Hemodynamic Effects of Dietary Sodium in Man

A Preliminary Report

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SUMMARY   The effect of dietary sodium manipulation was studied in 27 normal subjects and 19 patients with borderline hypertension. Sodium-loading caused an increase in blood pressure (BP) in 14 of 19 borderline hypertensive patients but in only 4 of 27 normal subjects (X^2 = 13.85, $p < 0.01$). In the normal subjects, a 10 mEq sodium diet resulted in a fall in supine mean blood pressure (MBP) of 4.3% after 4 days ($p < 0.05$). Cardiac index (CI) measured by echocardiography fell by 4.0%, while total peripheral resistance (TPR) remained unchanged. After the subjects had followed a 200 mEq sodium diet for 4 days, CI rose 6.9%, TPR fell 13%, and MBP fell 3.9%. Six normal subjects also received a 400 mEq sodium diet, which resulted in a 16% increase in MAP ($p < 0.01$). This was accompanied by an 11.1% increase in CI and an 11.5% increase in TPR. When subjected to sodium depletion, the 19 hypertensive subjects displayed a similar 4.7% fall in MBP ($p < 0.01$), a 14.1% fall in CI ($p < 0.05$) and a 17.1% increase in TPR. The hypertensive patients varied in their response to sodium repletion, 14 displayed a rise in diastolic blood pressure (DBP) (average 8.4%, $p < 0.01$) when receiving a 200 mEq sodium diet, while five displayed a fall (average: 13.0%). Those individuals whose DBP fell with sodium repletion had a fall in TPR of 20.5% ($p < 0.05$) and rise in CI of 14.3% ($p < 0.025$) similar to the changes seen in normal subjects. Those displaying a rise in DBP usually had a rise in CI (9 patients, average rise 20.9%, $p < 0.05$) while TPR fell 24.5%. The other five patients whose BP rose with salt repletion (10.3%) displayed a 21.9% rise in TPR and a 14.9% fall in CI. We conclude that many patients with borderline hypertension differ from normal subjects by displaying a BP increase due to a disproportionate rise in CI and an inadequate fall in TPR in response to an acute increase in dietary sodium.
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Key Words   •   hemodynamics   •   hypertension   •   sodium

A LARGE body of experimental and clinical evidence links dietary sodium with hypertension. Epidemiologic studies have shown that the frequency with which hypertension is found in a population rises in relation to the quantity of habitually used sodium by that population.[1-3] However, the majority of individuals, about 60%, remain normotensive even in those populations that consume the highest amounts of sodium.[3] This suggests that some individuals will respond to dietary sodium intake with an increase in blood pressure (BP) while others are relatively resistant to the pro-hypertensive effects of sodium. Indeed, Dahl et al.[4] have been able,

through selective inbreeding, to produce genetically salt-sensitive and salt-resistant strains of rats.

At present, other than through the clue provided by a positive family history, there are no ways to identify individuals with potentially salt-sensitive hypertension who might benefit from early dietary counseling. The present study was initiated to measure the hemodynamic response to dietary sodium of normal subjects and of patients with borderline hypertension as a possible means of identifying the salt-sensitive individual.

Methods

The protocol for this study was approved by the Patient Participation Committee of the University of Tennessee Center for the Health Sciences. All participants gave their informed consent.

The subjects were 27 normal volunteers whose average age was 28.8 years, with a range of 22 to 44 years. Nineteen of the subjects were male, eight female; 23 were white and four black.

Nineteen patients with borderline hypertension were also studied, i.e., their DBP was found to be above 90 mm Hg on at least three outpatient visits, falling to levels beneath 90 mm Hg at other times. These patients ranged in age between 16 and 51 years, for an average age of 27. Seventeen were male, two were female; 18 were white and one black.

All subjects were admitted to the Clinical Research Center of the University of Tennessee for interview, physical examination, and clinical laboratory studies that consisted of a complete blood cell count, urinalysis, serum creatinine, endogenous creatinine clearance, blood sugar and serum sodium, potassium, chloride, and bicarbonate.

To avoid the effects of hospitalization on BP, all participants went about their normal activities throughout the study. They returned three times a day for meals and for measurement of weight and BP. The latter was measured in triplicate, with an Arteriosonde, after 5 minutes of rest in the supine position, followed by 2 minutes in the standing position and then measurement.

Plasma renin activity, plasma aldosterone concentration, and 24-hour urinary excretion of sodium, potassium, and creatinine were measured on the first day of the study and at the end of each 4-day metabolic balance period. Plasma volume and hemodynamic studies were performed on the same days. Plasma volume was measured by an indicator dilution technique using Evan's blue dye. Plasma renin activity was measured by radioimmunoassay with incubation at pH 5.7.[5] Plasma aldosterone was also measured by immunoassay.[6] Urinary sodium and potassium were measured with a flame photometer. After measurements had been made while the subjects were following their usual diet, the subjects were placed on a diet calculated to contain 10 mEq sodium and 60 mEq potassium and all measurements repeated on the morning of the fifth day. Urine sodium at this time suggested that the actual daily sodium intake was approximately 20 mEq. Oral sodium intake was then increased to 200 mEq daily and measurements again repeated on the morning of the tenth day. The first 10 normal subjects participating in the study received the high and low salt diets in random order until it was established that the order of administration did not appear to make a difference in the results.

Six of the normal subjects were studied during a second high dietary salt period. After receiving a diet containing 400 mEq sodium and 60 mEq potassium for 4 days, the usual hemodynamic and metabolic studies were repeated.

Echocardiograms were obtained with a Smith-Kline Instruments Ekoline 20A M-mode cinegraph as described in detail elsewhere.[7] Each subject remained at rest for 30 minutes and measurement of heart rate and BP repeated until stable. Measurements were made by two observers who were not aware of the subject's dietary state. Systolic and diastolic volumes were calculated using the regression equation derived by Meyer et al.[8] Stroke volume was determined by subtracting systolic from diastolic volumes. Cardiac

output was calculated as the product of simultaneous heart rate and stroke volume averaged over 10 seconds and total peripheral resistance calculated from the Frank formula: $R(dyne\ cm^{-5}\ sec) = $ mean arterial pressure (mm Hg) $\times$ 1330/cardiac output (ml/sec), using BP measurements made simultaneously with the echocardiograms.

In separate experiments we have analyzed our method for reproducibility. We studied 53 subjects with normal ventricles after 30 minutes of rest in the supine position on two separate days of ad libitum diet. At the time of each study, duplicate measurements were made over a 20-minute period. The average variation of cardiac outputs calculated by this method was 11.6%. The accuracy and reproducibility of echographic measurement of left ventricular volume have been examined in several studies.[7] Linhart and his colleagues[9] have concluded that echographic measurements are particularly useful for following changes in volume with an intervention where each subject serves as his or her own control.

Data were tested for significance by the chi-square test or by analysis of variance, taking into account repeated measures. A Newman-Keul's *a posteriori* test was used to determine where differences lie.[10] All results are expressed as mean ± standard error.

Results

Effects of sodium depletion and repletion in the first 10 normal subjects are shown in figure 1. These 10 underwent daily echocardiographic study during the period of dietary sodium repletion. Salt depletion resulted in a reduced weight ($p < 0.001$) and heart size ($p < 0.025$). There was no significant change in cardiac index, total peripheral resistance, or mean BP. Plasma renin activity and plasma aldosterone concentration became significantly higher ($p < 0.005$). With sodium repletion, left ventricular dimensions became significantly larger ($p < 0.025$); weight rose significantly. Cardiac index rose, peripheral resistance changed very little, and mean arterial pressure (MAP) was even lower than it was during sodium depletion. The order of administration of the diets did not affect the response. All subjects studied later received the low salt diet before the period of sodium-loading, and echocardiographic studies were only recorded in the control period and on the last day of each metabolic diet.

The resting MAP of the normal subjects was significantly lower than that of the borderline hypertensives (82 ± 1.0 versus 94 ± 2.8 mm Hg, $p < 0.05$). The normal subjects showed significant changes in weight, cardiac dimensions, serum and urine sodium, plasma renin activity, and plasma aldosterone concentration among the three dietary states (table 1). The MAP fell slightly in 15 subjects during sodium restriction. Average MAP was again lowest during the high salt state. Only four of the 27 normal subjects displayed a slight BP rise during sodium repletion. The 10 subjects with and the 17 without a family history of hypertension were

analyzed separately and no significant differences found.

Six normal subjects participated in the study for an additional 4 days, during which time they received 400 mEq of sodium and 60 mEq of potassium in the diet (table 2). This diet was associated with a rise of MAP to 82.8 ± 3.3 mm Hg, significantly higher than when either 10 or 200 mEq diets were followed ($p < 0.01$). Although this elevation was associated with an increase in both cardiac index (11.1%) and peripheral resistance (11.5%), the latter changes were not significant. Serum and urine sodium concentrations were higher ($p < 0.05$ and < 0.01) while plasma renin activity was significantly lower ($p < 0.05$) than values obtained while the subjects followed the other diets.

Analysis of the results obtained in 19 subjects with borderline hypertension (table 3) showed that weight, serum, and urine sodium, plasma renin activity, and aldosterone concentration changed significantly with diet. The MAP fell insignificantly in 11 of 19 subjects during salt restriction. Cardiac index, stroke volume, and end diastolic volume fell significantly during salt

restriction. Although all three values rose with sodium repletion, only the increase in end diastolic volume reached statistical significance.

In contrast to the response of the normal subjects, 14 of the 19 patients with borderline hypertension displayed an increase in MAP and DBP ($p < 0.01$) during sodium repletion (fig. 2). Chi-square testing showed that they differed significantly from the normal subjects in this respect ($X^2 = 13.85$, $p < 0.01$). Those salt-resistant subjects who failed to show this increase in pressure had significantly greater urinary potassium excretion during each of the three diets than those who did (table 4). Serum potassium levels were also invariably higher in this group than in the other groups of patients.

Examination of the hemodynamic mechanism of the salt-induced BP elevation in these 14 patients (fig. 3) disclosed that nine had an increase in cardiac index ($p < 0.05$). Although resistance fell in eight of the nine patients, the change was not significant. This group also showed the greatest fall in DBP during sodium restriction (fig. 2). The other five salt-sensitive patients showed an increase in peripheral resistance and a fall in cardiac index ($p < 0.05$) during salt-loading (fig. 4).

Supine and upright plasma renin activity and plasma aldosterone concentration did not differ significantly among the groups on any of the diets and were highest on the low salt diet ($p < 0.01$).

Analysis of the 46 normotensive and borderline hypertensive patients, as a single group, to assess the common response to the changes in dietary sodium,
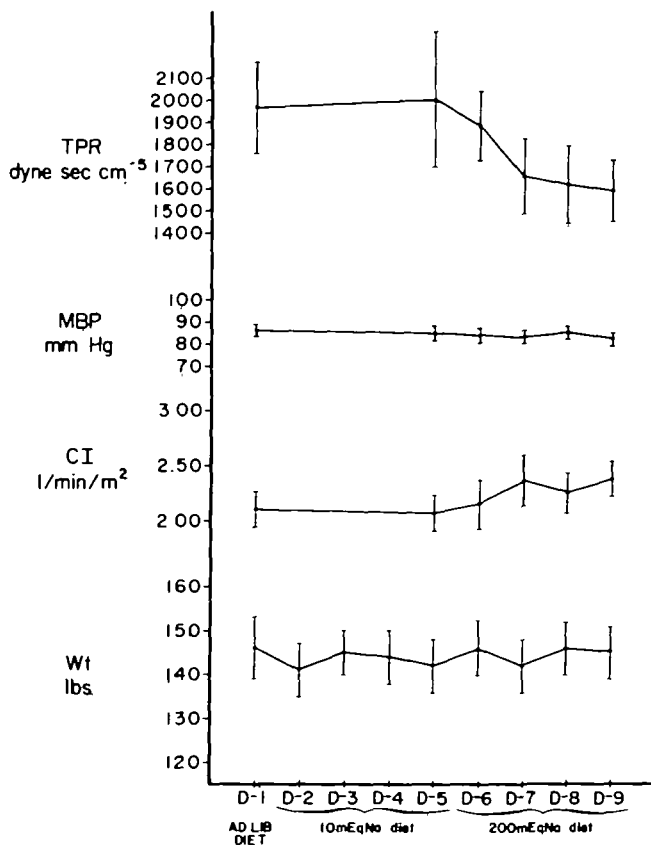

FIGURE 1. *Daily changes in total peripheral resistance (TPR), cardiac index (CI), mean arterial blood pressure (MBP) and body weight (Wt) during the transition from a 10 mEq sodium (Na) diet to a 200 mEq sodium diet. Vertical bars represent standard error.*
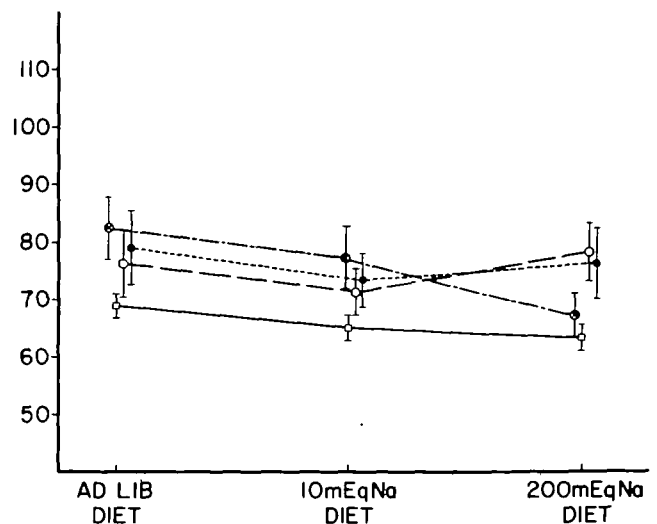

FIGURE 2. *Changes in diastolic blood pressure (mm Hg) in 27 normal subjects and 19 patients with labile hypertension during ad lib, 10 mEq sodium (Na) and 200 mEq sodium diets. During the 200 mEq sodium state, blood pressure rose in 14 of 19 labile hypertensive patients but in only four of 27 normal subjects. Open squares = normal subjects; open circle with black dot = salt-resistant hypertensives; open circle = salt-sensitive hypertensive output responders; black circle = salt-sensitive, hypertensive resistance responders.*
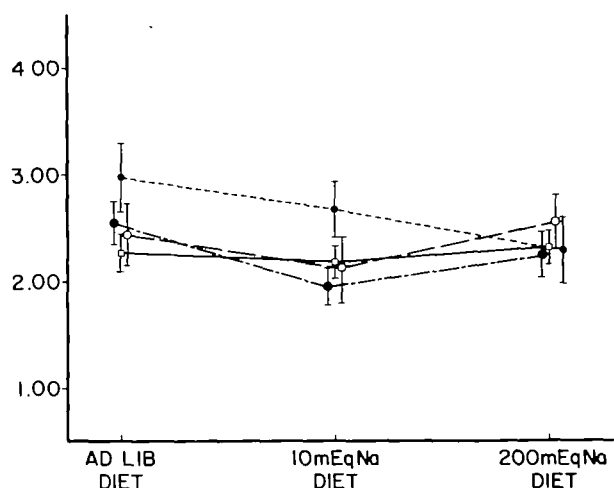
FIGURE 3. *Changes in cardiac index (1/min/M²) during ad lib, 10 mEq, and 200 mEq sodium diets. During sodium-loading, cardiac index rises in all labile hypertensive subjects with the exception of five patients with labile hypertension who have an increase in total peripheral resistance. Open square = normal subjects; open circle with black dot = salt-sensitive hypertensives; open circle = hypertensive output responders; black circle = hypertensive resistance responders.*

TABLE 1. *Hemodynamic Effects of Dietary Sodium in 27 Normal Subjects (mean ± SE)*

Variable	Ad lib	10 mEq sodium	200 mEq sodium
Weight (kg)	68.62 ± 2.9	66.5 ± 2.8	68.1 ± 2.8
		$p < 0.01$ $p < 0.01$	
Mean blood pressure (mm Hg)	82.0 ± 1.9	78.5 ± 2.1	75.4 ± 2.1
		$p < 0.01$	
Diastolic blood pressure (mm Hg)	67.1 ± 2.2	60.7 ± 1.7	59.6 ± 2.0
Plasma volume (1)	3.8 ± 0.4	3.6 ± 0.3	3.5 ± 0.2
Cardiac index (1/min/M²)	2.26 ± 0.16	2.17 ± 0.14	2.32 ± 0.14
Total peripheral resistance (dyne sec cm⁻⁵)	1836.6 ± 176.6	1834.9 ± 160.3	1596.7 ± 122.8
Heart rate	63 ± 2.0	63 ± 2.1	61 ± 2.4
End diastolic volume (ml)	110.8 ± 5.8	103.3 ± 6.1	112.5 ± 5.7
		$p < 0.05$ $p < 0.05$	
End systolic volume (ml)	44.3 ± 2.8	39.3 ± 2.9	41.8 ± 2.3
		$p < 0.05$ $p < 0.05$	
Stroke volume (ml)	66.7 ± 4.1	63.1 ± 4.1	70.9 ± 4.0
Ejection fraction	60.3 ± 1.7	61.6 ± 1.7	62.6 ± 1.1
Urine sodium (mEq/24 hr)	167.1 ± 24.1	24.2 ± 3.5	170.2 ± 15.3
		$p < 0.01$ $p < 0.01$	
Urine potassium (mEq/24 hr)	47.3 ± 7.6	51.0 ± 12.8	45.1 ± 7.4
Serum:			
Creatinine (mg/dl)	1.12 ± 0.72	1.15 ± 0.36	1.09 ± 0.49
Sodium (mEq/1)	139.4 ± 0.8	137.8 ± 0.6	140.5 ± 0.4
		$p < 0.05$ $p < 0.01$	
Potassium (mEq/1)	3.81 ± 0.06	3.74 ± 0.06	3.83 ± 0.06
Supine:			
Plasma renin activity (ng/ml/hr)	1.9 ± 0.8	3.3 ± 0.5	0.7 ± 0.08
		$p < 0.05$	
Aldosterone (ng/dl)	5.8 ± 0.97	16.7 ± 2.79	5.7 ± 1.20
		$p < 0.01$ $p < 0.01$	

showed the following statistically significant results: body weight changed between the states ($p < 0.01$). Heart rate and hematocrit were lowest during the high salt state ($p < 0.01$). MAP was highest during the control state ($p < 0.01$). Left ventricular dimensions were smallest during the low salt diet ($p < 0.01$), as was stroke volume ($p < 0.05$), confirming our earlier observations.[7] Serum and urine sodium concentrations were lowest, ($p < 0.01$) and plasma renin activity and aldosterone highest ($p < 0.01$) during the low salt state.

Discussion

Our studies show that, following a period of sodium restriction, a diet containing 200 mEq of sodium causes BP to rise with significantly greater frequency in a group of young subjects with borderline hypertension (74%) than it did in a group of normal subjects of comparable age, race, and sex (15%) (fig. 5). As a whole, the combined two groups showed a 39% prevalence of individuals who respond to sodium repletion with an increase in BP.

Our finding that 85% of our 27 normal subjects were able to consume 200 mEq of sodium a day for 4 days without a rise in pressure is in accord with earlier observations in smaller groups of volunteers. Kirkendall et al.[11] observed that four normal subjects were able to follow a 410 mEq NA diet for 1 month with an average increase of supine MAP of only 1 mm Hg.

More recently, Luft et al.,[12] in studies of the response of 14 normal subjects to diets containing as much as 1600 mEq of sodium a day, found that BP did not increase significantly until the daily intake of sodium exceeded 800 mEq. Our six normal subjects showed a small but significant rise while following a 400 mEq sodium diet. Like ourselves, Luft and co-workers[12] found that normal individuals responded to short periods of sodium-loading with an increase in cardiac output and a fall in calculated total peripheral resistance. Similarly, Kirkendall et al.[11] had noted that the forearm vascular resistance of normal subjects fell as dietary sodium was increased. To determine whether this salt-induced elevation of blood flow persists or falls as a result of total body autoregulation[13] will require additional study.

Luft and co-workers[14] also noted that sodium-loading resulted in lower plasma norepinephrine levels in normal subjects. Although we did not measure catecholamines, we noted that the heart rate of our normal subjects was significantly reduced during sodium-loading, even though BP was slightly lower on the average.

Because our normal control subjects were mostly white males, we cannot comment on the effects of race or sex on these observations. We did not find that the individuals with a family history of hypertension differed from those without such a history in any significant manner.

TABLE 2. *Hemodynamic Effect of a 400 mEq Sodium Diet in Six Normal Subjects (mean ± se)*

|	Ad lib	10 mEq sodium	200 mEq sodium	400 mEq sodium
Weight (kg)	70.3 ± 5.5	68.2 ± 5.4	69.4 ± 5.4	70.1 ± 4.9
				$p < 0.01$
		$p < 0.01$		
Mean blood pressure (mm Hg)	77.7 ± 4.2	72.5 ± 4.1	69.0 ± 4.5	82.8 ± 3.3
				$p < 0.01$
		$p < 0.01$		
Diastolic blood pressure (mm Hg)	62.0 ± 2.9	56.2 ± 3.0	54.2 ± 3.4	69.7 ± 2.9
				$p < 0.05$
Cardiac index (1/min/m^2)	2.68 ± 0.27	2.50 ± 0.32	2.51 ± 0.27	2.79 ± 0.37
Total peripheral resistance (dyne sec cm^{-5})	1348.7 ± 176.5	1398.2 ± 226.8	1309.8 ± 202.2	1461.0 ± 273.1
Serum sodium (mEq/1)	139.0 ± 1.1	138.7 ± 0.8	140.3 ± 0.7	142.5 ± 1.2
			$p < 0.01$	
Urine sodium (mEq/24 hr)	140.3 ± 26.9	19.8 ± 3.7	143.0 ± 12.0	411.5 ± 75.5
			$p < 0.01$	
Supine:				
Plasma renin activity (ng/ml/hr)	0.90 ± 0.26	4.13 ± 0.88	0.86 ± 0.13	0.88 ± 0.51
			$p < 0.01$	
Aldosterone (ng/dl)	4.22 ± 1.37	20.88 ± 6.03	8.67 ± 2.88	2.95 ± 0.39
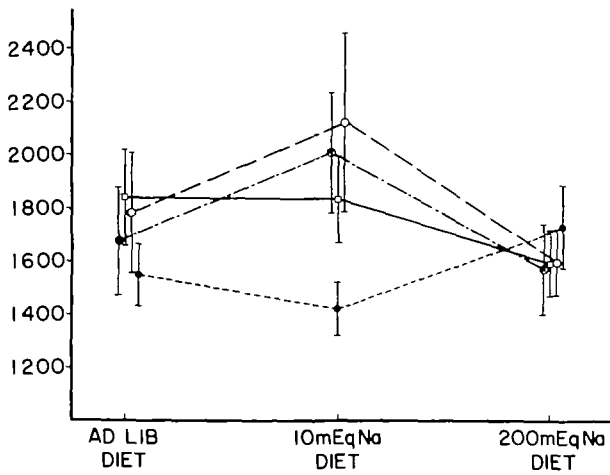
FIGURE 4. *Effect of dietary sodium on total peripheral resistance (dyne sec cm^{-5}). During sodium-loading, resistance falls in all labile hypertensive subjects except a subgroup of five "resistance-responders." Open square = normal subjects; open circle with black dot = salt resistant hypertensives; open circle = hypertensive output responders; black circle = hypertensive-resistant responders.*

TABLE 3. *Hemodynamic Effects of Dietary Sodium in 19 Patients with Borderline Hypertension (mean ± SE)*

	Ad lib	10 mEq sodium	200 mEq sodium
Weight (kg)	77.6 ± 3.5	75.6 ± 3.5	76.8 ± 3.3
		$p < 0.01$ $\qquad$ $p < 0.01$	
Mean blood pressure (mm Hg)	94.0 ± 2.8	89.5 ± 2.4	89.9 ± 2.7
Diastolic blood pressure (mm Hg)	78.8 ± 3.4	73.5 ± 2.6	74.7 ± 3.1
Plasma volume (1)	3.75 ± 0.27	3.76 ± 0.39	3.70 ± 0.27
Cardiac index (1/min/M²)	2.6 ± 0.2	2.2 ± 0.2	2.4 ± 0.1
		$p < 0.01$	
			$p < 0.05$
Total peripheral resistance (dyne sec cm^{-5})	1639.8 ± 123.7	1908.2 ± 178.6	1634.3 ± 77.5
Heart rate	68 ± 2.4	66 ± 3.2	64 ± 2.3
End diastolic volume (ml)	112.1 ± 9.2	102.7 ± 8.6	110.3 ± 8.6
		$p < 0.01$ $\qquad$ $p < 0.01$	
End systolic volume (ml)	43.8 ± 3.4	44.6 ± 4.7	42.6 ± 5.1
Stroke volume (ml)	73.2 ± 5.5	62.9 ± 4.3	69.0 ± 3.1
		$p < 0.05$	
Ejection fraction	62.3 ± 1.8	59.6 ± 2.6	64.2 ± 1.8
Urine sodium (mEq/24 hr)	175.6 ± 16.5	25.2 ± 3.4	178.0 ± 18.1
		$p < 0.01$ $\qquad$ $p < 0.01$	
Urine potassium (mEq/24 hr)	57.5 ± 5.0	49.4 ± 4.2	60.1 ± 5.5
Serum:			
Creatinine (mg/dl)	1.05 ± 0.03	1.10 ± 0.05	1.05 ± 0.04
Sodium (mEq/1)	140.6 ± 0.5	139.3 ± 0.7	141.0 ± 0.5
		$p < 0.05$ $\qquad$ $p < 0.01$	
Potassium (mEq/1)	4.09 ± 0.10	3.98 ± 0.10	3.95 ± 0.07
Plasma renin activity (ng/ml/hr)	1.2 ± 0.2	3.6 ± 0.5	1.3 ± 0.3
		$p < 0.01$ $\qquad$ $p < 0.01$	
Aldosterone (ng/dl)	5.5 ± 0.8	16.4 ± 2.6	5.5 ± 0.7
		$p < 0.01$ $\qquad$ $p < 0.01$	

TABLE 4. Differences in Serum and Urine Potassium

Group	n	Ad lib	10 mEq sodium	200 mEq sodium
Serum Potassium (mEq/1)				
Normals	27	3.81 ± 0.06 S.E.	3.74 ± 0.06	3.83 ± 0.06
Borderline hypertensives		$p < 0.01$	$p < 0.01$	$p < 0.01$
Salt resistant	5	4.36 ± 0.16	4.20 ± 0.23	4.20 ± 0.07
		$p < 0.01$	$p < 0.01$	$p < 0.01$
Output responders	9	3.83 ± 0.13	3.80 ± 0.11	3.83 ± 0.11
Resistance responders	5	4.20 ± 0.16	4.06 ± 0.19	3.96 ± 0.12
Urine Potassium (mEq/24 hr)				
Normals	27	47.29 ± 7.61	51.04 ± 12.81	45.11 ± 7.41
Borderline hypertensives:		$p < 0.01$	$p < 0.01$	$p < 0.01$
Salt resistant	5	71.40 ± 12.40	62.00 ± 7.27	76.2 ± 12.02
		$p < 0.01$	$p < 0.01$	$p < 0.01$
Output responders	9	49.90 ± 6.82	42.86 ± 6.63	49.93 ± 8.18
Resistance responders	5	55.66 ± 5.04	49.94 ± 6.29	60.14 ± 4.81

Despite the great interest that exists about the role of sodium in the genesis of experimental hypertension, and the relatively large numbers of epidemiologic studies that have investigated the relationship of salt and hypertension,[1-3] there is little information available about the hemodynamic response to dietary sodium in hypertensive humans. Mark et al.[15] noted that forearm vascular resistance rose in five of six patients with borderline hypertension following a 410 mEq sodium diet for 10 days, during which time MAP rose from 88.7 to 98.0 mm Hg. Kawasaki et al.[16] administered a 249 mEq sodium diet to 19 hypertensive subjects for 1 week and found that MAP increased by more than 10% in nine of the patients and rose to a lesser degree in another nine. Our results are similar, with 14 of 19 borderline hypertensive patients showing some degree of BP elevation after 4 days of a 200 mEq sodium diet.

In our present study, the hemodynamic response of nine of 14 labile hypertensives, whose pressure rose on a 200 mEq sodium diet, was qualitatively the same as that seen in the normal subjects: an increased cardiac index. However, the magnitude of the increase was relatively greater (20.9% versus 6.9%) and the fall in peripheral resistance not adequate to maintain pressure homeostasis. The BP of the labile hypertensive subjects was significantly higher than that of the normal subjects at each level of sodium intake, demonstrating a disturbed relationship between cardiac index and total resistance. Similar observations have been reported by Julius and co-workers,[17] who carried out hemodynamic studies of subjects with labile hypertension at rest and in response to sitting, exercise, dextran infusion, and blockade of the sympathetic nervous system. In our studies, the dispropor-

tion between cardiac index and resistance could be brought out by sodium repletion.

The five patients who responded to increased dietary sodium with increased peripheral resistance had an average daily MAP that was slightly but not significantly higher than the other borderline hypertensive subjects. The response of these individuals was similar to that reported by Onesti and his colleagues[18] who studied the hemodynamic effect of dietary sodium in patients with end stage renal disease after bilateral nephrectomy. Previously normotensive patients showed no significant change in BP, cardiac index, or total peripheral resistance when dietary sodium intake was liberalized and hemodialysis performed without ultrafiltration. In contrast, patients with a history of moderate, severe, or malignant hypertension invariably responded to sodium-loading with parallel increases in BP and total peripheral resistance, both of which could be reversed by sodium depletion. They concluded that either previous hypertension or a genetic predisposition determined the response to fluid expansion in anephric subjects.

In hemodynamic studies of mongrel dogs made hypertensive by the administration of metapyrone, Bravo and his co-workers[19] found a wide variation in cardiac outputs as BP rose. Prevention of an increase in cardiac output by blockade of beta-adrenergic receptors did not prevent the subsequent development of hypertension, while salt deprivation prevented the development of hypertension. Increasing the intake of sodium led to an increase in vascular resistance and BP, also pointing to a primary role of arteriolar resistance in the genesis of this type of salt-dependent hypertension.
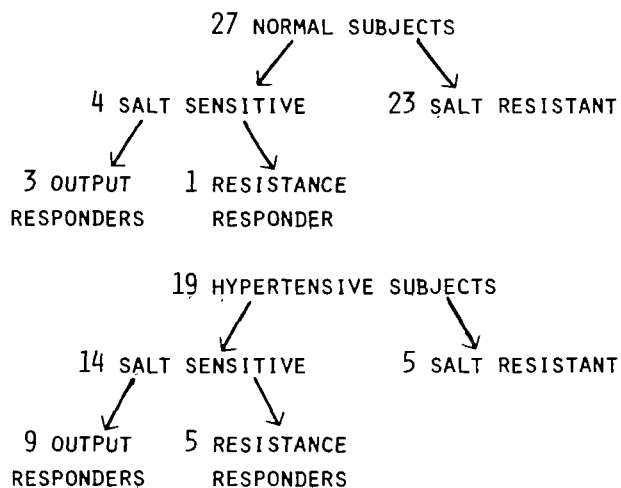
27 NORMAL SUBJECTS

4 SALT SENSITIVE   23 SALT RESISTANT

3 OUTPUT RESPONDERS   1 RESISTANCE RESPONDER

19 HYPERTENSIVE SUBJECTS

14 SALT SENSITIVE   5 SALT RESISTANT

9 OUTPUT RESPONDERS   5 RESISTANCE RESPONDERS

FIGURE 5. *Subdivision of normal subjects and patients with borderline hypertension based on their hemodynamic response to sodium repletion.*

Berecek and Bohr[20] have studied vascular resistance and reactivity in the hindlimb of the DOCA-hypertensive pig and found the animals to have an increased vascular resistance that consisted of two components. One appeared to be structurally based and could be prevented by protecting the hindlimb from the effects of elevated systemic pressure by ligating the external iliac artery. However, this maneuver did not prevent the development of increased vascular reactivity to norepinephrine. Thus, an increase in vascular smooth muscle reactivity may have initiated the elevation of blood pressure in this model of salt-dependent hypertension.

Although our earlier studies[7] failed to show a detectable hemodynamic effect of dietary potassium loading in normal man, analysis of the several variables examined in this study suggested that potassium might have modulated the response to dietary sodium in the salt-resistant borderline hypertensive subjects. Urine potassium was higher in the five borderline hypertensive patients whose BP did not increase in response to dietary sodium than in the 14 whose did. During all of their dietary states, these salt-resistant borderline hypertensives also had higher serum potassium levels than any of the other subgroups. There is evidence that potassium blunts the pro-hypertensive effect of sodium. Meneely et al.[21] found that potassium supplements prolonged the life of hypertensive, salt-sensitive rats. Dahl et al.[22] found the pressure of salt-sensitive rats receiving identical amounts of sodium to be highest in those whose diets contained the lowest amount of potassium. In studies of hypertensive man, Langford and Watson[23] have found evidence that the ratio of urinary sodium/potassium excretion allowed a correlation with

DBP that was not evident from sodium excretion alone. Although the reason for the differences in serum and urine potassium levels in our subjects is not clear (i.e., were they in negative potassium balance or simply eating more potassium?) our data contribute to the body of evidence suggesting that potassium intake is somehow involved in BP regulation.

The differences in response could not be explained by any differences in plasma renin activity or aldosterone concentration in any of the states. We did not measure cumulative sodium and potassium balances, since we chose to study subjects participating in their usual activities. Thus, we cannot assess differences in sodium retention, as did Kawasaki et al.[16] However, we did not find that any of the groups differed significantly in the amount of weight gained or lost.

In summary, we find that most normal subjects are able to tolerate a 200 mEq sodium diet for at least a 4-day period without a BP increase, while most subjects with borderline hypertension show an increase in BP of variable degree (fig. 5). Most normal and borderline hypertensive subjects respond to increased dietary sodium with an increase in cardiac index, which is greater in magnitude in the hypertensive subjects. A second, smaller, subgroup of hypertensive patients responded to dietary sodium with an increase in peripheral vascular resistance. These individuals tend to have higher BP and may be in a more advanced stage of the disease. A third subgroup of hypertensive subjects resists the effects of sodium, perhaps because of differences in potassium metabolism.

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