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Blood Pressure Responses to Extremes of Sodium Intake in Normal Man[1] (40364)

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Although a connection between dietary salt intake and the development of hypertension has been proposed by many observers, the evidence presently available is largely circumstantial (1). Increases in blood pressure have been observed with increases in salt intake in subjects with diminished renal function since the classic report of Ambard and Beaujard in 1904 (2); however, reports of increasing blood pressure with increasing salt intake in normal subjects have been few and anecdotal (3, 4).

Guyton and associates (5) have developed a systems analysis approach which provides a conceptual framework for integrating the various mechanisms that control blood pressure. Their analysis suggests that the kidney's ability to excrete salt and water is the overriding mechanism of blood pressure regulation. They termed the relationship between the state of salt balance and blood pressure the renal function curve. The renal function curve indicates the blood pressure for any state of salt balance in the intact organism. Alterations in the renal function curve may be important in the generation of chronic hypertension in man. We have undertaken studies in normal men and have observed increases in blood pressure with extremes of salt intake. Our data describes the relationship between the kidney's ability to excrete salt and water and the systemic blood pressure.

Methods. Eight normotensive, healthy male volunteers (mean age 32 years, range 22–40) were obtained by advertisement and were studied at the Indiana University Clinical Research Center. The protocol was approved by the Indiana University Medical Center Human Use and Clinical Research Center Committees and informed consent was obtained from each volunteer after detailed explanation of the procedures to be performed.

Protocol. The subjects were given a constant diet containing 10 mEq sodium, 80 mEq potassium, 65 gms protein, 50 gms fat, 270 gms carbohydrates, 400 mg calcium and 1000 mg phosphorus daily. Dietary sodium intake was maintained at 10 mEq for seven days, 290 mEq of sodium in the form of sodium chloride were added to the diet for 3 days (300 mEq sodium diet), and 790 mEq sodium were added to the diet for 6 days (800 mEq sodium diet). In order to achieve an 800 mEq sodium intake, sodium was given with bouillon between meals and at bed time. All meals were eaten in the Clinical Research Center; however, the subjects were not hospitalized until the final three days of the study when they received an additional 700 mEq sodium in the form of intravenous normal saline throughout the night. The design of the study was such that the subjects received 10 mEq Na/24 hr for 7 days, 300 mEq Na/24 hr for 3 days, 800 mEq Na/24 hr for 3 days, and 1500 mEq Na/24 hr for 3 days. Fluid intake (distilled water) was allowed *ad libitum.*

The subjects were weighed every morning before breakfast after voiding. Blood pressures were obtained daily before meals by the indirect auscultatory technique. The same mercury manometers (Baum, Inc., New York, NY) and the same cuffs were employed throughout the study. The subjects rested supine in a darkened room for 5 min after which blood pressure and measurements of heart rate were obtained in the nondominant

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arm each minute for 5 min. The same two observers (RB and FL) were responsible for these measurements throughout the study. Mean arterial blood pressure was calculated by adding one-third the pulse pressure to the diastolic pressure.

Twenty-four hour urine specimens were obtained daily for the determination of sodium, potassium, and creatinine concentrations. At 7:00 AM on the morning of the final day at each level of sodium intake, blood specimens were obtained following two hours of ambulation for hematocrit, creatinine, sodium, potassium, plasma renin activity, and plasma aldosterone concentrations. Stroke volume and cardiac output were measured noninvasively by echocardiography on the final day at each level of sodium intake (6). The echocardiograms were interpreted by two observers without knowledge of the regimens.

Subject safeguards. To tolerability of the diet was examined in an initial pilot study. Two of the investigators (RB and FL) and a medical student volunteer ingested first the 10 mEq/day sodium diet for 1 week, followed by the 800 mEq/day sodium diet for one week. We found that the diet was tolerable and that a generous intake of free water eliminated the tendency to develop diarrhea at the higher sodium loads. Additional sodium was also infused intravenously to total 1200 mEq/day and no ill effects were noted. Balance was achieved at the 10 mEq/day level by the 6th day in every subject. When sodium intake was increased to 300 mEq/day or higher, balance was approached by 72 hr.

Two of the eight subjects were physicians (RB and FL), one taught high school biology, and five were Indiana University Hospital employees. All were well aware of the nature and the potential risks of the study. The subjects were examined by a physician thrice daily except at the 1500 mEq/day sodium intake at which time they were examined four times daily. None developed any adverse symptoms other than the fatigue ostensibly related to the sleeplessness because of nocturia. At the 1500 mEq/day sodium intake, pedal edema became clinically detectable. No rales or gallop rhythms were heard in any subject; no electrocardiographic changes were observed. The chest roentgenograms revealed a detectable increase in cardiac size in five subjects and small pleural effusions in two subjects at the end of the last study day. Three days after the experiment, the subjects' weights, blood pressures, and chest roentgenograms had returned entirely to normal, as had their sense of well being.

Laboratory methods. Sodium and potassium concentrations in plasma and urine were measured by a flame photometer (Instrumentation Laboratories, Boston, MA). Creatinine was measured by an automated technique (Technicon, Chauncey, NY). Plasma renin activity and plasma aldosterone were measured by previously reported radioimmunoassay methods (7). The data was analyzed statistically by two way repeated measures analysis of variance. A computerized program was employed.

Results. The variables obtained on the last day at each level of sodium intake were tabulated and are outlined in Table I. Increasing sodium intake had a significant effect on body weight ($P < 0.001$), mean arterial blood pressure ($P < 0.001$), sodium excretion ($U_{Na}V$) ($P < 0.001$), potassium excretion (U_KV) ($P < 0.001$), creatinine clearance ($P < 0.025$), plasma renin activity (PRA) ($P < 0.001$), plasma aldosterone concentration (PA) ($P < 0.001$), stroke volume ($P < 0.01$), and cardiac output ($P < 0.025$). The heart rate remained unchanged.

Compared to the 10 mEq/day level of sodium intake, mean arterial blood pressure was significantly increased at the 800 mEq/day level ($P < 0.05$), but not at the 300 mEQ/day level. An additional increase ($P < 0.01$) occurred between the 800 mEq/day and 1500 mEq/day levels of sodium intake. The relationship between systemic blood pressure and sodium excretion is graphically displayed in Fig. 1. The interaction between systolic, diastolic and mean blood pressure, and sodium excretion was highly significant ($P < 0.001$).

The urinary potassium excretion and creatinine clearance were both increased significantly by the 800 mEq/day level of sodium intake ($P < 0.05$). The increase in sodium intake to 1500 mEq/day resulted in another increase in kaliuresis ($P < 0.01$); however, no further increase in creatinine clearance was observed ($P > 0.05$). Consistent changes in

TABLE I. CHARACTERISTICS FOLLOWING BALANCE AT EACH LEVEL OF SODIUM INTAKE (MEAN ± SD).

Sodium intake (mEq/24 hr)	10	300	800	1500
Weight (kg)	78.2 ± 12	79.5 ± 12	80.5 ± 12	83.1 ± 11
Mean blood pressure (mm Hg)	82.6 ± 6	83.8 ± 7	89.5 ± 8	99.2 ± 9
Heart rate (beats/min)	62 ± 12	63 ± 13	58 ± 9	60 ± 11
$U_{Na}V$ (mEq/24 hrs)	12 ± 4	265 ± 68	702 ± 67	1442 ± 100
U_KV (mEq/24 hrs)	66 ± 18	74 ± 10	142 ± 20	182 ± 36
Plasma Na (mEq/L)	138.8 ± 4	139.5 ± 3	132.6 ± 6	135.6 ± 2
Plasma K (mEq/L)	3.7 ± .3	3.6 ± .2	3.9 ± .4	3.6 ± .2
Creatinine clearance (ml/min)	110 ± 23	126 ± 8	131 ± 22	137 ± 12
Plasma renin activity (ng AI/ml/3 hr)	13.5 ± 8.0	2.6 ± 2.0	1.3 ± 1.0	0.7 ± 0.4
Plasma aldosterone (ng/100 ml)	39 ± 22	9.0 ± 7.0	2.6 ± 2.0	1.6 ± 0.4
Stroke volume (ml/beat)	86 ± 12	93 ± 13	100 ± 11	115 ± 10
Cardiac output (L/min)	5.3 ± 0.5	5.9 ± 1.2	5.8 ± 1	6.9 ± 1.8

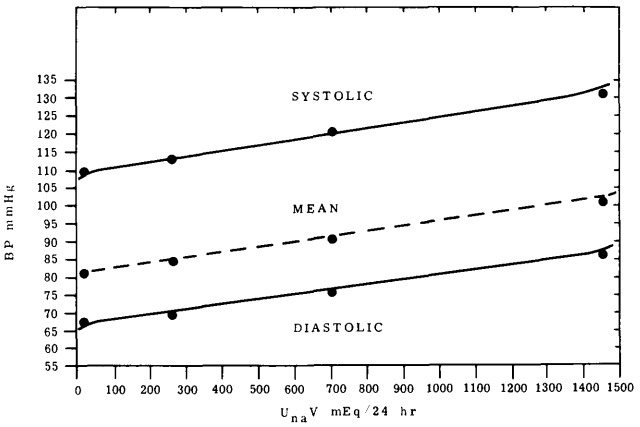

FIG. 1. The relationship between systolic, diastolic and mean arterial blood pressure and sodium excretion in eight normal subjects.

plasma sodium and plasma potassium concentration were not observed. The plasma sodium concentration obtained at the 800 mEq/day level of sodium intake differed from the two lower levels of sodium intake ($P < 0.05$); however, there was no difference in mean plasma sodium concentration between the lowest and highest levels of sodium intake. The plasma potassium concentration at the 800 mEq/day level of sodium intake differed from the plasma potassium concentration at the 300 and 1500 mEq/day levels of sodium intake. Plasma renin activity and plasma aldosterone concentration decreased ($P < 0.01$) between the 10 and 300 mEq/day levels of sodium intake. Stroke volume increased at the 800 mEq/day ($P < 0.05$) and again at the 1500 mEq/day ($P < 0.05$) levels of sodium intake. The cardiac output increased at the 1500 mEq/day level of sodium intake ($P < 0.05$).

Discussion. These results demonstrate a relationship between the states of sodium balance and systemic blood pressure in our normotensive subjects which was similar to that predicted by Guyton's systems analysis (5). Although there was no apparent effect on systemic blood pressure by increasing sodium intake from 10 to 300 mEq/day, increases to 800 mEq/day and 1500 mEq/day resulted in a stepwise significant increase in systemic blood pressure. Kirkendall *et al.* (8) studied normotensive human volunteers after four week exposure to 10 mEq/day, 210 mEq/day and 410 mEq/day levels of sodium intake. They were unable to document an increase in systemic blood pressure in their subjects. Relman and Schwartz (9) studied normotensive volunteers under conditions of sodium intake up to 450 mEq/day. Their subjects received intramuscular injections of desoxy-corticosterone acetate. They observed

occasional slight elevations of arterial diastolic pressure in two of three subjects. These results are consistent in that they suggest that massive increases in sodium intake are necessary in normal subjects to effect an increase in systemic blood pressure.

These data support much earlier observations that massive increases in sodium intake can evoke an increase in systemic blood pressure in man. McDonough and Wilhelmj (3) gave 637 mEq sodium daily to a single normotensive subject for 23 days and observed an increse in systemic blood pressure. Facial puffiness also occurred in their patient. McQuarrie, Thompson, and Anderson (4) administered the adult equivalent (by body weight) of from 1204 to 2408 mEq of sodium daily to diabetic children. They noted 30% –50% increases in both systolic and diastolic blood pressures above control values. Although the state of sodium balance was not documented in these early reports, and statistical analyses were not applied, they indicate that sodium may be associated with increases in systemic blood pressure if huge amounts are given.

The mean 24 hr urinary sodium excretion measurements obtained in our subjects at the different levels of sodium intake indicate that a state of sodium balance was approached at each level. The difference between ingested and recovered sodium in our study likely reflect fecal and cutaneous losses of the ion and do not reflect inadequate urine collections.

Urinary potassium excretion increased progressively with increasing sodium intake. Similar findings were reported by Kirkendall *et al.* (8), who raised the possibility that the kaliuresis was engendered by physical displacement of potassium from intracellular stores by sodium. The kaliuresis may also have been the result of enhanced rates of distal tubular fluid flow at the higher levels of sodium intake (10).

Creatinine clearance increased significantly with increasing sodium intake, suggesting that glomerular filtration rate increased in man with sodium loading. The same phenomenon was observed by Kirkendall *et al.* (8) using inulin clearance.

Plasma renin activity and plasma aldosterone concentrations decreased progressively with increasing sodium intake. Kirkendall *et al.* (8) noted a similar relationship between plasma renin activity and urinary aldosterone excretion. Conceivably, the suppression of the renin–angiotensin–aldosterone system coupled with an increase in glomerular filtration rate served to permit our subjects to excrete enormous sodium loads. The possible participation of other systems cannot be ascertained from these studies. The increase in arterial blood pressure observed in our patients may be attributed to an increase in cardiac output. Permission was not obtained in our study to measure right atrial pressure directly at each level of sodium intake; however, assuming that the value remained constant at 5 mm Hg, systemic vascular resistance decreased in our subjects from 1171 to 1092 dynes/sec/cm^{-5}. It is likely that right atrial pressure increased during the study, which suggests that the actual decrease in systemic vascular resistance was greater than our estimate. These short term studies do not address the concept of whole body circulatory autoregulation (5). Long term studies at extremes of sodium intake would be necessary to determine whether or not an increase in systemic vascular resistance would eventually be provoked.

Guyton and colleagues (5) postulate that hypertensive disorders are characterized by quantitative and/or qualitative alterations in the kidney's ability to excrete sodium at a given blood pressure. Our results support Guyton's conceptual relationship as applied to normotensive individuals; however, we can make no comments about the relationships between the state of sodium balance and systemic blood pressure in hypertension. Appropriately modified protocols applied to subjects with various categorized forms of hypertension will be necessary to define the kidney's behavior under these conditions.

Summary. The relationship between blood pressure and the state of salt balance was evaluated at four levels of salt intake (10 mEq/day, 300 mEq/day, 800 mEq/day, and 1500 mEq/day) in eight normal men. Increasing salt intake resulted in progressive increases in weight, blood pressure, potassium excretion, and creatinine clearance, while plasma renin activity and plasma aldosterone concentration decreased. Cardiac output in-

creased with increasing salt intake, while calculated systemic vascular resistance decreased. The curve defining the relationship between salt excretion and blood pressure was derived. These results support the conceptual framework integrating blood pressure regulation through the final common pathway of renal salt excretion. Moreover, they underscore the importance of salt regulation in the pathogenesis of hypertension.

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