery (usually the left), and a Blalock clamp was placed around the aorta either between the renal arteries or above both renal arteries and secured in place by attachment to the body wall. Plastic catheters were inserted into a femoral vein and artery for recording vena caval and aortic pressures below the level of the Blalock clamp, and for withdrawal of aortic blood samples. In nine experiments in which the clamp was placed between the renal arteries a plastic catheter was inserted into the thoracic aorta through a carotid artery for recording aortic pressure above the level of the clamp. Patency of the intravascular catheters was maintained by slow infusions of isotonic saline (totaling approximately 2 ml/min).

3–4 hr before experiments each animal received an intramuscular injection of 10 mg of deoxycorticosterone acetate and 5 U of vasopressin in oil. 2 hr before experiments, a maintenance infusion (isotonic saline) was begun intravenously at 0.3–0.4 ml/min which delivered inulin and *p*-aminohippurate (PAH) at rates permitting clearance measurements, and deoxycorticosterone and vasopressin at 20–25 μg/min and 40–50 mU/kg per hr, respectively. Clearance periods varied from 5 to 30 min depending on the rates of urine flow. During 5-min collections arterial and renal venous blood samples were withdrawn at the midpoint of alternate periods, and at the midpoint of each period during longer collections. Experimental collections were begun 1–2 hr after completing the surgical procedures, and after a minimum of three control collection periods experiments were continued according to one of the following protocols.

Saline loading and infusion of hyperoncotic albumin. In 17 experiments, after control collections, the animals received an intravenous infusion of an isotonic Ringer's solution ("saline"; Na, 145; Cl, 129.5; K, 4.5; and HCO_3, 20 mEq/liter) at 30 ml/min. After 600 ml was infused the rate was slowed to 8–10 ml/min, and approximately 30 min later additional collections were taken. In seven of these experiments after multiple collections had been taken during a stable rate of urine flow, a solution of 30 g /100 ml of bovine albumin in isotonic saline was infused at 5 ml/min and continued until a total of 75 g of albumin was infused, during which time collections were continued. During the infusion of albumin the rate of infusion of saline was decreased by 3 ml/min. After infusing the 30 g/100 ml albumin solution, we continued the infusion of saline at 10 ml/min in five experiments, and in two experiments replaced the infusion of saline by an infusion of 5 g/100 ml albumin in saline at 10 ml/min. In six of these experiments the aorta was constricted above the left renal artery before and/or after the infusion of albumin in order to provide observations at similar levels of arterial pressure and glomerular filtration. In order to minimize the effects on sodium excretion that could result from the profound reduction in renal vascular resistance resulting from the infusion of the concentrated solution of albumin, in two of these studies we vasodilated the left kidney by an arterial infusion of 40 μg/min of acetylcholine before the saline infusion, and continued the vasodilatation throughout the remainder of the experiments.

Renal vasodilatation and "plasma" loading. In all experiments, after control collections, the left kidney was vasodilated by changing the renal arterial infusion of saline (1 ml/min) to saline with acetylcholine (40 μg/min) in order to minimize the vascular effects of the subsequent infusion of "plasma." 10 min later additional multiple collections were taken after which an intravenous infusion of 4.5 or 5 g/100 ml of bovine albumin in isotonic Ringer's solution ("plasma") was begun at 30 ml/min. After the infusion of 400 or 600 ml of "plasma" the infusion was slowed to 8–10 ml/min. Approximately 30 min later additional collections were taken. In seven of these experiments the aorta was then constricted above both kidneys to reduce arterial pressure towards the preloading values. After further collections the aortic constriction was released, and collections were continued.

Renal vasodilatation and blood loading. In addition to the surgical procedures described above, in 10 experiments cannulae were placed in a femoral artery and vein to permit external circulation of blood through a lucite reservoir by means of a 360° dual channel roller pump.[2] The reservoir and entire external circuit were primed with 600–800 ml of heparinized blood withdrawn immediately before from donor dogs into plastic bags. The two channels of the pump had been previously calibrated to maintain a constant level in the reservoir with a rate of circulation ranging from 45 to 70 ml/min. When the system had been filled with blood, inputs and outputs of the reservoir were connected to the femoral artery and vein, respectively, and the pump was started. When the external circulation had been running from 30–40 min control collections were begun. In eight of these experiments the protocol described above for unilateral renal vasodilatation was followed. Up to the loading procedure any positive or negative balance of blood was prevented by maintaining a constant level of blood in the reservoir. After collections during unilateral renal vasodilatation blood was infused into the experimental animal at 30 ml/min by increasing the output from the reservoir. After infusing 300 or 400 ml of blood we slowed the positive balance to 5 ml/min. Approximately 30 min later collections were again taken, after which perfusion pressure to the left kidney was reduced to the preloading values by constriction of the aorta between the renal arteries. Additional collections were taken, and then the aortic constriction was released. Finally the renal arterial infusion of acetylcholine was discontinued. In two experiments the same procedures were followed except that unilateral renal vasodilatation was not produced, and the effects of infusion of blood alone were observed.

Inulin, PAH, osmolality, sodium, potassium, total protein, and hematocrits were determined by techniques previously described for this laboratory (2, 4). Arterial and venous pressures were recorded by Sanborn pressure transducers and recorder (Sanborn Co., Cambridge, Mass.) Extraction ratios (each kidney) for PAH were

[2] American Optical Company, Southbridge, Mass.

calculated as $E = (A - R)/A$, where A is arterial and R renal venous concentrations of PAH. Renal plasma flow (RPF) was calculated as C_{PAH}/E_{PAH} or by the formula of Wolf (5): $RPF = V(U - R)/(A - R)$, where in addition, V is the rate of urine flow and U is the urinary concentration of PAH. Renal blood flow (RBF) = RPF/(1 − 0.95 hematocrit). Renal vascular resistance is calculated in peripheral resistance units (PRU) as (AP − VP)/RBF where AP is arterial and VP venous (vena caval) pressure.

Results

Comparison of the effects of infusion of saline, "plasma," and blood on renal hemodynamics and sodium excretion in the absence of manipulations of renal vascular resistance and perfusion pressure. The effects of infusions of saline, "plasma," and blood on renal hemodynamics and sodium excretion in the absence of renal vasodilatation or aortic constriction are summarized in Fig. 1. In the 30 kidneys of 15 animals the infusion of saline (600 ml followed by 10 ml/min) resulted in an average rate of sodium excretion of 556 μEq/min per kidney compared to preinfusion rates which averaged 94 μEq/min per kidney. Glomerular filtration rate (GFR) increased an average of 3 ml/min per kidney. Renal blood flow was not increased and averaged 218 ml/min per kidney before the infusion of saline and 224 ml/min per kidney after the infusion. Arterial pressure increased from an average of 135 to an average of 151 mm Hg (Fig. 1). Filtration fractions (GFR/RBF) were unchanged by the infusion of saline (Fig. 2). This lack of effect of small infusions of saline to increase renal blood flow is in contrast to the striking increases in blood flow and larger natriuretic responses produced by larger and more rapid infusion of saline (1).

In 13 kidneys of 11 animals the infusion of "plasma" resulted in an average rate of sodium excretion of 451 μEq/min per kidney compared to an average preinfusion rate of 152 μEq/min per kidney. Glomerular filtration rate increased an average of 5 ml/min. These changes are similar to those occurring during the infusion of saline. However, in striking contrast to the lack of effect of the infusion of saline to increase renal blood flow, the infusion of "plasma" resulted in an average renal blood flow of 421 ml/min per kidney compared to an average preinfusion rate of 228 ml/min per kidney. Arterial pressure increased

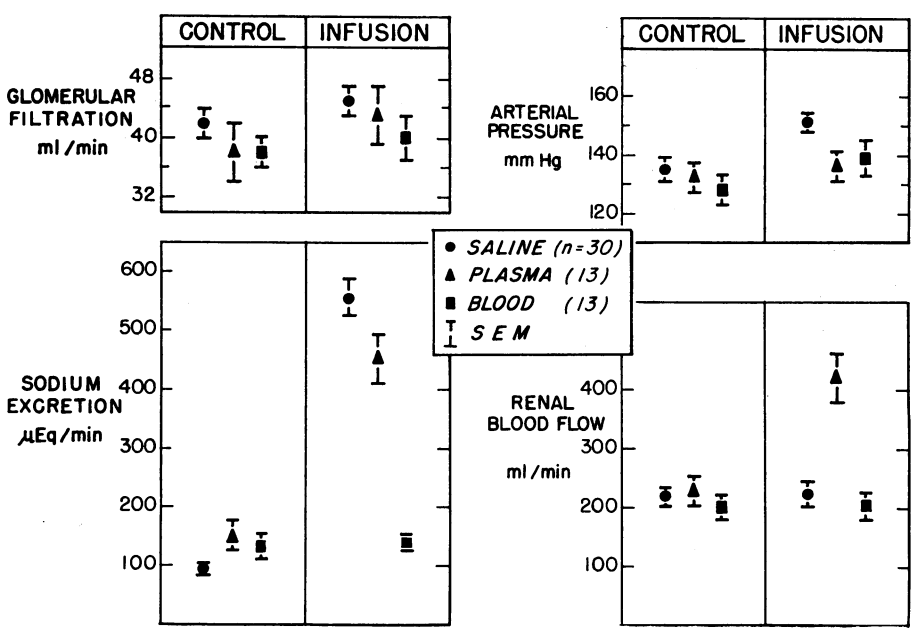

FIG. 1. COMPARISON OF HEMODYNAMIC AND NATRIURETIC EFFECTS OF VOLUME EXPANSION WITH SALINE, "PLASMA," AND BLOOD. Points are the means and SEM of multiple consecutive collections from individual kidneys before and after the loading procedure (see Methods). In the experiments involving infusions of "plasma" or blood, the data represent the control (nonvasodilated) kidneys in the absence of manipulation of aortic pressure.

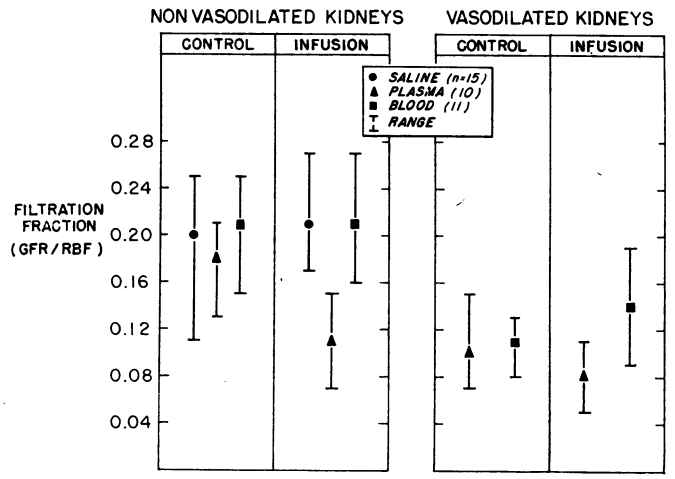

FIG. 2. EFFECTS OF INFUSIONS OF SALINE, "PLASMA," AND BLOOD ON THE FRACTION OF TOTAL RENAL BLOOD FLOW (*RBF*) FILTERED. Points are the over-all means and range of the means of multiple consecutive collections from individual kidneys. Only "plasma" infusion reduced filtration fraction, and vasodilatation alone resulted in filtration fractions similar to those produced by infusion of "plasma." In vasodilated kidneys the infusion of "plasma" produced little further change in filtration fractions, whereas filtration fraction usually increased during infusion of blood. GFR, glomerular filtration rate.

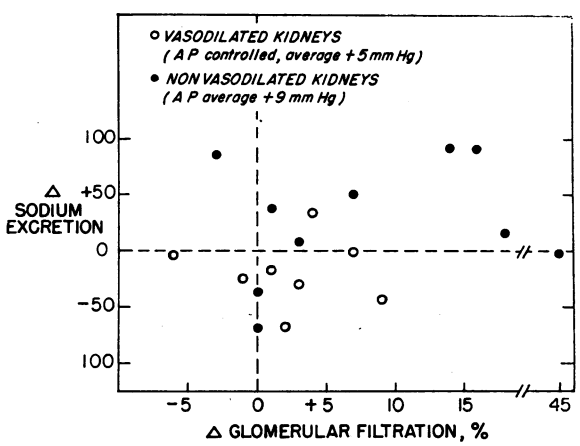

FIG. 3. THE EFFECTS OF INFUSION OF EQUILIBRATED WHOLE BLOOD ON SODIUM EXCRETION AND GLOMERULAR FILTRATION BY CONTROL KIDNEYS AND VASODILATED KIDNEYS WITH CONTROLLED PERFUSION PRESSURE. The infusion of 400–800 ml of equilibrated whole blood had minimal effects to increase sodium excretion by control kidneys (solid points) despite increases in glomerular filtration and increases in arterial pressure (*AP*). When left renal perfusion pressure was reduced by aortic constriction sodium excretion by vasodilated kidneys (open points) was returned to rates no greater than those present during vasodilatation before the loading procedure despite no reduction in glomerular filtration in six of the eight studies. Points represent changes in the mean of multiple consecutive collections before and after loading.

from an average of 132 to an average of 136 mm Hg (Fig. 1). Also in contrast to the effects of saline infusion, the infusion of plasma uniformly depressed the filtration fraction (Fig. 2).

In 13 kidneys of 7 animals the infusion of equilibrated whole blood had very limited effects to increase the excretion of sodium (Figs. 1 and 3), and over-all, the change in sodium excretion averaged + 6 μEq/min. Glomerular filtration rate increased an average of 2 ml/min, and arterial pressure increased from an average of 128 to an average of 139 mm Hg. In contrast to the effects of "plasma" to increase renal blood flow and reduce renal vascular resistance, the infusion of blood was accompanied usually by increased renal vascular resistance and unchanged renal blood flow (Figs. 1 and 4). Also, filtration fractions did not decrease during the infusion of blood (Fig. 2).

Effect of increasing plasma protein on saline diuresis. In seven experiments after collections had been taken during the stable diuretic phase of saline infusion, bovine albumin 30 g/100 ml was infused at 5 ml/min in order to observe the effects on sodium excretion of restoring the plasma protein concentration to presaline loading levels. Urine flow usually began to decrease during the

first 5 min of this infusion of concentrated albumin and continued to fall throughout the infusion. A representative experiment is detailed in Table I. The effects of the infusion of albumin during saline loading on sodium excretion and glomerular filtration for all of these experiments are summarized in Fig. 5. In each of these studies the infusion of concentrated albumin was associated with an increase in over-all tubular reabsorption of sodium. During the infusion of the albumin solution renal blood flow, and usually arterial pressure, increased (Fig. 6), and in association with a progressive fall in renal vascular resistance after infusing the albumin solution sodium excretion often began to increase despite unchanged glomerular filtration (Table I, 169–189 min).

In order to minimize the possible competitive effects on sodium excretion of decreased renal vascular resistance and increased plasma protein, in two experiments we vasodilated the left kidney, before the loading procedures (Table I). In these studies the infusion of saline resulted in natriuresis by the vasodilated kidneys which was 61 and 59% greater than the control kidneys, whereas glomeru-

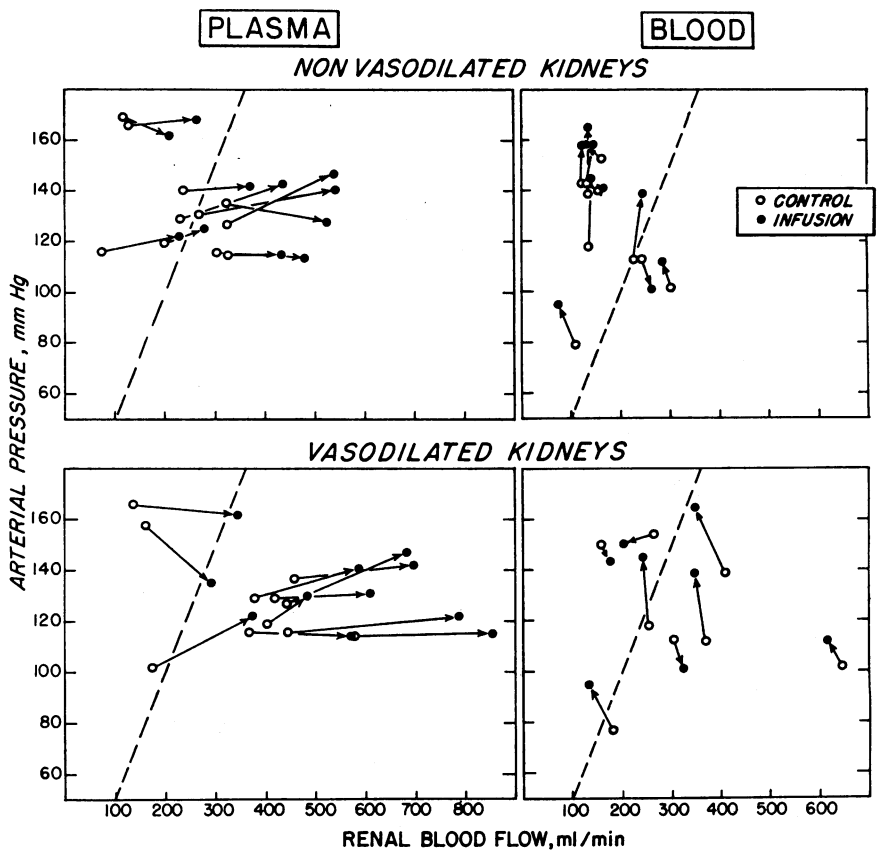

FIG. 4. EFFECT OF VOLUME EXPANSION WITH BLOOD AND "PLASMA" ON RENAL BLOOD FLOW, ARTERIAL PRESSURE, AND RENAL VASCULAR RESISTANCE, IN THE PRESENCE AND ABSENCE OF INDUCED RENAL VASODILATATION. Points are the means of multiple consecutive collections before (open points) and after (solid points) the loading procedure. The broken diagonal line represents a renal vascular resistance of 0.50 peripheral resistance units (PRU). Individual slopes less than that of the diagonal indicate decreasing vascular resistance, and slopes greater than that of the diagonal indicate increasing vascular resistance. The infusion of "plasma" resulted in increases in blood flow in both control and vasodilated kidneys, usually increases in arterial pressure, and marked reductions in renal vascular resistance. In contrast infusions of blood usually resulted in unchanged or decreased blood flow, increased arterial pressure, and increases in vascular resistance.

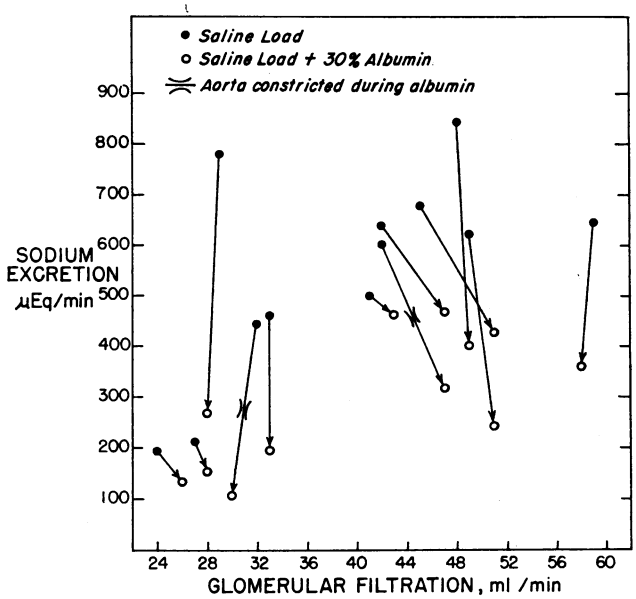

FIG. 5. THE EFFECTS OF INFUSING CONCENTRATED ALBUMIN ON SODIUM EXCRETION AND GLOMERULAR FILTRATION DURING SALINE LOADING. Solid points are the means of multiple collections from individual kidneys during the stable diuretic phase of saline loading. Open points are the means of usually the final collection periods during the infusion of 30 g/100 ml bovine albumin. In every experiment sodium excretion was decreased during the infusion of concentrated albumin despite unchanged or increased glomerular filtration. In two of these experiments the aorta was constricted above the left kidney in order to minimize the effect of the albumin infusion to increase renal perfusion pressure.

lar filtration differed by only 1 and 3 ml/min, respectively. The infusion of the concentrated albumin solution resulted in increased reabsorption and decreased excretion of sodium by both the vasodilated and control kidneys (Table I, 120–159 min). After completing the infusion of albumin, we reduced perfusion pressure to both kidneys by constricting the aorta. This reduction of perfusion pressure depressed sodium excretion to rates equal to or less than those present during vasodilatation alone, despite essentially the same glomerular filtration rate (Table I, left kidney, compare 45–60 min and 194–219 min). However, the control nonvasodilated kidney which underwent a reduction in vascular resistance during and after the infusion of albumin continued to display an increased excretion of sodium (compared to preloading rates) despite the reduced perfusion pressure (Table I, right kidney, compare 0–60 min and 194–219 min). As renal vascular resistance progressively decreased after the infusion of concentrated albumin increasing reductions in perfusion pressure were neecssary in order to maintain decreases in sodium excretion (Table I, both kidneys, compare 120–159 min and subsequent stages of aortic constriction).

The effects of the saline infusion and subsequent infusion of 30 g/100 ml albumin on plasma total protein concentrations in all of these experiments are summarized in Fig. 7.

Renal vasodilatation and plasma loading. In order to minimize the effect on sodium excretion of plasma-induced renal vasodilatation, we produced unilateral renal vasodilatation by the renal arterial infusion of acetylcholine before the loading procedure in 11 experiments. During vasodilatation ipsilateral sodium excretion increased an average of 231 μEq/min per kidney, glomerular filtration increased an average of 3 ml/min per kidney, and renal blood flow increased an average of 150

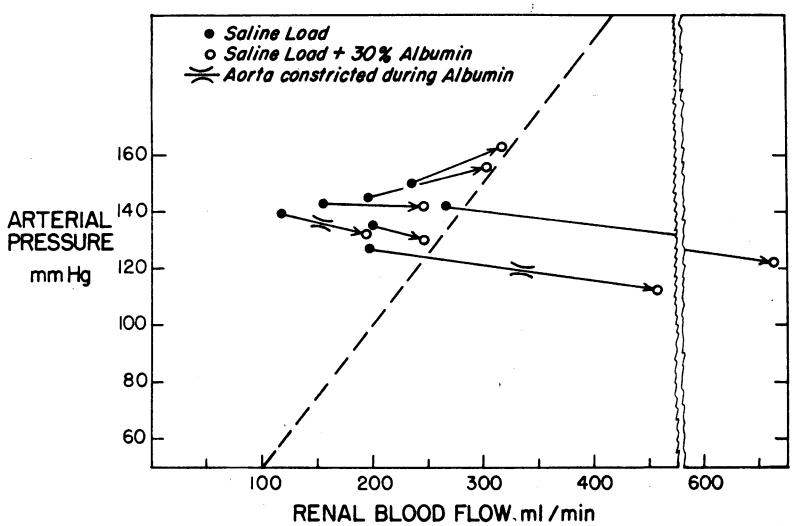

FIG. 6. THE EFFECTS OF INFUSING CONCENTRATED ALBUMIN ON RENAL BLOOD FLOW, ARTERIAL PRESSURE, AND RENAL VASCULAR RESISTANCE DURING SALINE LOADING. These points represent the same collection periods shown in Fig. 5 for the seven kidneys in which renal blood flow was measured. The broken diagonal line represents a vascular resistance of 0.50 PRU. In each experiment the infusion of 30 g/100 ml albumin resulted in increased renal blood flow and marked decreases in renal vascular resistance. Nevertheless, tubular sodium reabsorption increased during the albumin infusion (Fig. 5).

ml/min per kidney. Vasodilatation depressed filtration fractions to values similar to those resulting from the infusion of plasma alone (Fig. 2). Hemodynamics and sodium excretion in control kidneys were usually unaffected during the periods of unilateral vasodilatation. The infusion of plasma resulted in further increases in sodium excretion by the vasodilated kidneys which averaged 199 μEq/min per kidney in association with average increases in glomerular filtration and renal blood flow of 5 and 209 ml/min, respectively. However, in each experiment sodium excretion during the infusion of "plasma" increased less in the vasodilated kidney than in the control kidney, despite similar increases in glomerular filtration in some experiments (Fig. 8). This additional increment in sodium excretion by vasodilated kidneys during plasma infusion was associated with further decreases in renal vascular resistance, increases in glomerular filtration, and increases in renal blood flow and arterial pressure (Table II, Fig. 4). In eight of these experiments the aorta was constricted to reduce renal perfusion pressure after completing the loading procedure. This resulted in a return of sodium excretion by vasodilated kidneys to rates equal to or, in some experiments, less than those present during vasodilatation alone before the infusion of plasma despite no reduction of glomerular filtration (Table II, left kidney, compare 35–60 min and 150–165 min; Fig. 8). The control kidneys exposed to the

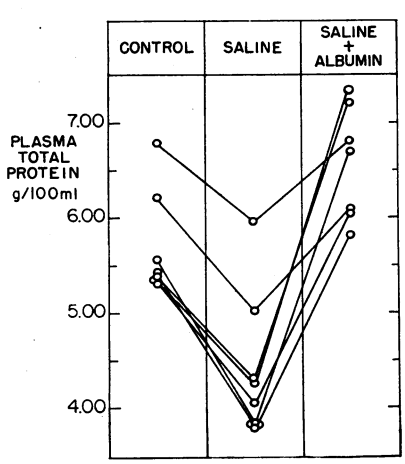

FIG. 7. CHANGES IN PLASMA TOTAL PROTEIN DURING SALINE INFUSION AND SUBSEQUENT INFUSION OF CONCENTRATED ALBUMIN. Values are the means of all control collections for each experiment and the means of the same collection periods shown in Figs. 5 and 6.

same reduction in perfusion pressure continued to display natriuresis in response to the infusion, in association with increased glomerular filtration and renal blood flow, and marked reductions in renal vascular resistance (Table II, right kidney, compare 0–60 min and 150–165 min; Figs. 4 and 8).

Renal vasodilatation and blood loading. As described above the infusion of equilibrated whole blood had minimal effects to increase the excretion of sodium by nonvasodilated kidneys despite some increase in glomerular filtration (Figs. 1 and 3; Table III, right kidney), and increases in arterial pressure (Fig. 4). This lack of natriuresis during the infusion of blood was associated with little or no increase in renal blood flow, unchanged or increased renal vascular resistance (Fig. 4; Table III, right kidney), and unchanged filtration fractions (Fig. 2). In eight of the experiments employing infusion of blood unilateral renal vasodilatation was produced as described above, and was associated with increases in sodium excretion averaging 271 μEq/min and increases in glomerular filtration and renal blood flow averaging 4 and 180 ml/min, respectively. In contrast to the lack of effect of the infusion of blood to increase sodium excretion by nonvasodilated kidneys, sodium excretion by vasodilated kidneys increased an average of 149 μEq/min during the infusion. This natri-

TABLE I

Effects of hyperoncotic albumin on renal hemodynamics and sodium excretion during saline loading in the presence and absence of renal vasodilatation

Time	V		GFR		E_{PAH}		RBF		RVR		$U_{Na}V$		Plasma		Hct	Arterial pressure
	R	L	R	L	R	L	R	L	R	L	R	L	TP	Na		
min	*ml/min*		*ml/min*				*ml/min*		*mm Hg/ ml per min*		*μEq/min*		*g/ 100 ml*	*mEq/ liter*		*mm Hg*
0–12	0.29	0.42	27	26	0.86	0.93	162	146	0.88	0.98	86	115	5.32	153	39	143
12–21	0.36	0.56	26	26	0.82	0.94	153	136	0.92	1.03	106	147	5.32	153	38	140
21–29	0.45	0.69	27	27	0.89	0.94	137	143	1.00	0.96	131	178	5.32	153	37	137
29–36	0.59	0.77	25	29	0.89	0.94	139	145	0.97	0.93	140	189	5.32	153	38	135
36	Begin infusion of acetylcholine at 40 μg/min into left renal artery.															
45–50	0.36*	2.10	21	27	0.90	0.82	148	302	0.82	0.41	103	384	5.32	152	39	124
50–55		2.18		28				327		0.35		401				115
55–60	0.25*	2.18	26	29	0.84	0.81	162	314	0.75	0.36	80	408	5.32	152	39	113
60–80	Infuse Ringer's solution intravenously at 30 ml/min, then continue at 9 ml/min.															
105–110	4.98	8.76	29	33	0.89	0.72	179	339	0.82	0.43	777	1261	4.16	151	32	146
110–115	5.00	8.64	29	32			149	325	0.96	0.44	790	1253				143
115–120	4.84	8.44	29	32	0.89	0.73	138	322	1.01	0.43	765	1207	4.34	151	34	139
120	Begin infusion of 30 g/100 ml bovine albumin intravenously at 5 ml/min, decrease rate of Ringer's solution to 6 ml/min.															
120–125	3.96	7.38	28	31			151	313	0.85	0.41	649	1085				129
125–135	2.81	5.66	32	31	0.86	0.72	209	344	0.63	0.38	520	854	5.75	151	34	136
135–143	1.20	4.00	28	32	0.82	0.59	215	440	0.65	0.32	260	636	6.73	152	30	140
143–148	1.16	3.90	29	28			246	454	0.57	0.30	258	620				140
148–153	1.28	3.88	29	30	0.80	0.57	251	490	0.58	0.30	276	617	7.56	165	28	145
153–159	1.45	3.71	28	28	0.78	0.50	269	546	0.53	0.26	299	590	7.84	153	27	143
159	End infusion of 30 g/100 ml albumin, discontinue infusion of Ringer's solution, and begin infusion of 5 g/100 ml bovine albumin in saline at 6 ml/min.															
160–169	Adjust constriction of aorta above both renal arteries.															
169–174	1.85	3.50	35	28	0.78	0.49	337	567	0.36	0.21	350	560	7.56	153	26	120
174–179	2.28	3.80	31	29	0.77	0.48	291	611	0.42	0.20	420	597	7.44	155	26	123
179–184	2.60	4.02	29	29			268	589	0.47	0.21	460	623				125
184–189	2.84	4.10	33	30	0.75	0.47	312	587	0.41	0.22	500	640	7.36	153	25	127
189	Increase constriction of aorta above both renal arteries.															
194–199	0.70	1.36	30	27	0.80	0.54	268	501	0.37	0.20	164	272	7.27	155	24	100
199–204	1.20	1.93	31	28			253	499	0.40	0.20	282	359				101
204–209	1.14	1.60	28	28	0.81	0.53	215	464	0.47	0.21	236	294	7.02	154	23	100
209–214	1.26	1.70	27	26			229	495	0.42	0.20	249	315				97
214–219	1.38	1.78	27	27	0.80	0.52	241	517	0.41	0.19	265	328	6.73	154	23	98

Abbreviations are as follows: V, rate of urine flow; GFR, glomerular filtration rate (clearance of inulin); E_{PAH}, extraction ratio for *p*-aminohippurate; RBF, renal blood flow (see Methods); RVR, renal vascular resistance (see Methods); $U_{Na}V$, rate of excretion of sodium; TP, total protein concentration; Hct, hematocrit; R, right; L, left.

* Consecutive collection periods covering the total time of collections from the left kidney.

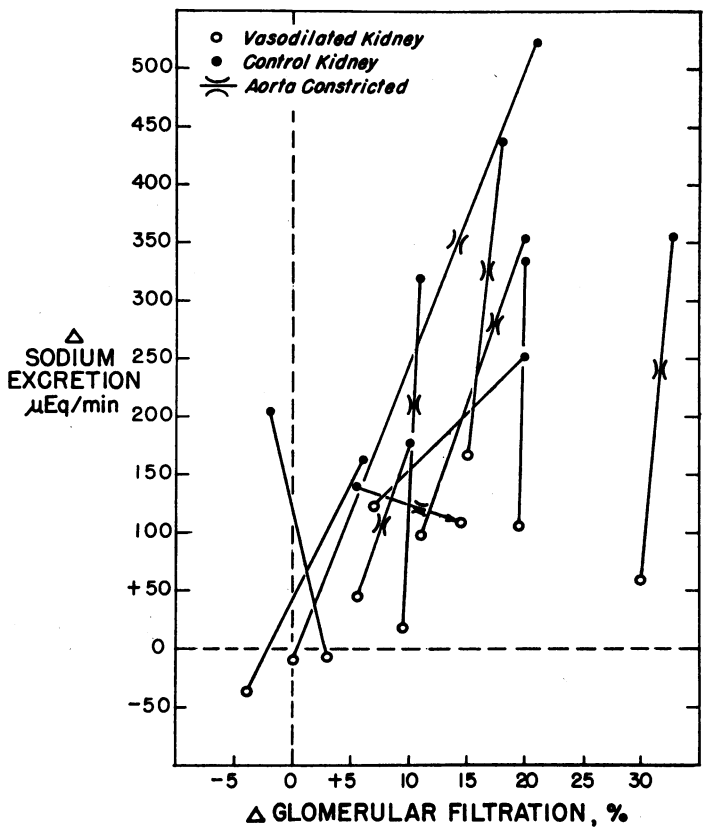

FIG. 8. THE EFFECTS OF INFUSION OF "PLASMA" ON GLOMERULAR FILTRATION AND SODIUM EXCRETION IN THE PRESENCE AND ABSENCE OF INDUCED RENAL VASODILATATION. The lines connect the vasodilated kidney (open points) and nonvasodilated kidney for each experiment. Vasodilated kidneys were natriuretic before infusing "plasma." In each experiment the absolute increase in sodium excretion was less in the vasodilated kidney despite similar or greater increases in glomerular filtration in 5 of the 11 experiments. In seven experiments the aorta was constricted above the renal arteries to reduce glomerular filtration and to minimize the effect of increased arterial pressure during "plasma" loading. In vasodilated kidneys with minimal increases in glomerular filtration and perfusion pressure there was little or no additional natriuretic response to the infusion of "plasma," (open points at the lower left, also see Table II).

uretic response by vasodilated kidneys was not associated with further increases in renal blood flow (Fig. 4) or further reductions in filtration fraction (Fig. 2), but glomerular filtration increased an average of 2 ml/min and arterial pressure increased an average of 20 mm Hg. However, when perfusion pressure was reduced by constricting the aorta above the natriuretic vasodilated (left) kidney the excretion of sodium was returned to rates equal to or less than those present during vasodilatation alone, despite equal or greater rates of glomerular filtration (Fig. 3; Table III, left kidney, compare 45–60 min and 140–155 min). Thus, the increment in sodium excretion by vasodilated kidneys during the infusion of blood appeared to be related to increased perfusion pressure.

Discussion

It has been demonstrated repeatedly in the dog that infusions of isotonic saline or plasma-like solutions result in depression of over-all tubular reab-

TABLE II

Effects of vasodilatation and controlled renal perfusion pressure on the hemodynamic and natriuretic response to infusion of "plasma."

Time	V		GFR		E_{PAH}		RBF		RVR		$U_{Na}V$		Plasma		Hct	Arterial pressure
	R	L	R	L	R	L	R	L	R	L	R	L	TP	Na		
min	*ml/min*		*ml/min*				*ml/min*		*mm Hg/ ml per min*		*μEq/min*		*g/ 100 ml*	*mEq/ liter*		*mm Hg*
0–8	0.48	0.54	29	27	0.87	0.86	165	169	0.68	0.67	113	137	4.69	151	37	121
8–16	0.42	0.53	31	31	0.85	0.84	171	188	0.65	0.59	104	137	4.50	151	36	119
16–24	0.43	0.49	32	29	0.83	0.81	195	195	0.57	0.57	105	124	4.48	150	36	119
24	Begin infusion of acetylcholine at 40 μg/min into left renal artery.															
35–40		2.30		32		0.69		388		0.30		400	4.40	151	38	121
40–45	0.39*	2.60	30	33	0.84		192	406	0.59	0.27	96	455				118
45–50		2.60		33		0.68		400		0.28		458	4.47	150	38	119
50–55		2.60		35				402		0.28		463				118
55–60	0.36*	2.82	31	36	0.82	0.70	205	413	0.55	0.28	89	499	4.58	152	39	121
60–80	Infuse 5 g/100 ml bovine albumin in saline intravenously at 30 ml/min, then continue at 10 ml/min															
90–95	1.30	3.88	39	39	0.83	0.63	266	491	0.45	0.23	285	679	5.08	151	25	130
95–100	1.36	3.92	37	37			245	479	0.48	0.25	299	682				129
100–105	1.56	4.04	38	39	0.84	0.63	241	488	0.49	0.24	335	703	5.25	150	26	130
105	Adjust constriction of aorta above both renal arteries.															
111–116	1.56	3.44	38	38	0.81	0.62	268	523	0.44	0.21	334	616	5.28	151	26	120
116–121	1.64	3.10	38	37			297	521	0.39	0.22	338	552				116
121–126	1.64	2.68	39	38	0.76	0.60	354	553	0.29	0.18	321	477	5.28	150	25	112
126	Release constriction of aorta.															
131–136	2.40	3.62	38	39	0.73	0.58	375	575	0.29	0.19	420	568	5.44	150	25	124
136–141	2.66	3.80	38	38			374	618	0.30	0.18	436	570				125
141–146	2.66	3.92	36	38	0.72	0.55	350	643	0.33	0.18	418	572	5.49	150	25	128
146	Adjust constriction of aorta above both renal arteries.															
150–155	2.94	3.60	37	36	0.75	0.56	342	633	0.32	0.18	426	500	5.56	151	26	124
155–160	2.90	3.40	33	36			347	610	0.32	0.18	412	462				125
160–165	2.82	3.40	36	40	0.73	0.57	349	699	0.32	0.16	400	457	5.56	152	26	123

Abbreviations are the same as in Table I.
* Consecutive collection periods covering the total time of collections from the left kidney.

sorption of sodium as the excretion of sodium increases (1, 4, 6–8). The micropuncture studies of Dirks et al. have indicated that large depressions occur in both fractional and absolute reabsorption of sodium in superficial proximal tubules during saline infusions (9). Other evidence indicates that increases in glomerular filtration rate alone may result in only minimal changes in sodium excretion (10), and, therefore, changes in tubular reabsorption independent of mineralocorticoids may be the major means of altering sodium excretion during acute volume expansion. The pathways through which volume expansion brings about changes in sodium reabsorption and excretion are obscure. Some studies employing cross-circulation between saline loaded and hydropenic animals have supplied evidence *suggestive* that some circulating factor(s) may be involved in the natriuretic response to infusions of saline (11–13). However, from such studies it cannot be concluded whether natriuresis in the recipient animal is the result of an increase or decrease of some humoral agent, or even if such response, as does occur in the recipient, is due to subtle compositional changes resulting from the loading procedure. Recently, Martinez-Maldonado et al. have demonstrated the existence in plasma from saline-loaded rats of a factor which depresses proximal tubular reabsorptive capacity as determined in the rat by the stop-flow microperfusion technique (14). However, despite such an effect on proximal tubular "reabsorptive capacity" the intravenous infusion of plasma from saline loaded animals did not significantly alter sodium excretion in the studies of these latter authors (14). Therefore, it appears that factors in addition to any yet identified humoral effect are important in determining the extent to which over-all tubular reabsorption is

TABLE III

Effects of vasodilatation and controlled renal perfusion pressure on the hemodynamic and natriuretic response to infusion of whole blood

Time	V		GFR		E_{PAH}		RBF		RVR		$U_{Na}V$		Plasma		Hct	Arterial pressure	
	R	L	R	L	R	L	R	L	R	L	R	L	TP	Na		R*	L
min	*ml/min*		*ml/min*				*ml/min*		*mm Hg/ml per min*		*μEq/min*		*g/100 ml*	*mEq/liter*		*mm Hg*	
0– 10	0.37	0.60	34	36	0.83	0.80	155	161	0.94	0.90	96	137	5.95	150	36		150
10– 20	0.31	0.48	35	37	0.81	0.80	146	154	0.99	0.94	82	109	5.95	150	35		150
20– 30	0.32	0.44	38	37	0.81	0.80	158	158	0.91	0.91	83	98	5.95	150	35		150
39	Begin infusion of acetylcholine 40 μg/min into the left renal artery.																
45– 50		3.78		42		0.57		343		0.42		544	5.85	148	35		149
50– 55	0.28‡	3.88	38	44	0.81		164	349	0.87	0.40	74	563					144
55– 60	0.25‡	3.80	37	45	0.83	0.62	160	354	0.92	0.38	65	566	6.15	148	35		141
60– 75	Infuse 300 ml whole blood from reservoir into femoral vein.																
75	Infuse whole blood from reservoir into femoral vein at 5 ml/min.																
95–100	0.54	5.04	40	46	0.84	0.70	183	343	0.79	0.48	155	806	6.21	147	37		150
100–105	0.44	5.04	36	47			158	349	0.91	0.47	132	806					150
105–110	0.40	5.22	36	42	0.84	0.66	158	354	0.92	0.53	125	835	6.40	147	38		152
110–117	Adjust constriction of aorta between the renal arteries.																
120–125	0.38	3.92	40	45	0.83	0.70	173	322	0.85	0.43	116	686	6.40	147	39	154	144
125–130	0.37	4.10	38	46			159	335	0.93	0.42	108	701				154	148
130–135	0.34	4.20	36	46	0.84	0.73	164	309	0.90	0.46	100	718	6.44	146	38	154	149
135	Increase aortic constriction																
140–145	0.36	2.70	39	44	0.85	0.73	160	278	0.97	0.49	107	524	6.44	151	39	162	142
145–150	0.37	3.04	39	44			165	286	0.94	0.48	109	568				162	143
150–155	0.32	2.92	34	42	0.84	0.73	149	310	1.03	0.44	95	502	6.50	145	39	161	145

Abbreviations are the same as in Table I.
* Pressure recorded from thoracic aorta during periods when aorta was constricted between the renal arteries.
‡ Consecutive collection periods covering the total time of collection from the left kidney.

depressed and sodium excretion is increased during volume expansion.

In a series of publications from this laboratory we have demonstrated (*a*) that renal vasodilatation alone results in depressed tubular reabsorption and increased excretion of sodium (2), (*b*) that sodium reabsorption relates inversely and sodium excretion directly to renal perfusion pressure if the pressure changes are transmitted along the intrarenal circulation (3, 4), and (*c*) that increases in plasma protein concentration, superimposed during infusion of saline, result in increased reabsorption and decreased excretion of sodium (4). Utilizing an indirect technique, we suggested that these physically induced changes in the reabsorption and excretion of sodium probably occur, at least in part, in the proximal nephron (4), the site where micropuncture studies indicate that infusion of saline depresses reabsorption (9). On the basis of this series of observations we suggested that these phyical effects on the reabsorption of sodium may be mediated by way of inverse changes in the renal interstitial volume, as a consequence of changes in peritubular capillary perfusion (3, 4), and that such an inverse relationship between renal interstitial volume and proximal tubular reabsorption could be effected by reciprocal changes in tubular volume (15–17). Renal interstitial volume and/or pressure should increase in response to decreases in precapillary (peritubular) resistance or increased perfusion pressure, if the pressure change is transmitted to the capillary circulation. Likewise the renal interstitial volume should increase as plasma oncotic pressure (protein concentration) is decreased. Either of these changes could limit tubular volume and thereby depress or limit the reabsorption of sodium (14–17). However, it is possible that changes in the renal interstitial volume and pressure may influence tubular sodium absorption through other pathways such as changes in cellular or intercellular configuration. The idea that tubular volume may be involved has received support from the recently published micropuncture studies of Rector et al.,

which suggest that some limitation of tubular distension may be necessary to effect a net decrease in proximal tubular reabsorption during saline infusion despite the possibility of hormonally determined decreases in "reabsorptive capacity" (18). However, it has not been demonstrated previously that the natriuretic response to *volume expansion* may be causually related to changes in the physical variables that are known to independently alter sodium excretion (viz., perfusion pressure, renal vascular resistance, or plasma oncotic pressure). Other studies from this laboratory demonstrated that large and rapid infusions of saline result in increased renal blood flow, and that sodium reabsorption may relate inversely to renal blood flow (or perfusion pressure) during such infusions (1). Yet, smaller infusions of saline also depress tubular sodium reabsorption and increase sodium excretion but may not increase renal blood flow (2, 19). However, since proximal tubular reabsorption of sodium may relate in a direct manner to plasma oncotic pressure (4), reduced plasma protein concentration during saline infusion could be an important factor leading to increased excretion of sodium by the above mechanism, even in the absence of changes in perfusion pressure or vascular resistance. On the other hand, infusion of isooncotic "plasma-like" solutions could depress over-all tubular reabsorption of sodium via hemodynamic changes (reduced renal vascular resistance, increased perfusion pressure). The purpose of the present studies was to systematically control or manipulate plasma oncotic pressure, renal vascular resistance, and renal perfusion pressure in order to assess the importance of each of the factors as determinants of the natriuretic response to volume expansion.

These studies extend our previous observations (4) and demonstrate that increasing the plasma protein concentration under normal conditions of saline diuresis increases over-all tubular sodium reabsorption and decreases sodium excretion, despite increased glomerular filtration, increased renal blood flow, and increased arterial pressure. We conclude, therefore, that depressed plasma protein concentration is a major determinant of the natriuresis resulting from infusion of saline. This effect of hyperoncotic albumin to diminish the response to saline infusion is all the more impressive since the simultaneous increases in renal blood flow and arterial pressure (and reduced renal vascular resistance) are changes which should depress sodium reabsorption and increase sodium excretion (2, 3). These hemodynamic changes occurring during the infusion of concentrated protein could account for the failure of sodium excretion to decrease even more as plasma protein concentration was increased. Evidence for this is provided by the experiments in which we produced natriuresis by vasodilating one kidney before infusing saline, in which we reduced the excretion of sodium after restoring plasma protein concentration and controlling perfusion pressure to levels below that present during vasodilatation alone, despite the same rate of glomerular filtration (Table I).

The infusion of 4.5 or 5 g/100 ml albumin solution ("plasma") precluded depression of plasma oncotic pressure as the mediator of natriuresis during volume expansion. In these experiments the infusion of "plasma" resulted in increased arterial pressure and profound decreases in vascular resistance in control (nonvasodilated) kidneys, and these hemodynamic changes were accompanied by increased sodium excretion. In kidneys which were vasodilated before the infusion of plasma, renal vasacular resistance was already reduced (increased renal blood flow) and natriuresis was present before volume expansion. During the infusion of plasma these vasodilated kidneys underwent further increases in sodium excretion (and in some instances demonstrable decreases in tubular reabsorption of sodium) as arterial pressure increased and renal vascular resistance decreased further during the infusion. However, when arterial pressure was reduced by aortic constriction the additional natriuretic effect of the "plasma" infusion was either completely abolished or reduced to values only slightly above those present during vasodilatation alone, despite continued increases in glomerular filtration and the filtered load of sodium. Thus, when arterial pressure was controlled, and the kidney was vasodilated before infusing "plasma," the infusion resulted in little or no additional natriuresis at a time when control kidneys were exhibiting continued natriuresis in response to the infusion. Therefore, when plasma protein concentration was not depressed the natri-

uretic response to infusion of "plasma" appeared to relate predominantly to perfusion pressure in the presence of decreased renal vascular resistance.

The infusion of blood resulted in renal hemodynamic changes strikingly different from those produced by the infusion of "plasma." Renal vascular resistance *increased* during the infusion of blood in seven of eight studies, and despite increases in arterial pressure renal blood flow was usually unchanged or decreased. In these studies the infusion of blood was associated with decreased, as often as with increased, excretion of sodium in nonvasodilated kidneys even though glomerular filtration rate usually increased. It does not appear that the use of donor blood in these experiments precluded a natriuretic response to volume expansion since in the kidneys which were previously vasodilated the infusion of blood resulted in additional natriuresis as arterial pressure increased. However, when arterial pressure was reduced to preloading values there was no evidence of any effect of the infusion to increased sodium excretion, despite unchanged or continued increases in glomerular filtration. Thus, infusion of blood *increased* renal vascular resistance and had virtually no natriuretic effect if renal perfusion pressure was controlled, but the presence of induced renal vasodilatation did permit increased sodium excretion which related to increased renal perfusion pressure during loading.

These observations are entirely consistent with the conclusion that changes in plasma oncotic pressure, renal vascular resistance, or arterial pressure, either alone, or in combination, are determinants of the *natriuretic* response to volume expansion, and there was no evidence from the present studies that other factors were of major importance as determinants of sodium reabsorption and excretion under the conditions of these experiments. Evidence for an association between postglomerular capillary pressure and sodium excretion (as suggested above) is afforded by a comparison of the fractions of total blood flow filtered under the various conditions of these experiments. Vasodilatation with acetylcholine reduced post glomerular resistance predominantly as the filtration fraction (GFR/RBF) decreased from 0.18 to 0.12. The infusion of plasma resulted in natriuresis and similar reductions in filtration fraction. However, infusions of blood which usually had little or no natriuretic effect resulted in unchanged or increased filtration fractions, which suggested no decrease in post glomerular resisatnce. The reasons for the striking difference between the effects of infusing "plasma" and infusing blood on renal vascular resistance are not entirely clear. It is likely that the infusion of "plasma" reduced resistance to renal blood flow in part by lowering the hematocrit and reducing the viscosity of blood, and this would not require that the total effect on resistance be mediated through changes in vascular tone. The infusion of equilibrated whole blood would have no such effect to reduce viscosity and the internal resistance (of blood) to flow.

The present studies do not rule out the possibility that volume expansion results in a change in tubular sodium reabsorption by some other pathway, but which cannot be expressed as increased sodium excretion except when complemented by physical changes which could reduce or limit proximal tubular distension. Such is, in fact, the conclusion reached by Rector et al. who, on the basis of recent micropuncture studies, suggested that saline infusion depressed proximal tubular "reabsorptive capacity," but that an actual net decrease in reabsorption is dependent upon a limitation of tubular distention (18). In addition, the possibility must be considered that these physical factors influence sodium reabsorption in the distal nephron. Sellman and his associates have reported that in the rat relatively small infusions of saline result in a depression of sodium reabsorption by the proximal tubule which does not decrease further despite increasing sodium excretion during further saline infusion (20). This latter observation suggests that extensive saline loading may progressively increase the excretion of sodium by limiting distal tubular reabsorption. Consistent with this view are our earlier observations that large and rapid infusions of saline result in increased renal blood flow and greater natriuresis than observed in the present studies employing smaller infusions of saline which did not increase renal blood flow (1). Also, the natriuretic effect of induced renal vasodilatation is greater in the presence of small infusions of saline which alone have limited natriuretic effects (2). Therefore, if minimal volume expansion results in a maximal

hormonally determined depression of proximal reabsorption but limited increases in sodium excretion (14), the additional effect of these physical factors could be to further depress proximal reabsorption (4) and to limit distal reabsorption (1, 2) and thereby augment sodium excretion. However, the present studies do not suggest that the natriuresis after volume expansion was attributable to factors other than renal vascular resistance, perfusion pressure, or oncotic pressure. This does not exclude the possible action of humoral or other factors for several reasons. (*a*) The infusion of the albumin solutions and/or reductions in perfusion pressure may have been sufficiently antinatriuretic to offset other factors which depress sodium reabsorption. (*b*) The induced renal vasodilatation could have produced a maximal depression of proximal tubular reabsorption which was not augmented by other (humoral) factors activated during the subsequent volume expansion. (*c*) In the present studies control rates of sodium excretion were increased moderately, possibly as a result of infusions necessary to maintain patency of the mulitple vascular catheters required for these measurements, and therefore factors which depress proximal reabsorption but have limited effects to increase sodium excretion (14) could have been operative before volume expansion. Nevertheless, the present observations demonstrate the essential role of these physical changes in determining the extensive natriuretic response observed after volume expansion in the dog.

The additional natriuretic response of vasodilated kidneys to increases in arterial pressure during infusions of blood or "plasma" are entirely similar to the natriuretic response of vasodilated kidneys to pressor infusions of angiotensin or norepinephrine (3). The natriuretic effect of increased pressure in the presence of reduced renal vascular resistance during "plasma" infusion, and the absence of such an effect of pressure in the presence of *increased* renal vascular resistance during infusions of blood, are also similar to the effect of pressor infusions of norepinephrine or angiotensin to produce natriuresis only in the presence of vasodilatation (3). The interdependent relationship of renal vascular resistance and arterial pressure on sodium reabsorption and excretion was evident in experiments in which larger reductions in perfusion pressure were necessary to reduce sodium excretion in the presence of decreasing renal vascular resistance. These presently observed effects of combinations of arterial pressure and renal vascular resistance on sodium reabsorption and excretion were the result of the infusions of "plasma" or blood, and, therefore, lend considerable support to our previous suggestion that these hemodynamic effects are independent of the specific agents used in the earlier studies (3). Although the present studies do not eliminate the possibility that the renal arterial infusion of acetylcholine has some direct effect on tubular transport of sodium over and above the effect of vasodilatation, this appears unlikely in view of the similar natriuretic effects of a variety of unrelated vasodilators (2).

The conclusion that reduced plasma oncotic pressure, reduced renal vascular resistance, or increased arterial pressure are important, either alone or in combination, for the natriuretic response to volume loading is not negated by observations that natriuresis and decreased reabsorption of sodium persist during saline infusion despite aortic (or renal arterial) constriction sufficient to reduce perfusion pressure, glomerular filtration, and renal blood flow to levels below preloading values (1, 9, 19). If the effects of these physical factors are mediated by increases in the renal interstitial volume and pressure so that the relationship between tubular volume and glomerular filtration is disrupted (tubular volume/filtered volume, reduced), then such an altered relationship could persist and maintain depressed *fractional* reabsorption of sodium even though the absolute level of filtration and renal blood flow is reduced experimentally. Also, during saline loading reduced plasma oncotic pressure could result in increased renal interstitial volume largely independent of arterial pressure and vascular resistance which should persist, in a relative sense, even in the presence of decreased glomerular filtration, renal blood flow, and arterial pressure. However, when arterial pressure is the major variable determining sodium reabsorption and excretion, as appeared to be the case in the vasodilated kidneys during infusions of "plasma" or blood, then it is likely that sodium reabsorption and excretion would be sensitive to even small

changes in perfusion pressure, and such was the case in the present studies.

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