Journal of Clinical Investigation
Vol. 45, No. 4, 1966

The Effects of Combined Renal Vasodilatation and Pressor Agents on Renal Hemodynamics and the Tubular Reabsorption of Sodium *

LAURENCE E. EARLEY † AND ROBERT M. FRIEDLER

(From the Thorndike Memorial Laboratory, Second and Fourth [Harvard] Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.)

A considerable body of evidence indicates that the net tubular reabsorption of sodium may be diminished during extracellular volume expansion, independent of the tubular effects of salt-retaining hormones. Since the report by De Wardener, Mills, Clapham, and Hayter (1), several other studies employing clearance techniques have demonstrated diminished net tubular reabsorption of sodium during saline loading in the dog (2–5). In addition, Dirks, Cirksena, and Berliner have reported recently that fractional reabsorption in the proximal nephron of the dog may be diminished strikingly during saline loading (6). Thus, natriuresis in response to salt loading could be due largely to diminished tubular reabsorption of sodium unrelated to aldosterone. However, such studies have not revealed mechanisms and pathways whereby expansion of the extracellular volume leads to diminished reabsorption of sodium. We recently suggested that increased renal blood flow, and perhaps increased medullary blood flow specifically, may be one factor that by way of intrarenal mechanisms contributes to diminished reabsorption of sodium during saline loading (5). Furthermore, natriuresis in the absence of salt loading accompanies increased renal blood flow when local vasodilatation is produced by a variety of agents (7–13), and we have observed that the unilateral natriuresis accompanying increased renal blood flow during the renal arterial infusion of acetylcholine is due in part to diminished net tubular reabsorption of sodium (14). Leyssac has suggested that angiotensin may depress proximal tubular reabsorption (15), and it has been demonstrated that under certain conditions angiotensin may produce natriuresis (16–19). If the reabsorption of sodium distally to the proximal convolution relates in part in some inverse manner to blood flow, then the vasoconstrictor effects of angiotensin could limit the natriuretic effect that the agent could exert by way of depressing proximal tubular reabsorption. Such a dual effect of angiotensin on tubular reabsorption and renal blood flow could explain the inconsistent effects of the agent on sodium excretion. The present studies were therefore undertaken to examine the combined effects of renal vasodilatation and angiotensin on tubular reabsorption and sodium excretion. By producing unilateral renal vasodilatation it was possible to compare the effects of angiotensin on sodium excretion in two kidneys receiving different blood flows in the same animal.

Methods

Twenty-one mongrel dogs of either sex ranging in weight from 19.1 to 26.8 kg were deprived of food and water for 18 hours and anesthetized with pentobarbital. The animals were respired automatically with room air. Each ureter was cannulated through flank incisions, and a 23-gauge needle was inserted in the direction of flow into one renal artery (usually the left) near its origin at the aorta. The techniques used for collecting and handling renal venous blood samples have been described elsewhere (14). Arterial blood samples were collected, and arterial pressure was measured through a catheter inserted into the aorta through a femoral artery. Approximately 3 hours before experimental collections each animal received an im injection containing 5 U of Pitressin Tannate [1] and 10 mg of deoxycorticosterone acetate.[2] Two hours before experimental measurements an iv in-

* Submitted for publication September 29, 1965; accepted December 16, 1965.

Aided in part by grants AM-5401-04 from the National Institutes of Health and NsG595 from the National Aeronautics and Space Administration.

† Address requests for reprints to Dr. Laurence E. Earley, Boston City Hospital, 818 Harrison Ave., Boston, Mass. 02118.

[1] Parke, Davis, Detroit, Mich.

[2] Organon, West Orange, N. J.

fusion of 0.9% saline was begun at a constant rate between 0.4 and 0.5 ml per minute to deliver inulin at 20 to 25 mg per minute, *p*-aminohippurate at 3.2 to 3.8 mg per minute, vasopressin (Pitressin) [1] at 40 to 60 mU per kg per hour, and deoxycorticosterone [3] at 25 to 30 μg per minute. The total rate of infusion of this maintenance solution and infusions into the renal venous, renal arterial, and femoral arterial catheters was approximately 2.0 ml per minute. A minimum of 2 hours elapsed after completing the operative procedure before beginning experimental collections. Renal venous and arterial blood samples were collected simultaneously at the midpoint of clearance periods, except in some cases where short periods (5 minutes) were employed during stable phases of the experiment and blood samples were collected during alternate clearance periods. Clearances were not calculated during transitional phases of the experiments when urine flow was changing abruptly.

The following experimental protocols were employed, and 3 to 6 clearance periods were collected during each phase of the experiment. After collection of control periods the renal arterial infusion was changed to saline containing acetylcholine bromide,[4] bradykinin,[5] or kallidin [5] to deliver 40 μg, 5 μg, or 1 to 3 μg per minute, respectively. After collections for clearances during a stable phase of unilateral renal vasodilatation, angiotensin II (Hypertensin) [6] was added to the renal arterial infusion in 6 experiments at a constant rate ranging from 0.1 to 0.5 μg per minute. After collections during combined renal vasodilatation and angiotensin infusion, the angiotensin was usually discontinued, and after further collections the vasodilator was discontinued, and additional control collections were made. In 11 other experiments a similar protocol was followed except that angiotensin was infused intravenously at a rate of 1.0 to 10.0 μg per minute. In 4 experiments the infusion of the vasodilator was discontinued while continuing the infusion of angiotensin, and in 5 experiments angiotensin was infused before starting the infusion of the vasodilator. The exact sequences of drug infusions are detailed in Tables II and III. In all instances 10 to 30 minutes was allowed for stabilization of blood pressure and urine flow before making collections during each phase of the experiments.

In 5 experiments the effects of equipressor infusions of angiotensin and norepinephrine were compared during unilateral renal vasodilatation. After control clearance periods an infusion of acetylcholine was begun into the left renal artery at 40 μg per minute. Further collections were made, and then an infusion of angiotensin or norepinephrine was begun intravenously at 5 or 10 μg per min-

[3] Steraloids, Queens, N. Y.

[4] Eastman Organic Chemicals, Rochester, N. Y.

[5] Kindly supplied by Sandoz Pharmaceuticals, Hanover, N. J.

[6] Ciba Pharmaceuticals, Summit, N. J.

TABLE I

*Effects of systemically infused angiotensin on renal hemodynamics and electrolyte excretion in the presence of unilateral renal vasodilatation in experiment no. 2**

Time	V		GFR		C_{PAH}		E_{PAH}	RPF	NCPF	$U_{Na}V$		U_KV		P_{Na}	Arterial pressure
	R	L	R	L	R	L	L	L	L	R	L	R	L		
min	*ml/min*		*ml/min*		*ml/min*			*ml/min*	*ml/min*	*μEq/min*		*μEq/min*		*mEq/L*	*mm Hg*
0– 15	0.31	0.21	51	41	137	110	0.867	127	17	39	31	26	20	143	124
15– 43	0.37	0.30	51	53	145	149	0.868	174	25	36	35	29	29	144	120
43– 52	0.71	0.51	52	52	170	171	0.844	203	32	45	34	38	35	144	110
Begin infusion of acetylcholine bromide at 40 μg per minute into left renal artery															
52– 62	1.24	2.26								74	154	42	61		119
62– 68	1 70	3 14	51	50	174	220	0.686	321	101	99	214	43	50	146	125
68– 74	1.75	2.77	49	44	158	206	0.717	287	81	103	186	40	47	147	120
74– 80	1.58	2.47	48	44	146	189	0.727	260	71	96	158	38	44	146	117
Begin infusion of angiotensin 5.0 μg per minute intravenously															
80– 92	0.56	5.16								36	402	17	57		
92–103	0.38	6.76	58	47	107	125	0.782	160	35	20	573	25	47	149	193
103–114	0.33	4.21	38	42	76	112	0.836	134	22	16	327	20	36	148	183
114–120	0.25	4.00	33	40	100	104	0.845	123	19	10	300	16	36	149	170
Discontinue infusion of angiotensin															
120–142	0.22	1.68								6	108	17	27		137
142–152	0.17	0.41	40	37	97	105	0.856	123	18	4	20	17	21	149	103
152–162	0.16	0.40	38	36	92	106	0.841	126	20	3	20	17	22	147	100
Discontinue infusion of acetylcholine															
162–187	0.17	0.19								3	7	20	19		
187–202	0.18	0.20	40	39	102	99	0.879	113	14	4	5	24	22	147	115
202–217	0.18	0.20	41	37	104	101	0.870	116	15	5	6	26	24	146	115

* Abbreviations are as follows: V = rate of urine flow; GFR = glomerular filtration rate (clearance of inulin); C_{PAH} = clearance of *p*-aminohippurate; E_{PAH} = extraction ratio for *p*-aminohippurate; RPF = renal plasma flow; NCPF = "noncortical" plasma flow (RPF − C_{PAH}); $U_{Na}V$ = rate of excretion of sodium; U_KV = rate of excretion of potassium; P_{Na} = concentration of sodium in plasma.

ute, respectively. When further periods of stable urine flow had been collected, the infusion of the pressor agent was discontinued, and approximately 30 minutes was allowed for blood pressure and urine flow to stabilize. Then an intravenous infusion of the alternate pressor agent was begun and adjusted to a rate producing the same blood pressure as during the infusion of the first pressor agent. After collections during stable blood pressure and urine flow the same procedure was followed to return to the first pressor agent.

Analytical procedures for inulin, *p*-aminohippurate, sodium, potassium, and osmolality were the same as employed previously (14). Arterial blood pressure was recorded by a Sanborn pressure transducer and recorder. Renal plasma flow (RPF) was calculated from the clearance of *p*-aminohippurate (C_{PAH}) and the extraction ratio for PAH (E_{PAH}) ($RPF = C_{PAH}/E_{PAH}$). "Noncortical" plasma flow (NCPF) was calculated as the difference between RPF and C_{PAH} ($NCPF = RPF - C_{PAH}$).

TABLE II

*Effects of combined intravenously infused angiotensin and unilateral (left) renal vasodilatation on renal hemodynamics and sodium excretion**

Experiment		GFR		C_{PAH}		RPF	$U_{Na}V$		P_{Na}	Arterial pressure	Angiotensin
		R	L	R	L	L	R	L			
		ml/min		*ml/min*		*ml/min*	*μEq/min*		*mEq/L*	*mm Hg*	*μg/min*
1.	Control	81	82	209	215	242	172	150	149	142	10.0
	Acetylcholine	64	75	160	257	312	98	229	148	128	
	Acetylcholine and angiotensin	80	77	146	215	254	11	409	148	185	
	Acetylcholine	49	65	145	210	255	3	18	148	105	
3.	Control	44	48	120	135	152	138	184	152	127	5.0
	Acetylcholine	43	43	130	191	272	90	196	151	125	
	Acetylcholine and angiotensin	39	39	83	130	175	25	255	152	153	
	Acetylcholine	26	21	81	109	155	2	2	152	97	
4.	Control	29	31	72	78	92	177	193	143	131	2.5
	Acetylcholine	32	36	84	109	129	247	424	143	125	
	Acetylcholine and angiotensin	27	30	56	85	106	104	572	143	162	
	Acetylcholine	25	31	67	90	115	37	295	145	110	
	Control	26	34	65	83	95	38	89	146	115	
5.	Control	26	36	60	83	90	190	193	148	158	2.0
	Acetylcholine	25	41	63	139	160	191	729	149	153	
	Acetylcholine and angiotensin	21	42	43	114	126	40	933	148	183	
	Acetylcholine	22	40	59	128	141	13	307	150	120	
6.	Control	29	29	66	66	77	250	171	143	182	2.5
	Acetylcholine	29	29	72	108	136	156	264	145	165	
	Acetylcholine and angiotensin	31	32	80	110	138	286	498	145	224	
	Acetylcholine	20	28	48	92	111	107	146	145	128	
7.	Control	41	33	85	75	89	54	89	158	133	2.0
	Kallidin	36	32	72	103	151	39	242	159	131	
	Kallidin and Angiotensin	34	35	57	89	129	120	507	158	146	
	Angiotensin	31	30	57	56	69	139	310	156	151	
8.	Control	24	26	62	69	78	236	330	144	130	1.0
	Kallidin	18	25	46	70	85	117	340	144	124	
	Control	19	20	52	54	62	66	147	144	118	
	Angiotensin	19	20	47	49	55	170	308	143	147	
	Angiotensin and kallidin	13	20	32	52	65	82	358	143	134	
9.	Control	63	57	174	161	183	254	281	147	141	2.0
	Kallidin	56	55	154	206	249	198	355	146	133	
	Control	61	54	168	151	172	160	156	146	133	
	Angiotensin	59	54	109	105	114	261	341	147	179	
	Angiotensin and kallidin	54	48	100	132	161	108	381	148	164	
	Angiotensin	49	47	88	83	89	89	123	149	169	
	Angiotensin and acetylcholine	40	50	74	120	165	43	518	148	156	
	Acetylcholine	36	50	88	159	193	23	268	149	122	
10.	Control	50	48	145	142	152	89	90	143	133	2.5
	Bradykinin	49	49	152	269	349	70	92	143	127	
	Bradykinin and angiotensin	46	45	101	187	224	227	214	143	168	
	Angiotensin	44	43	88	95	105	262	156	143	171	
	Control	42	44	129	119	137	23	22	144	122	

* Each phase of experiments is the mean of multiple uniform collection periods, and phases of experiments are consecutive. Transition periods of 5 to 25 minutes when drug infusions were started or stopped and when urine flow was abruptly changing have been omitted from the calculations. Rates of renal arterial infusions: acetylcholine, 20 or 40 μg per minute; kallidin, 1 to 3 μg per minute; bradykinin, 5 μg per minute.

TABLE III

*Effects of combined renal arterial infusions of acetylcholine and angiotensin on renal hemodynamics and sodium excretion**

Experiment		GFR R	GFR L	C_{PAH} R	C_{PAH} L	RPF L	$U_{Na}V$ R	$U_{Na}V$ L	P_{Na}	Arterial pressure	Angiotensin
		ml/min		*ml/min*		*ml/min*	*μEq/min*		*mEq/L*	*mm Hg*	*μg/min*
11.	Control	44	45	100	98	106	140	161	147		0.5
	Acetylcholine	45	51	113	206	257	101	350	147		
	Acetylcholine and angiotensin	40	48	78	134	151	17	359	148		
	Acetylcholine	37	47	96	171	225	14	112	148		
	Control	40	47	110	116	137	7	36	148		
12.	Control	44	39	170	152	186	155	188	146	147	0.5
	Angiotensin	44	34	116	93	107	140	209	146	161	
	Control	43	33	170	136	172	77	74	146	133	
	Acetylcholine	39	38	166	205	330	33	239	146	118	
	Acetylcholine and angiotensin	36	41	104	158	231	16	520	146	136	
	Acetylcholine	34	40	117	185	268	6	175	147	106	
	Control	36	32	114	110	136	8	7	147	104	
13.	Control	60	60	169	171	191	256	262	149	192	0.25
	Angiotensin	61	60	154	146	160	303	271	149	195	
	Control	61	56	218	206	247	157	125	149	146	
	Acetylcholine	52	55	188	230	277	104	195	149	135	
	Acetylcholine and angiotensin	50	55	132	179	205	43	297	149	153	
	Acetylcholine	46	45	220	192	227	9	50	148	123	
	Control	54	56	183	198	228	20	21	150	123	
14.	Control	69	78	140	164	186	238	250	145	179	0.5
	Acetylcholine	76	83	155	252	324	150	404	144	142	
	Acetylcholine and angiotensin	70	81	127	228	302	70	626	143	163	
	Angiotensin	71	65	129	112	126	71	91	142	164	
	Control	74	72	164	178	208	65	33	142	120	
15.	Control	64	68	201	261	†	40	115	143	137	0.5
	Angiotensin	70	56	168	119		26	15	142	143	
	Control	64	65	211	260		9	79	144	130	
	Acetylcholine	62	71	217	325		2	86	144	126	
	Acetylcholine and angiotensin	63	57	164	176		3	136	144	145	
	Acetylcholine	71	68	243	301		3	90	145	135	
16.	Control	43	42	96	97	112	109	163	147	139	0.1
	Acetylcholine	43	45	110	155	261	71	352	148	120	
	Acetylcholine and angiotensin	45	46	96	133	191	62	477	149	120	
	Acetylcholine	34	46	81	156	241	27	344	149	104	

* Infusions into left renal artery.
† Extraction of PAH not measured in this experiment.

Results

The effects of angiotensin in the presence of unilateral renal vasodilatation. Details of a representative experiment are given in Table I, and the results of 15 other experiments are summarized in Tables II and III. The renal arterial infusion of either acetylcholine, bradykinin, or kallidin resulted in an ipsilateral increase in urine flow within 60 seconds after infusion of the vasodilator was begun. In the experimental kidney RPF increased by an average of 94 ml per minute (range, 7 to 197 ml per minute), and E_{PAH} decreased by an average of 0.11 (range, 0.01 to 0.27). The C_{PAH} by the control kidney was usually unchanged or slightly decreased during this phase of unilateral renal vasodilatation. Sodium excretion by the vasodilated kidneys increased by an average of 132 μEq per minute (range, 2 to 536 μEq per minute), and sodium excretion by the control kidneys was usually decreased moderately. This increased renal blood flow and sodium excretion by the vasodilated kidneys was associated with unchanged or decreased glomerular filtration in 8 of these 16 experiments (experiment 2, Table I; experiments 1, 3, and 6 to 9, Table II; and experiment 13, Table III).

In 6 of the 16 experiments (experiments 11 to 16, Table III) angiotensin was infused into the renal artery of the vasodilated kidney, and in the remaining 10 experiments (Tables I and II) angiotensin was infused intravenously during continued infusion of the vasodilator into the renal

artery. For reasons to be discussed the effects of the renal arterial infusion of angiotensin were usually indistinguishable from the effects of the systemic infusions, and therefore results of all 16 experiments are discussed together.

When the infusion of angiotensin was begun in the presence of unilateral renal vasodilatation, urine flow from the vasodilated kidney increased within 5 to 20 minutes. An earlier rise occurred in the mean arterial blood pressure, and during stable clearance periods mean arterial pressure was elevated by an average of 31 mm Hg (range, 0 to 61 mm Hg) above the levels present during vasodilatation before the infusion of angiotensin. Angiotensin resulted in an increased excretion of sodium by the vasodilated kidney that averaged 141 μEq per minute greater than the rates during vasodilatation alone (range of increase, 9 to 281 μEq per minute). In each experiment angiotensin resulted in decreased C_{PAH}, decreased RPF (Tables I to IV), and usually increased E_{PAH} (Figure 1) in the vasodilated kidney. This reduction of hemodynamics and increased excretion of sodium was associated with unchanged or reduced glomerular filtration (below the level present during the vasodilatation alone) in 10 of the 16 experiments (experiment 2, Table I; experiments 3, 4, and 8 to 10, Table II; and experiments 11 and 13 to 15, Table III). Thus, the infusion of angiotensin was accompanied by further increases in sodium excretion by the vasodilated kidney despite a reduction in renal plasma flow and usually a reduction in GFR and filtered sodium. When the infusion of angiotensin was discontinued in the presence of continued renal vasodilatation (experiment 2, Table I; experiments 1, 3 to 6, and 9, Table II; and experiments 11 to 13, 15, and 16, Table III), urine flow and sodium excretion decreased, usually within 25 minutes. This diminished excretion of sodium after discontinuing the infusion of angiotensin was usually accompanied by an increased RPF and decreased E_{PAH}. Glomerular filtration often, but not always, decreased after stopping the infusion of angiotensin.

Control kidneys. The infusion of angiotensin usually resulted in large decreases in C_{PAH} in the nonvasodilated control kidneys (average decrease, 29 ml per minute), and C_{PAH} in the control kidney during angiotensin infusion was always lower than C_{PAH} in the vasodilated kidney. In 3 experiments

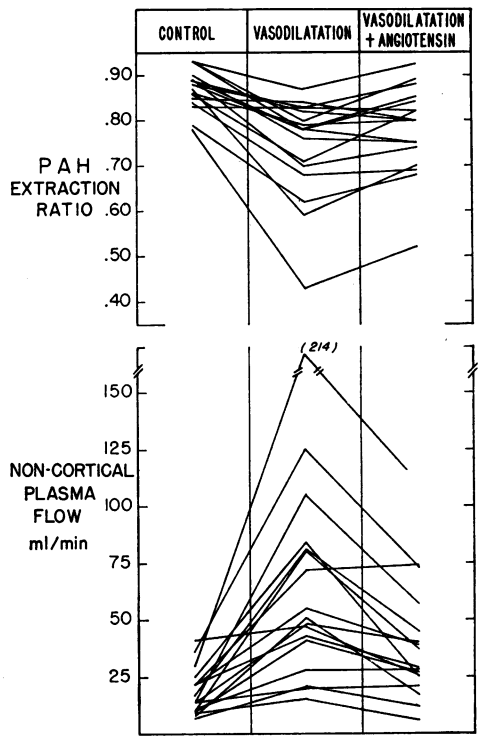

FIG. 1. EFFECTS OF INFUSION OF ANGIOTENSIN DURING UNILATERAL RENAL VASODILATATION ON THE EXTRACTION RATIO OF *p*-AMINOHIPPURATE (E_{PAH}) AND "NONCORTICAL PLASMA FLOW." The means of three or more uniform collections from the vasodilated kidneys are represented in each column for each experiment (experiments 1 to 16, 20, 21). Vasodilatation alone usually decreased E_{PAH} and increased noncortical plasma flow. The superimposition of angiotensin usually increased E_{PAH} and decreased noncortical plasma flow. The Figure represents the same collection periods summarized in Tables I to IV.

(experiments 6, 7, and 10, Table II) small increases in sodium excretion by the control kidney occurred during the systemic infusion of angiotensin. However, in the remaining 13 experiments the excretion of sodium by the control kidney decreased during the infusion of angiotensin at a time when marked natriuresis was present in the vasodilated kidney. Although GFR in control kidneys was usually decreased during the infusion of angiotensin, in 8 of the 16 experiments (experiments 1, 3, 6, 7, 9, and 10, Table II; experiments 15 and 16, Table III) GFR in control kidneys during the infusion of angiotensin was no more than 1 ml per minute less than in the vasodilated kidney despite the marked differences in sodium excretion.

These relationships between renal hemodynamics and sodium excretion during the major

phases of the experiments are summarized in Figure 2.

Comparison of equipressor infusions of angiotensin and norepinephrine during unilateral renal vasodilatation. After collections during the stable phase of unilateral renal vasodilatation, an infusion of angiotensin (5 μg per minute) or norepinephrine (10 μg per minute) was begun intravenously. After 20 to 30 minutes when blood pressure and urine flow were stable, collections for clearances were made, and the infusion of the pressor was discontinued. Another 15 to 30 minutes was allowed for the blood pressure to fall and the urine flow to decrease, and then the alternate pressor was infused intravenously. Usually the rate of infusion of the second pressor required 5 to

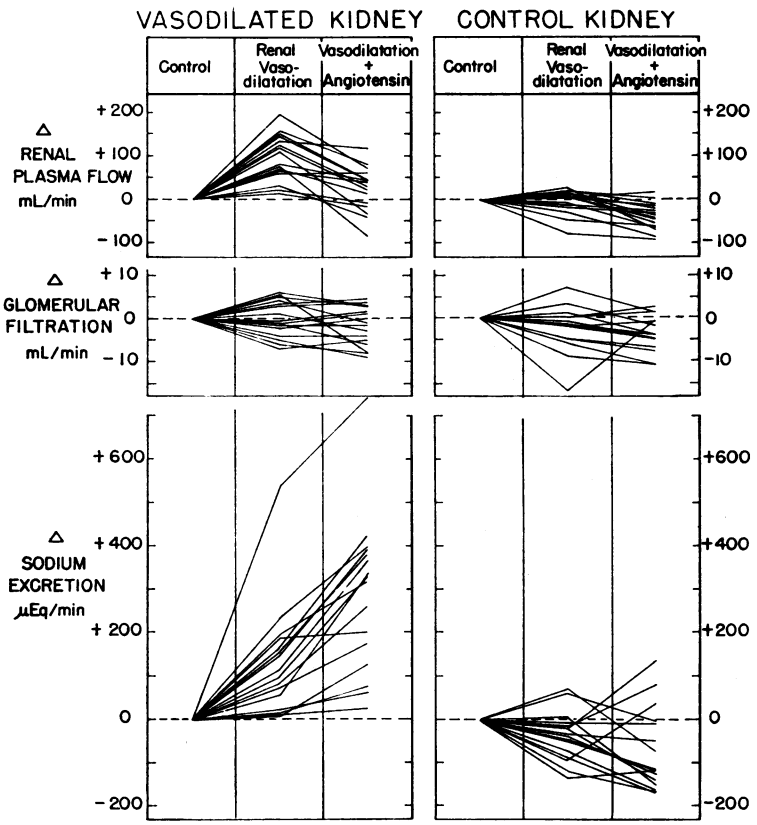

FIG. 2. EFFECTS OF INFUSION OF ANGIOTENSIN DURING UNILATERAL RENAL VASODILATATION ON RENAL HEMODYNAMICS AND SODIUM EXCRETION. The means of three or more uniform collections are represented in each column for each experiment (experiments 1 to 16). The clearance of PAH rather than true renal plasma flow is shown for control kidneys. During unilateral vasodilatation alone increased renal plasma flow was accompanied by increased sodium excretion and variable changes in glomerular filtration, whereas sodium excretion usually decreased in control kidneys with similar changes in glomerular filtration, but with unchanged or reduced plasma flow (C_{PAH}). The superimposition of angiotensin uniformly resulted in a further increase in sodium excretion by vasodilated kidneys despite variable changes in glomerular filtration and a return toward control of renal plasma flow. During the infusion of angiotensin sodium excretion by control nonvasodilated kidneys exceeded control rates in only three experiments despite changes in glomerular filtration similar to those in vasodilated experimental kidneys. In any individual experiment plasma flow (C_{PAH}) during the infusion of angiotensin was lower in the control kidney than in the experimental kidney.

TABLE IV

Comparison of the effects of equipressor infusions of angiotensin and norepinephrine on renal hemodynamics and sodium excretion during unilateral renal vasodilatation

Experiment		V		GFR		C_{PAH}		E_{PAH}	RPF	NCPF	$U_{Na}V$		$\frac{T_{Na}}{F_{Na}} \times 100$*		Arterial pressure
		R	L	R	L	R	L				R	L	R	L	
		ml/min		*ml/min*		*ml/min*			*ml/min*	*ml/min*	*μEq/min*		%		*mm Hg*
17.†	Control	1.08		38		93					198		96.4		126
	Acetylcholine	2.00		39		114					295		94.8		116
	Angiotensin	5.55		43		109					686		89.1		167
	Norepinephrine	3.59		39		89					477		91.8		159
	Angiotensin	3.94		37		84					515		90.6		145
18.‡	Control	0.26	0.22								13	10			150
	Acetylcholine	0.21	0.53	46	39	135	164	0.770	213	47	7	91	99.9	98.4	136
	Norepinephrine	0.19	2.28	39	41	135	150	0.773	194	44	9	416	99.8	93.2	173
	Angiotensin	0.33	3.84	36	38	78	126	0.750	168	42	38	507	99.3	91.0	173
	Norepinephrine	0.17	1.84	44	37	98	111	0.732	152	41	5	311	99.9	94.3	169
19.‡	Control	0.60	0.56								130	126			139
	Acetylcholine	0.47	2.55	32	38	99	198	0.655	302	104	76	288	98.3	94.9	129
	Angiotensin	0.18	4.76	34	43	70	114	0.861	132	18	14	464	99.7	92.4	151
	Norepinephrine	0.05	3.30	16	40	40	111	0.852	130	19	2	387	99.9	93.9	154
	Angiotensin	0.10	4.01	37	37	80	102	0.827	123	21	2	347	99.9	93.6	147
20.	Control	1.38	1.83	35	32	97	90	0.904	100	10	261	315	94.8	93.0	140
	Acetylcholine	0.30	3.99	32	36	81	131	0.762	172	41	53	539	98.9	89.5	116
	Norepinephrine	0.14	5.35	32	35	71	105	0.836	126	21	10	693	99.8	86.1	167
	Angiotensin	0.14	4.79	31	30	65	81	0.752	108	27	11	589	99.8	86.2	158
	Norepinephrine	0.09	5.07	23	25	51	69	0.720	96	27	5	613	99.9	83.3	163
21.	Control	0.55	0.80	34	29	114	110	0.783	140	30	130	166	97.4	96.0	145
	Acetylcholine	0.26	2.74	31	33	99	161	0.429	375	214	66	429	98.5	91.0	143
	Angiotensin	0.05	5.72	5	34	12	124	0.516	240	116	13	785	98.2	84.5	195
	Norepinephrine	0.02	4.50	5	35	13	105	0.655	160	55	2	620	99.7	88.1	187
	Angiotensin	0.06	5.50	13	35	34	103	0.624	165	62	8	689	99.6	86.4	188

* Additional abbreviation: $(T_{Na}/F_{Na}) \times 100$ = per cent of filtered sodium reabsorbed.
† Urine collected only from right kidney and no renal venous samples collected.
‡ Blood samples not collected for clearance determinations during preacetylcholine control periods.

10 minutes of adjustment to achieve a blood pressure similar to that present during the initial infusion. After collections were made during infusion of the second pressor, the same sequence was followed to return to infusion of the first pressor agent. The infusion of acetylcholine (40 μg per minute) was continued uninterrupted into the left renal artery. The results of these 5 studies are summarized in Table IV. Both angiotensin and norepinephrine decreased RPF below the levels present during vasodilatation alone, and both agents produced decreases in C_{PAH} in the control kidney. However, during the infusion of the pressor agents C_{PAH} was greater in the vasodilated kidney then in the control kidney. Norepinephrine resulted in increases in sodium excretion by the vasodilated kidneys and decreases in sodium excretion by control kidneys, responses qualitatively similar to those observed during the infusion of angiotensin. Also, the increased sodium excretion by the vasodilated kidneys during the infusion of norepinephrine was not necessarily associated with increased GFR (experiments 18 and 20, Table IV). However, in all but one study (experiment 20) the absolute rate of sodium excretion was greater, and the over-all fractional reabsorption of sodium was less during the infusion of angiotensin than during the infusion of norepinephrine. These small differences between the effects of angiotensin and norepinephrine on sodium excretion and reabsorption did not relate to differences in GFR. Thus, the infusion of equipressor amounts of angiotensin or norepinephrine resulted in qualitatively similar changes in hemodynamics and sodium excretion in the vasodilated kidneys.

Discussion

The present results agree with previous studies indicating that renal vasodilatation per se may increase sodium excretion and decrease the net tubular reabsorption of sodium (8, 14). In our study unilaterally increased renal plasma flow re-

sulting from three different vasodilators was accompanied by decreased tubular reabsorption of sodium. These observations strengthen the concept that it is the vasodilatation which results in diminished reabsorption of sodium and not some more direct effect of the infused agent on tubular transport (14). We have suggested previously that increased renal medullary blood flow may diminish the absolute reabsorption of sodium by the ascending limb of Henle's loop (4, 5), and Leyssac has suggested that angiotensin may diminish proximal tubular reabsorption of sodium (15). Although the effects have not been entirely predictable, angiotensin does produce natriuresis under some conditions (16–19). If diminished renal blood flow increased sodium reabsorption in Henle's loop or more distal portions of the nephron, then the vasoconstrictor effects of angiotensin could mask the effects that the agent could have to diminish proximal reabsorption by enhancing sodium reabsorption at a more distal site, and perhaps also by reducing GFR and the filtered load of sodium. If so, then induced renal vasodilatation could minimize the vascular effects of angiotensin and permit the agent to produce natriuresis as the result of diminished proximal reabsorption of sodium. To a large extent the present results are consistent with this view. In the presence of renal vasodilatation the infusion of angiotensin invariably was associated with natriuresis that in some cases was comparable to that associated with saline loading (2, 5).

This angiotensin-induced natriuresis was accompanied by a reduction in RPF and in most cases by a reduction in GFR. In nonvasodilated control kidneys the infusion of angiotensin usually produced decreased sodium excretion in the presence of lower plasma flows (as judged by the clearance of PAH) than were present simultaneously in the natriuretic vasodilated kidneys. It did not appear likely that vasodilatation permitted the natriuresis during the systemic infusion of angiotensin simply by maintaining a higher GFR and filtered load of sodium, since in 10 experiments GFR in control kidneys undergoing sodium retention was similar to or greater than GFR in the vasodilated natriuretic kidneys. Therefore, it appears that the maintenance of some critical level of blood flow was necessary to demonstrate the natriuretic effect of angiotensin. Even though the clearance of PAH during the infusion of angiotensin was greater in vasodilated than in control kidneys, this measurement, as well as total renal plasma flow and noncortical plasma flow, was reduced below the levels present during vasodilatation alone. Therefore, the additional natriuretic effect of angiotensin cannot be attributed to a further increase in any of these hemodynamic measurements. These observations make it unlikely that increased renal blood per se decreases the reabsorption of sodium as suggested previously (5, 14).

The present studies do not demonstrate that angiotensin exerts a direct effect to decrease the tubular reabsorption of sodium, and the results are more consistent with the view that it is the pressor effect of angiotensin that diminishes sodium reabsorption. In support of this conclusion are the present observations that angiotensin resulted in natriuresis only when given in pressor amounts, and that both angiotensin and norepinephrine produced qualitatively and quantitatively similar changes in renal hemodynamics and sodium excretion when given in equipressor amounts. However, since each of these pressor agents produced natriuresis only in the presence of induced renal vasodilatation, it is apparent that some critical level of renal blood flow or renal vascular resistance is necessary for the effect of increased arterial pressure to decrease the reabsorption of sodium. Since the natriuretic effect of the pressors was not associated with a further increase in hemodynamics in the vasodilated kidney, the natriuresis appears to be the result of the increased perfusion pressure per se. There is other evidence that increased renal perfusion pressure may increase sodium excretion (20–24), and that this effect of pressure is mediated through intrarenal mechanisms (20, 22). The present studies extend such observations and demonstrate that the natriuretic effect of increased arterial pressure is dependent upon prevention of the intense renal vasoconstriction usually associated with the infusion of angiotensin or norepinephrine, since vasoconstriction was minimized in the vasodilated kidneys.

The mechanism whereby increased renal perfusion pressure could decrease sodium reabsorption is unknown. The dependence of this effect of perfusion pressure on induced renal vasodilatation suggests that transmission of the increased perfu-

sion pressure to some sensitive portion of the renal vasculature may be responsible for this natriuretic effect. There is some evidence that proximal tubular reabsorption may relate in some direct manner to tubular distension (25). If so, then constriction of the lumen of the proximal tubule should decrease the reabsorption of sodium and water at that site. If the increased arterial pressure produced in our studies were transmitted to some extent to the postglomerular capillary, then capillary perfusion pressure would be increased, and as a result the cortical interstitial volume should increase. Such an increased interstitial volume could result in some degree of collapse of the tubule, especially when the flow into the tubule as judged by GFR was unchanged or decreased. The effect of vasodilatation alone to decrease sodium reabsorption could be explained by the same mechanism, since a reduction of precapillary resistance would allow a more complete transmission of the existing perfusion pressure to the capillary circulation. Confirmation or rejection of such a mechanism to account for these hemodynamic effects on sodium reabsorption will be dependent upon direct measurements of changes in interstitial volume, tubular distension, and reabsorption in response to hemodynamic changes such as those produced in the present studies.

It does not appear likely that the natriuresis observed in the present studies was due to some direct synergistic effects of the agents on tubular transport, since similar results were observed with combinations of angiotensin or norepinephrine and acetylcholine, bradykinin, or kallidin. Although the natriuretic effect of angiotensin quantitatively was slightly greater than that observed during equipressor infusions of norepinephrine, the effects of the two agents were qualitatively the same. Therefore, even though angiotensin may have a direct effect to decrease the tubular reabsorption of sodium, the present study does not permit such a conclusion. Laragh and his associates found striking differences in the natriuretic effects of angiotensin and norepinephrine in patients with cirrhosis who exhibited natriuretic responses to infusions of angiotensin (18), in contrast to the similar effects of the two agents observed in the present study. However, it is possible that subtle differences in the renal vasoconstriction produced by the agents could account for the different responses in the patients studied by these latter authors (18), and in the present study such a possible difference in the renal vascular effects of the two agents was minimized by the induced renal vasodilatation.

Summary

The combined effects of unilateral renal vasodilatation and angiotensin infusion on renal hemodynamics and sodium excretion and reabsorption were studied in anesthetized hydropenic dogs. Unilateral renal vasodilatation alone with either acetylcholine, bradykinin, or kallidin resulted in an ipsilateral increase in renal plasma flow and an ipsilateral decrease in net tubular reabsorption of sodium. The infusion of angiotensin or norepinephrine in the presence of unilateral renal vasodilatation resulted in a sustained marked increase in sodium excretion and decreased sodium reabsorption by the vasodilated kidney. These changes occurred in association with decreases in glomerular filtration rate, clearance of *p*-aminohippurate, renal plasma flow, and "noncortical" plasma flow. Sodium excretion usually decreased in control nonvasodilated kidneys during the infusion of angiotensin or norepinephrine, although glomerular filtration rate was often similar in the two kidneys. The clearance of *p*-aminohippurate, however, was always distinctly lower in the control nonvasodilated kidney.

These results are consistent with the view that the proper combination of two physiologically important variables, arterial pressure and renal vascular resistance, can effect large changes in the tubular reabsorption of sodium, probably through intrarenal mechanisms. We suggest, therefore, that changes in these two variables may be of major importance in the regulation of sodium excretion.

Acknowledgments

The authors are indebted to Susan Howard and Barbel Juergens for their assistance with these studies.

References

1. De Wardner, H. E., I. H. Mills, W. F. Clapham, and C. J. Hayter. Studies on the efferent mechanism of the sodium diuresis which follows the administration of intravenous saline in the dog. Clin. Sci. 1961, 21, 249.

2. Levinsky, N. G., and R. C. Lalone. The mechanism of sodium diuresis after saline infusion in the dog. J. clin. Invest. 1963, **42**, 1261.
3. Rector, F. C., Jr., G. Van Giesen, F. Kiil, and D. W. Seldin. Influence of expansion of extracellular volume on tubular reabsorption of sodium independent of changes in glomerular filtration rate and aldosterone activity. J. clin. Invest. 1964, **43**, 341.
4. Earley, L. E., and R. M. Friedler. Observations on the mechanism of decreased tubular reabsorption of sodium and water during saline loading. J. clin. Invest. 1964, **43**, 1928.
5. Earley, L. E., and R. M. Friedler. Changes in renal blood flow and possibly the intrarenal distribution of blood during the natriuresis accompanying saline loading in the dog. J. clin. Invest. 1965, **44**, 929.
6. Dirks, J. H., W. J. Cirksena, and R. W. Berliner. The effect of saline infusion on sodium reabsorption by the proximal tubule of the dog. J. clin. Invest. 1965, **44**, 1160.
7. Vander, A. J. Effects of acetylcholine, atrophine, and physostigmine on renal function in the dog. Amer. J. Physiol. 1964, **206**, 492.
8. Pinter, G. G., C. C. C. O'Morchoe, and R. S. Sikand. Effect of acetylcholine on urinary electrolyte excretion. Amer. J. Physiol. 1964, **207**, 979.
9. Williams, R. L., J. E. Pearson, Jr., and M. K. Carter. The saluretic effects of arecoline hydrochloride infused into the left renal artery of dogs. J. Pharmacol. exp. Ther. 1965, **147**, 32.
10. McDonald, R. H., Jr., L. I. Goldberg, J. L. McNay, and E. P. Tuttle, Jr. Effect of dopamine in man: augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow. J. clin. Invest. 1964, **43**, 1116.
11. Gombos, E. A., and T. H. Lee. Renal functional response to pyrogen induced renal hyperemia (abstract). Clin. Res. 1965, 13, 306.
12. Webster, M. E., and J. P. Gilmore. Influence of kallidin-10 on renal function. Amer. J. Physiol. 1964, **206**, 714.
13. Meyer, M. B., and L. I. Goldberg. Natriuretic effect of papaverine. Fed. Proc. 1965, **24**, 258.
14. Earley, L. E., and R. M. Friedler. Studies on the mechanism of natriuresis accompanying increased renal blood flow and its role in the renal response to extracellular volume expansion. J. clin. Invest. 1965, **44**, 1857.
15. Leyssac, P. P. The effect of partial clamping of the renal artery on pressures in the proximal and distal tubules and peritubular capillaries of the rat kidney. Acta physiol. scand. 1964, **62**, 449.
16. Hughes-Jones, N. C., G. W. Pickering, P. H. Sanderson, H. Scarborough, and J. Vandenbroucke. The nature of the action of renin and hypertension on renal function in the rabbit. J. Physiol. (Lond.) 1949, **109**, 288.
17. Corcoran, A. C., and F. Del Greco. Mechanisms of renin diuresis in dogs. Fed. Proc. 1955, **14**, 31.
18. Laragh, J. H., P. J. Cannon, C. J. Bentzel, A. M. Sicinski, and J. I. Meltzer. Angiotensin II, norepinephrine, and renal transport of electrolytes and water in normal man and in cirrhosis with ascites. J. clin. Invest. 1963, **42**, 1179.
19. Healy, J. K., C. Barcena, J. M. B. O'Connell, and G. E. Schreiner. Renal and pressor action of angiotensin in the normal dog. Amer. J. Physiol. 1965, **208**, 1093.
20. Selkurt, E. E. Effect of pulse pressure and mean arterial pressure modification on renal hemodynamics and electrolyte and water excretion. Circulation 1951, **4**, 541.
21. Tobian, L., K. Coffee, D. Ferreira, and J. Meuli. The effect of renal perfusion pressure on the net transport of sodium out of distal tubular urine as studied with the stop-flow technique. J. clin. Invest. 1964, **43**, 118.
22. Selkurt, E. E., I. Womack, and W. N. Dailey. Mechanisms of natriuresis and diuresis during elevated renal arterial pressure. Amer. J. Physiol. 1965, **209**, 95.
23. McDonald, S. J., and H. E. de Wardener. The relationship between the renal arterial perfusion pressure and the increase in sodium excretion which occurs during an infusion of saline. Nephron 1965, **2**, 1.
24. Handley, C. A., and J. H. Moyer. Unilateral renal adrenergic blockade and the renal response to vasopressor agents and to hemorrhage. J. Pharmacol. exp. Ther. 1954, **112**, 1.
25. Brunner, F. P., F. C. Rector, Jr., and D. W. Seldin. Regulation of proximal tubular fluid reabsorption as studied by stopped flow microperfusion in the rat kidney (abstract). J. clin. Invest. 1965, **44**, 1031.