THE RESPONSE TO THE ADMINISTRATION OF AN ISOTONIC SODIUM CHLORIDE–LACTATE SOLUTION IN PATIENTS WITH ESSENTIAL HYPERTENSION

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Many studies indicate that patients with essential hypertension have a greater natriuretic response to rapidly administered sodium chloride solutions than have normotensive individuals (1–7). However, in most instances other factors known to influence the rate of sodium excretion in the normal subject such as diet, posture, and time of day have not been rigidly controlled (8, 9). Dietary control is of particular importance in view of observations suggesting that patients with hypertension may habitually ingest more salt than do normotensive individuals (10–11). If this is indeed the case it might well be responsible for the enhanced response of the hypertensive patient to administered salt.

The present report is concerned with a comparison of the response of hypertensive and normotensive individuals to the intravenous administration of an "isotonic-balanced" salt solution under rigidly controlled conditions and at three different levels of dietary salt ingestion. The results indicate that patients with essential hypertension excrete the infused sodium load more rapidly than do normotensive individuals at each level of salt consumption.

METHODS

Four normal Caucasian males aged 29 to 36 and 6 Caucasian patients aged 24 to 63 with essential hypertension were studied. The patients were selected on the basis of their maintaining a resting diastolic blood pressure of at least 100 mm Hg while hospitalized and consuming a diet containing approximately 10 mEq of sodium daily. Five of the 6 subjects were observed in this manner for 13 to 47 days prior to study, while Patient 8 received the low salt diet for 8 days prior to study. No patient had congestive heart failure, although no. 5 had had a myocardial infarct 6 years earlier. All 6 had electrocardiographic evidence of left ventricular strain, but were free of gross cardiomegaly on radiographic examination. Three patients had a history of mild hemiparesis 3 months to 10 years before study; Patients 5 and 8 made complete recovery while Patient 9 had mild neurological residua. Ocular fundi varied from normal to Grade 2[1] arteriolar narrowing without hemorrhage, exudate or papilledema. Renal function (including endogenous creatinine clearance, phenolsulfonephthalein (PSP) excretion, intravenous pyelogram and concentration test) was normal except in Patients 9 and 10 who had modest reduction in creatinine clearance.

Three of the 4 normal subjects and 5 hypertensive patients were provided a diet containing 10 to 15 mEq of sodium daily (low salt diet). After equilibrium was established (i.e., a minimum of 4 days of dieting and 2 consecutive days during which time the 24 hour urinary sodium excretion did not exceed 15 mEq) the following two studies were done within a period of 3 days.

1. "Blank Day." The subject had his usual breakfast including 500 ml of water. At 8 a.m. he assumed the recumbent position and remained so until 3 p.m. except to void. From 10 a.m. to 2 p.m. each subject drank 100 ml of water hourly and ingested 5 g of carbohydrate each half hour. Spontaneously voided urine was collected at one-half hour intervals. Venous blood was collected at least twice (10 a.m. and 2 p.m.).

2. "Infusion Day." The protocol was essentially the same as on Blank Day except that 2,000 ml of a solution containing 130 mEq per L of sodium, 105 mEq per L of chloride and 25 mEq per L of lactate was administered intravenously from 10 to 11:30 a.m., and hourly drinking commenced at 12 noon. Venous blood samples were collected immediately prior to and at the end of the infusion period and again at 2 p.m. An additional normal subject (no. 4) and one hypertensive patient (no. 10) were studied as described for Infusion Day without a prior Blank Day.

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[1] The grading system employed is that recommended to the American Ophthalmological Society by the committee on Classification of Hypertensive Disease of the Retina: Wagener, H. P., Clay, G. E., and Gipner, J. F. Classification of retinal lesions in the presence of vascular hypertension. Trans. Amer. Ophthal. Soc. 1947, 45, 57.

TABLE I

Fluid and electrolyte excretion in subjects with normal blood pressure

Subject no. Age Blood pressure	Dietary Na	Without infusion							With infusion							
															Clearances	
		Time	Na	K	Cl	Solute	Flow	Creatinine clearance	Time	Na	K	Cl	Solute	Flow	Creatinine	Osmolar	Free water
			μEq/min	*μEq/min*	*μEq/min*	*μOsm/min*	*ml/min*	*ml/min*		*μEq/min*	*μEq/min*	*μEq/min*	*μOsm/min*	*ml/min*	*ml/min*	*ml/min*	*ml/min*
1	Low	8:30–10 a.m.	9.3	74	16	548	4.1	106	8:30–10 a.m.	4.7	72	15	503	3.1	131	1.8	1.3
31		10 –11:30	7.4	117	18	572	2.2	120	10 –11:30*	24	145	29	693	4.2	136	2.4	1.8
114/80		11:30–3 p.m.	7.5	74	14	468	1.9	122	11:30–3 p.m.	51	100	32	548	1.9	128	1.9	0
		11:30–12:30†	*9.1*	*108*	*17*	*528*	*2.2*	*122*	*1:30–2:30*	*57*	*96*	*33*	*536*	*1.8*	*132*	*1.9*	*−0.1*
	Medium	8:30–10 a.m.	406	96	367	1,305	5.5	127	8:30–10 a.m.	273	90	294	1,061	4.6	150	3.7	0.9
		10 –11:30	364	126	339	1,257	5.2	124	10 –11:30*	416	129	381	1,366	6.7	146	4.7	2.0
		11:30–3 p.m.	186	45	166	704	2.7	128	11:30–3 p.m.	280	61	243	894	3.9	144	3.1	0.8
		9:30–10:30	*439*	*127*	*397*	*1,402*	*3.5*	*128*	*10:30–11:30*	*460*	*134*	*399*	*1,443*	*8.4*	*146*	*5.0*	*3.4*
	High	8:30–10 a.m.	502	59	489	1,459	3.4	145	8:30–10 a.m.	533	69	508	1,582	6.8	149	5.5	3.3
		10 –11:30	422	89	400	1,306	3.7	134	10 –11:30	826	113	718	2,199	9.5	143	7.7	1.8
		11:30–3 p.m.	228	54	227	833	2.9	122	11:30–3 p.m.	461	57	420	1,278	4.0	137	4.5	−0.5
		9:30–10:30	*518*	*87*	*474*	*1,488*	*3.2*	*137*	*10:30–11:30*	*883*	*119*	*742*	*2,329*	*11.5*	*142*	*8.2*	*3.3*
2	Low	8:30–10 a.m.	32	126	34	852	1.5	156	8:30–10 a.m.	13	67	14	553	2.5	143	2.0	0.5
29		10 –11:30	33	126	49	914	3.6	149	10 –11:30*‡	33	142	36	730	4.8	156	2.6	2.2
122/80		11:30–3 p.m.	17	89	31	706	2.9	152	11:30–3 p.m.	73	112	31	666	2.7	156	2.4	0.3
		9 –10	*39*	*133*	*38*	*853*	*1.3*	*154*	*2 –3*	*88*	*83*	*27*	*608*	*1.9*	*166*	*2.5*	*−0.6*
	Medium	8:30–10 a.m.	267	110	246	1,067	3.1	162	8:30–10 a.m.	161	98	199	945	4.7	160	3.3	1.4
		10 –11:30	368	155	356	1,339	4.6	149	10 –11:30*‡	316	173	363	1,303	6.5	154	4.6	1.9
		11:30–3 p.m.	221	75	195	834	3.8	139	11:30–3 p.m.	267	117	253	1,018	11.3	144	3.6	7.7
		9:30–10:30	*402*	*148*	*358*	*1,377*	*3.5*	*157*	*10 –11*	*340*	*167*	*388*	*1,306*	*3.4*	*160*	*4.6*	*−1.2*

* A solution of 2,000 ml containing approximately 130 mEq/L of sodium, 105 mEq/L chloride and 25 mEq/L lactate was administered intravenously from 10 to 11:30 a.m. unless otherwise indicated.

† Italics indicate a 60-minute period of maximum rate of sodium excretion (two consecutive 30 minute periods were pooled).

‡ Infusion given 10:15 to 11:55 a.m.

TABLE I (*Continued*)

Subject no. Age Blood pressure	Dietary Na	Without infusion							With infusion						Clearances		
		Time	Na	K	Cl	Solute	Flow	Creatinine clearance	Time	Na	K	Cl	Solute	Flow	Creatinine	Osmolar	Free water
			μEq/min	*μEq/min*	*μEq/min*	*μOsm/min*	*ml/min*	*ml/min*		*μEq/min*	*μEq/min*	*μEq/min*	*μOsm/min*	*ml/min*	*ml/min*	*ml/min*	*ml/min*
	High	8:30–10 a.m.	512	101	532	1,742	2.9	161	8:30–10 a.m.	644	134	658	2,126	3.4	168	7.4	−4.0
		10 –11:30	629	149	640	1,993	3.6	148	10 –11:30*	446	142	461	1,653	3.3	146	5.8	−2.5
		11:30–3 p.m.	222	76	239	1,005	5.0	146	11:30–3 p.m.	329	100	265	1,216	5.4	151	4.3	1.1
		9:30–10:30	*731*	*128*	*738*	*2,223*	*3.5*	*156*	*9 –10*	*673*	*146*	*695*	*2,221*	*4.0*	*159*	*7.7*	*−3.7*
3	Low	8:30–10 a.m.	22	81	20	718	2.1	146	8:30–10 a.m.	47	98	30	712	1.5	170	2.5	−0.1
29		10 –11:30	25	103	23	695	1.6	139	10 –11:30*	33	162	28	697	3.6	155	2.5	1.1
120/78		11:30–3 p.m.	16	51	12	539	1.4	138	11:30–3 p.m.	108	106	45	715	2.6	153	2.5	0.1
		9:30–10:30	*30*	*102*	*25*	*702*	*1.4*	*140*	*1:30–2:30*	*136*	*90*	*47*	*722*	*2.2*	*158*	*2.6*	*−0.4*
	Medium	8:30–10 a.m.	167	70	156	938	4.4	167	8:30–10 a.m.	247	102	251	1,154	4.6	175	4.1	0.5
		10 –11:30	373	141	336	1,340	3.0	157	10 –11:30*	409	194	291	1,514	2.8	162	5.4	−2.6
		11:30–3 p.m.	209	84	207	888	3.1	153	11:30–3 p.m.	243	115	209	1,005	3.4	167	3.6	−0.2
		10 –11	*384*	*145*	*337*	*1,403*	*3.4*	*161*	*10 –11*	*446*	*184*	*416*	*1,562*	*2.8*	*160*	*5.6*	*−2.8*
	High	8:30–10 a.m.	335	42	323	1,323	5.1	173	8:30–10 a.m.	458	105	463	1,561	3.0	192	5.4	−2.4
		10 –11:30	377	93	283	1,329	3.5	155	10 –11:30*	593	129	539	1,052	3.4	182	3.7	−0.3
		11:30–3 p.m.	269	59	271	1,034	3.9	158	11:30–3 p.m.	329	82	304	1,122	4.4	175	4.0	0.4
		9:30–10:30	*453*	*67*	*299*	*1,464*	*3.0*	*162*	*10 –11*	*710*	*123*	*623*	*1,973*	*3.0*	*186*	*6.9*	*−3.9*
4	Low								9 –10 a.m.	16	118	36	660	2.6	194	2.4	0.2
36									10 –11:30*	33	134	47	504	4.4	144	1.8	2.6
112/68									11:30–3 p.m.	118	69	56	575	3.2	130	2.1	1.1
									2 –3	*147*	*58*	*58*	*598*	*3.2*	*132*	*2.2*	*1.0*

Three normal subjects and three hypertensive patients were similarly studied after equilibrium was established while taking the same 10 mEq sodium diet with approximately 35 mEq of sodium chloride (non-enteric coated tablets) added to each meal and again at bedtime for a total of 150 mEq sodium intake daily (medium salt diet). On both Blank Day and Infusion Day each subject ate his usual breakfast and 35 mEq of additional salt in tablet form. At the end of the Blank Day experimental period, the subjects were given sufficient food and sodium to maintain caloric intake and the 150 mEq daily quantity of sodium.

Three normal subjects and three hypertensive patients were similarly studied while they were taking approximately 300 mEq of sodium daily (high salt diet).

Blood pressure was determined at one-half hour intervals in the hypertensive patients during both experimental days at each dietary level, and less often in the normal subjects.

Serum and urine were analyzed for sodium, potassium, chloride, creatinine and total solute content by methods employed in this laboratory and previously described (12). Serum protein, blood hemoglobin concentration and hematocrit were also determined.

RESULTS

1. On Blank Day there was no significant difference between the normotensive and hypertensive subjects, taking the low sodium diet, in the quantities of sodium and chloride excreted from 10 a.m. to 3 p.m. In five of six instances, while provided with medium and high salt intakes, the hypertensive patients excreted more sodium and chloride than did the normal individuals from 10 a.m. to 3 p.m. (Tables I and II, Figure 1).

2. On Infusion Day the preinfusion rates of sodium excretion were no higher in the hypertensive than in the normal group at each dietary level of sodium ingestion. In fact, the hypertensive patients had slightly lower rates of sodium excretion prior to infusion while taking the medium salt diet (Tables I and II, Figure 1).

3. In each instance at all levels of salt intake, the hypertensive patient had a far greater natriuresis after intravenous salt loading than had the normal. The maximal rates of sodium excretion after salt loading occurred more promptly in the hypertensive patient at the low level of salt intake (Tables I and II, Figures 1 and 2).

4. By the morning after salt loading the hypertensive patients had excreted more sodium than had the normal subjects at each dietary level. This difference is attributed to the prompt response (10 a.m. to 3 p.m.) rather than to any continued difference in sodium excretion throughout the remainder of the day (Table III).

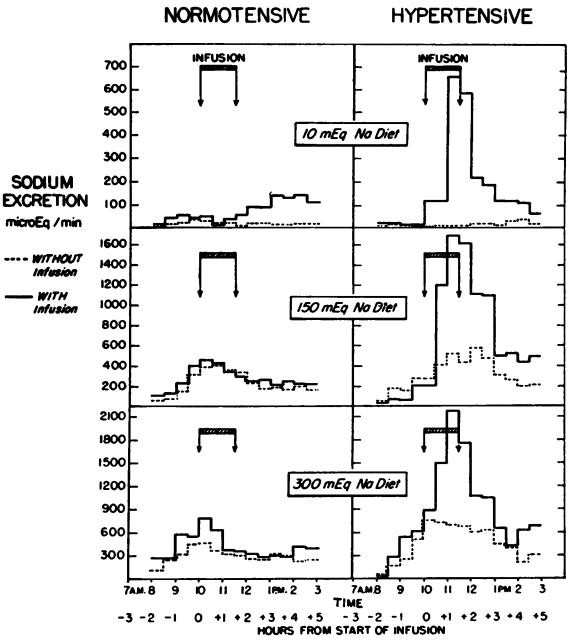

FIG. 1. SODIUM EXCRETION WITH AND WITHOUT INFUSION IN ONE NORMOTENSIVE (SUBJECT 3) AND ONE HYPERTENSIVE (SUBJECT 6) WHILE PROVIDED WITH LOW, MEDIUM AND HIGH SALT DIETS. The ordinate scale for the 150 mEq and 300 mEq sodium diets is double and triple, respectively, the scale for the 10 mEq sodium diet.

5. Endogenous creatinine clearance generally increased in both normal and hypertensive subjects when dietary salt was increased from low to medium salt intake levels. The change in clearance was less conspicuous between the medium and high salt intakes. It is also apparent that the 8:30 to 10 a.m. endogenous creatinine clearance often varied significantly in the two studies carried out in a single individual on different days. The differences in natriuretic response observed were not consistently or uniformly correlated with preinfusion differences in endogenous creatinine clearance or with change in clearance following infusion (Tables I and II).

6. In nine experiments in patients with hypertension, the infusion of sodium chloride-lactate solution was not associated with a rise in blood pressure. In the remaining two experiments a rise in diastolic blood pressure of 10 to 12 mm Hg was observed following infusion.

TABLE II

Fluid and electrolyte excretion in subjects with hypertension

Subject no. Age Blood pressure	Dietary Na	Without infusion							With infusion						Clearances		
		Time	Na	K	Cl	Solute	Flow	Creatinine clearance	Time	Na	K	Cl	Solute	Flow	Creatinine	Osmolar	Free water
			μEq/min	*μEq/min*	*μEq/min*	*μOsm/min*	*ml/min*	*ml/min*		*μEq/min*	*μEq/min*	*μEq/min*	*μOsm/min*	*ml/min*	*ml/min*	*ml/min*	*ml/min*
5	Low	8:30–10 a.m.	1.5	32	7.3	359	1.0	94	8:30–10 a.m.	9	31	14	298	2.0	87	1.0	1.0
63		10 –11:30	18	84	30	591	1.9	89	10 –11:30*	345	117	288	1,186	9.4	94	4.1	5.3
160/102		11:30–3 p.m.	35	50	28	409	1.9	99	11:30–3 p.m.	479	88	409	1,231	5.4	115	4.3	1.1
		12:30–1:30†	*45*	*55*	*34*	*452*	*1.7*	*90*	*11:30–12:30*	*683*	*130*	*599*	*1,409*	*9.2*	*93*	*4.9*	*4.3*
	Medium	8:30–10 a.m.	114	55	136	606	4.0	115	8:30–10 a.m.	104	43	127	565	2.2	109	2.0	0.2
		10 –11:30	472	90	427	1,465	4.4	118	10 –11:30*	634	72	520	1,598	10.3	111	5.6	4.7
		11:30–3 p.m.	289	49	255	839	3.3	97	11:30–3 p.m.	778	66	659	1,795	6.5	109	6.3	0.2
		10 –11	*506*	*96*	*458*	*1,632*	*5.1*	*113*	*11 –12*	*1,133*	*90*	*920*	*2,548*	*15.0*	*110*	*8.9*	*6.1*
	High	8:30–10 a.m.	170	45	214	666	1.0	124	8:30–10 a.m.	189	42	231	756	1.4	114	2.6	−1.2
		10 –11:30	499	62	472	1,319	4.5	115	10 –11:30*	1,218	79	1,071	2,780	12.5	117	9.8	2.7
		11:30–3 p.m.	399	42	360	1,035	4.5	107	11:30–3 p.m.	1,037	72	943	2,411	9.1	103	8.5	0.6
		10:30–11:30	*525*	*66*	*485*	*1,353*	*5.2*	*111*	*11 –12*	*2,037*	*112*	*1,698*	*4,358*	*20.8*	*116*	*15.3*	*5.5*
6	Low	8:30–10 a.m.	8	45	11	503	2.1	94	8:30–10 a.m.	9	47	12	488	1.8	108	1.7	0.1
44		10 –11:30	6	56	9	439	1.2	99	10 –11:30*	294	100	237	1,186	7.7	123	4.1	3.6
174/112		11:30–3 p.m.	15	64	19	464	1.3	100	11:30–3 p.m.	201	71	165	863	2.9	118	3.0	−0.1
		1:30–2:30	*29*	*77*	*25*	*581*	*1.9*	*108*	*11 –12*	*621*	*140*	*520*	*1,967*	*11.9*	*138*	*6.9*	*5.0*
	Medium	8:30–10 a.m.	201	45	226	938	1.3	131	8:30–10 a.m.	105	44	110	672	0.8	141	2.3	−1.5
		10 –11:30	387	61	384	1,303	2.4	123	10 –11:30*	1,026	92	959	2,685	9.3	141	9.3	0
		11:30–3 p.m.	339	67	349	1,153	2.9	112	11:30–3 p.m.	793	81	756	2,063	5.7	123	7.2	−1.5
		11 –12	*468*	*88*	*472*	*1,560*	*3.7*	*122*	*11 –12*	*1,650*	*145*	*1,545*	*3,935*	*15.1*	*133*	*13.7*	*1.4*
	High	8:30–10 a.m.	317	69	320	1,176	1.6	143	8:30–10 a.m.	474	69	481	1,582	2.6	137	5.4	−2.8
		10 –11:30	723	90	702	1,989	2.5	132	10 –11:30*	1,504	130	2,050	3,609	12.5	131	12.5	0
		11:30–3 p.m.	475	60	475	1,383	2.1	121	11:30–3 p.m.	887	68	852	2,476	6.2	117	8.7	−2.5
		10 –11	*737*	*92*	*717*	*2,013*	*2.6*	*135*	*11 –12*	*1,950*	*156*	*2,787*	*4,441*	*17.5*	*128*	*15.5*	*2.0*

*† See footnotes to Table I.

TABLE II (*Continued*)

Subject no. Age Blood pressure	Dietary Na	Without infusion							With infusion						Clearances		
		Time	Na	K	Cl	Solute	Flow	Creatinine clearance	Time	Na	K	Cl	Solute	Flow	Creatinine	Osmolar	Free water
			μEq/min	*μEq/min*	*μEq/min*	*μOsm/min*	*ml/min*	*ml/min*		*μEq/min*	*μEq/min*	*μEq/min*	*μOsm/min*	*ml/min*	*ml/min*	*ml/min*	*ml/min*
7	Low	8 –10:30 a.m.	11	53	23	473	3.3	128	9 –10 a.m.	20	80	43	626	3.7	131	2.2	1.5
24		10:30–11:30	12	42	23	439	2.7	107	10 –11:30*	546	151	493	1,822	11.1	133	6.6	4.5
172/120		11:30–3 p.m.	29	38	38	423	2.0	103	11:30–2:30 p.m.	443	84	352	1,258	4.5	113	4.5	0
		1:30–3 p.m.	*36*	*37*	*44*	*413*	*1.5*	*103*	*11 –12*	*1,013*	*163*	*826*	*2,658*	*13.7*	*133*	*9.6*	*4.1*
8	Medium	8:30–10 a.m.	186	57	221	896	1.5	101	8:30–10 a.m.	68	56	84	665	0.9	116	2.4	−1.5
62		10 –11:30	195	71	232	893	2.1	94	10 –11:30*	470	92	463	1,537	5.3	106	5.5	−0.2
182/104		11:30–3 p.m.	213	57	246	915	2.7	91	11:30–3 p.m.	655	79	622	1,725	5.9	104	6.2	−0.3
		1:30–2:30	*285*	*59*	*274*	*1,095*	*3.3*	*103*	*11 –12*	*812*	*119*	*788*	*2,163*	*10.0*	*105*	*7.7*	*2.3*
	High	8:30–10 a.m.	234	57	272	971	1.2	111	8:30–10 a.m.	523	80	356	1,211	1.6	124	4.3	−2.7
		10 –11:30	272	62	301	1,004	1.3	99	10 –11:30*	1,118	167	705	1,869	4.6	111	6.6	−2.0
		11:30–3 p.m.	465	68	470	1,263	2.4	103	11:30–3 p.m.	1,274	121	803	1,984	6.4	107	7.1	−0.7
		2 –3	*515*	*61*	*503*	*1,406*	*2.9*	*99*	*11 –12*	*1,435*	*241*	*907*	*2,244*	*7.8*	*108*	*7.9*	*−0.1*
9	Low	8:30–10 a.m.	18	2	12	465	5.9	75	8:30–10 a.m.	95	105	78	747	10.2	86	2.6	7.6
38		10 –11:30	10	2	12	414	3.8	69	10 –11:30*	847	198	697	2,184	12.2	85	7.1	5.1
230/154		11:30–2:30 p.m.	24	2	28	406	3.2	69	11:30–2:30 p.m.	546	117	427	1,487	5.7	80	5.1	0.6
		1:30–2:30	*31*	*3*	*33*	*395*	*2.5*	*69*	*11 –12*	*1,212*	*205*	*1,042*	*2,982*	*14.8*	*88*	*10.2*	*4.6*
10	Low								8:30–10 a.m.	70	94	105	649	3.1	60	2.3	0.8
44									10 –11:30*	639	184	614	1,924	7.7	62	6.8	0.9
214/136									11:30–3 p.m.	485	98	446	1,407	5.8	59	5.0	0.8
									11 –12	*1,003*	*201*	*953*	*2,266*	*12.0*	*63*	*8.1*	*3.9*

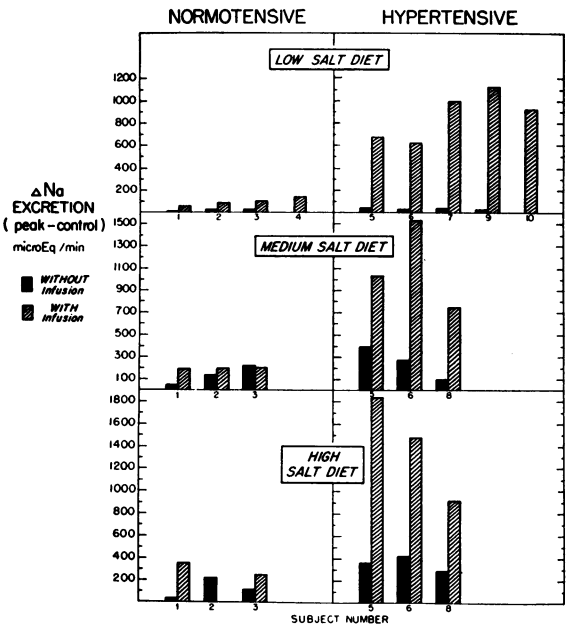

FIG. 2. THE DIFFERENCE IN THE RATE OF SODIUM EXCRETION BETWEEN THE 60 MINUTE PERIOD OF MAXIMUM NATRIURESIS AFTER 10 A.M. AND THE MEAN SODIUM EXCRETION BETWEEN 8:30 AND 10 A.M. (While on a high salt diet, Subject 2 had a maximal natriuresis prior to the infusion period.)

7. Potassium excretion varied considerably but there was no consistent difference between the hypertensive and normotensive subjects (Tables I and II).

8. On Infusion Days urine flow and free water clearance (as well as osmolar clearance) were greater in the hypertensive patients than in the normal subjects.

TABLE III

Sodium excretion during and after infusion*

	I 10 a.m.–3 p.m.		II 3 p.m.–7 a.m.		III(I+II) 10 a.m.–7 a.m.	
	Normo-tensive	Hyper-tensive	Normo-tensive	Hyper-tensive	Normo-tensive	Hyper-tensive
I. Low salt diet	18	131	24	41	42	172
	26	72	48	22	74	94
	13	185		60		245
	28	158		68		226
II. Medium salt diet	97	211		168		379
	83	260	186	138	269	398
	87	179	183	151	270	330
III. High salt diet	171	327	238	634	409	961
	109	322	336	222	445	544
	122	367	265		387	

* Total number of milliequivalents excreted in each time interval.

9. Serum concentration of sodium and chloride did not change significantly (− 1 to + 3 mEq per L) following the infusion of the sodium chloride-lactate solution. A small decrease in hematocrit (1 to 4 points) and total protein concentration (0.2 to 1.1 g per 100 ml) was observed following infusion.

DISCUSSION

The present study confirms other observations that patients with essential hypertension have a greater natriuretic response to administered salt solution than have normal individuals. In addition it establishes the fact that this difference in sodium excretion is short-lived and is not due to differences in dietary ingestion of salt prior to the test. Indeed, the data demonstrate that the exaggerated natriuresis of the hypertensive individual is apparent at all levels of salt intake ranging from 10 to 300 mEq daily. Furthermore, the study suggests that the difference in natriuretic response is probably not due to an alteration in diurnal rhythm. Thus, on Blank Days on the low salt diet, the normal and the hypertensive subjects excreted comparable quantities of sodium. The present data do not provide final proof on this point since the change in sodium excretion (peak minus control) on Blank Days was greater in the patients with hypertension than in the normal subjects. This difference seems to be related primarily to a generally lower control (8:30 to 10 a.m.) rate of sodium excretion in the hypertensive subjects on Blank Days, compared with the normal individuals, rather than to a consistently higher peak excretory rate for sodium. That this may have been fortuitous is perhaps suggested by the fact that the preinfusion values on Infusion Days while taking the low salt diet do not bear out this difference in control values. Clearly, more studies are required to resolve the role of diurnal rhythm with complete certainty. That the hypertensive subject excreted more sodium than did the normal individual on Blank Days at medium and high dietary levels is probably due to the fact that added salt was taken on these days at breakfast time and in effect constituted a small but effective "salt load." In addition, the present study makes it quite clear that the exaggerated natriuretic response is not due to a difference in baseline rates of sodium excretion

prior to infusion. Finally, the infusate was such that serum sodium concentration was not changed significantly during any experiment, thus precluding the possibility that the exaggerated natriuresis may be related to a peculiarly distorted response to hypertonic salt solutions in patients with hypertension.

While the present study documents the existence of abnormal sodium excretion in hypertension under controlled conditions, the data do not provide an understanding of the mechanisms involved. In these studies, as in others, in which there is no consistent relationship between endogenous creatinine clearance (or inulin clearance) and sodium excretion, it is virtually impossible to establish or exclude the importance of small but significant changes in glomerular filtration rate in determining differences in sodium excretion. From the present studies it would appear that the exaggerated natriuretic response is not clearly attributable to increased glomerular filtration rate either in the basal period or in response to salt administration. Consequently, it seems reasonable to focus attention on the renal tubular handling of sodium in patients with hypertension. The possibility exists that the renal tubular cell itself is abnormal or that a normal tubular cell is responding normally to abnormal influences or to stimuli that are abnormally mediated. While a specific tubular "defect" cannot be excluded, there is little evidence in support of this concept (7). Among the variety of known and unknown extrarenal factors that might influence renal tubular handling of sodium in the hypertensive patient are hormonal factors (e.g., adrenocortical and adrenomedullary), neurogenic factors and intrarenal circulatory phenomena (8). There is little direct evidence to support the causal role of any of these at the present time. The amount of sodium in the body, perhaps as expressed in terms of "effective" extracellular fluid volume, seems to be an important determinant of sodium excretion in the normal individual (8). How the kidney is made aware of changes in this factor is not at all clear. There are data which suggest increased total body sodium as well as increased extracellular fluid volume in patients with essential hypertension, although other data are not in accord with these findings (13–17). Nonetheless, no causal relationship between alterations in extracellular volume or body sodium content and the observed exaggerated natriuretic response to administered sodium seems warranted by the data at this time. The present study does not clarify the relationship of the disturbances in sodium excretion to other aspects of the condition called "essential hypertension," including the elevation of blood pressure.

SUMMARY AND CONCLUSIONS

1. The natriuretic response to the infusion of an isotonic solution of sodium chloride-lactate was studied in four normal subjects and in six patients with essential hypertension, under conditions rigidly controlled in respect to the amount of sodium ingested, posture, and time of day.

2. At each of three levels of daily sodium ingestion (10, 150 and 300 mEq) the patients with hypertension had a far greater natriuretic response to administered sodium than had the normal individuals.

3. Without infusion, at the low salt dietary level, there was no difference in the quantity of sodium excreted between normal subjects and patients with hypertension, suggesting that variations in basic diurnal rhythm probably do not account for the enhanced rate of sodium excretion.

4. The exaggerated natriuresis is not attributable to differences in preinfusion rates of sodium excretion or to greater increase in serum sodium concentration. In addition, the difference in natriuresis following infusion between the hypertensive and normotensive subjects is not associated with clearly consistent differences in endogenous creatinine clearance or further augmentation in blood pressure.

5. The "abnormal" response to salt administration in patients with essential hypertension remains unexplained.

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