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# Sympathetic Nervous System Activity during Sodium Restriction in Essential Hypertension*,†

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**Summary:** Sympathetic nervous system activity was studied in 38 patients with essential hypertension during high- and low-sodium diets. Salt restriction was associated with a modest (6 mmHg) decline in mean arterial pressure, while the urinary excretion of catecholamines, metanephrines, and vanillylmandelic acid increased significantly. Plasma renin activity also increased. It is concluded that short-term low-sodium diet therapy for essential hypertension results in only small decrements in mean arterial pressure and may be limited in hypotensive effect by activation of the sympathetic nervous system. Support is offered for the rationale of sympatholytic drug therapy as an initial step in the management of hypertensive patients requiring arterial pressure reductions greater than those afforded by diet alone.

**Key words:** hypertension, sympathetic nervous system, sodium

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## Introduction

Drugless therapy of essential hypertension has been advocated in recent years in the form of low-sodium diet (Meneely and Battarbee, 1976) or simple weight reduction (Reisin *et al.*, 1978). Aside from low cost, such strategies recognize the importance of blood volume in the pathogenesis of hypertension (Dahl, 1972; Coleman *et al.*, 1972). The consequences of blood volume manipulation, however, in terms of sympathetic nervous system (SNS) outflow, have not been completely studied. Because of the association of SNS activity and at least some cases of hypertension (Axelrod and Weinshilboum, 1972), we chose to study SNS outflow in hypertensive patients undergoing rigid week-long sodium restriction. Our findings, while preliminary, support the hypothesis that SNS activity may limit the hypotensive response to salt deprivation. The rationale of beginning antihypertensive therapy with a sympatholytic agent is discussed.

## Patients and Methods

### Patient Population

The study population consisted of 38 patients with essential hypertension (mean age 38.3 years). The patients were predominantly white (5 blacks). Secondary causes for hypertension were excluded by history, physical examination, pyelography, and the determination of these laboratory tests: urinalysis, serum sodium, potassium, chloride, and bicarbonate; blood urea nitrogen and serum creatinine, fasting serum glucose; urinary vanillylmandelic acid excretion; electrocardiography; and chest x ray.

### Methods (19-Day Protocol)

Subjects were either newly discovered hypertensives or they had been off all medication for at least 4 weeks. Outpatient mean arterial pressure (average of three readings) was 109±2 mmHg (mean arterial pressure is defined as diastolic plus one-third of the pulse pressure). Informed consent was obtained and each subject was hospitalized at the Veterans Administration Hospital, San Diego, California, for 3 weeks.

During the first 4–5 d of hospitalization, patients were given a 3-g sodium diet and placed on bed rest with bathroom privileges. This maneuver alone produced a fall in mean arterial pressure from 109±2 mmHg to an average of 103±2 mmHg. When blood pressure had stabilized for 3 consecutive days, each patient began day 1 of the initial study week. This first study week was the so-called "high-salt" study period (7 d) during which time dietary intake of sodium was approximately 180 mEq/24 h. On high-salt day 7, supine measurements of mean arterial pressure, heart rate, plasma volume, plasma renin activity, and the 24-h excretion of sodium, catecholamines, metanephrines, and vanillylmandelic acid were made. These measurements were repeated on the seventh day of the following week (low-salt study period, 7 d), this time with dietary salt intake approximately 30 mEq/24 h. The completeness of all urinary collections was verified by simultaneous urinary creatinine measurements. Diets were specially prepared for the metabolic ward to conform to the prescribed sodium composition.

### Chemistries and Statistics

Supine fasting plasma volume was determined utilizing $^{125}$I-labeled human albumin. Isotopes were injected and peripheral blood samples were collected at 10 and 20 min for counting.

Blood plasma renin activity (PRA) measurement was drawn without a tourniquet into chilled EDTA tubes which were placed on ice until the samples were centrifuged and the plasma frozen at −30° C. Blood plasma renin activity was determined by the method of Haber *et al.* (1969) by the radioimmunoassay of angiotensin I ($A_I$) generated after 1 h of incubation at pH 5.5.

Standard colorimetric and fluorometric methods were used for determination of urinary concentrations of catecholamines, metanephrines, and vanillylmandelic acid (Von Euler and Lishajko, 1961).

Paired two-tailed Student's *t*-tests were performed using standard methods (Bliss, 1970). Results are expressed as mean ± standard error of the mean.

### Results (Tables I and II)

During the "high-salt" study period, sodium intake, as reflected by 24-h urinary sodium excretion in steady state, was 177 mEq/24 h or slightly over 4 g of sodium/d. By day 7, blood pressure was 102.9±2 mmHg, not different from the 103 mmHg reached during controlled bed rest and 3-g sodium diet. The effectiveness of sodium restriction during the "low-salt" period is indicated by the decline in urinary sodium excretion to 35 mEq/d. Mean arterial pressure showed a small but significant decline following salt restriction (102 to 97 mmHg), with a parallel decrease in plasma volume. Heart rate and plasma renin activity increased during the "low-salt" period.

All three indices of sympathetic nervous outflow (urinary excretion of catecholamines, metanephrines, and vanillylmandelic acid) increased significantly during sodium excretion (Table II).

TABLE I Hemodynamic variables and sodium excretion during high- and low-salt study periods

| Variable | Study period | | p Value[a] |
|---|---|---|---|
| | High salt | Low salt | |
| MAP | 102.9±2.3 | 97.0±1.8 | <0.01 |
| HR | 75.0±3.0 | 82.0±3.0 | <0.01 |
| PV | 2490.8±101.4 | 2193.1±101.0 | <0.05 |
| PRA | 0.9±0.1 | 6.2±0.8 | <0.01 |
| UNaV | 177.4±17.1 | 35.0±11.6 | <0.01 |

Values are expressed as mean ± SEM
Abbreviations: MAP, mean arterial pressure (mmHg); HR, heart rate (beats/min); PV, plasma volume (ml); PRA, plasma renin activity (ng $A_I$/ml/h); UNaV, urinary $Na^+$ excretion (mEq/24 h)
[a] Paired *t* values

TABLE II Indices of sympathetic nervous outflow during high- and low-salt study periods

| Variable | Study period | | p Value[a] |
|---|---|---|---|
| | High salt | Low salt | |
| CAT | 215.1±20.2 | 258.0±25.1 | <0.05 |
| MET | 307.4±38.6 | 529.9 ± 66.2 | <0.01 |
| VMA | 5.2±0.2 | 6.3±0.4 | <0.05 |

Values are expressed as mean ± SEM
Abbreviations: CAT, urinary excretion of catecholamines (μg/24 h); MET, metanephrines (μg/24 h); VMA, vanillylmandelic acid (mg/24 h)
[a] Paired *t* values

### Discussion

It has long been suspected that the sympathetic nervous system plays a role in the pathogenesis of hypertension. While sympathetic activity, as measured by such tests as plasma norepinephrine levels, shows abrupt changes in response to acute hemodynamic maneuvers such as standing or handgrip in both normal and hypertensive subjects (Kopin *et al.*, 1978),

the notion that SNS measurements have a bearing on clinically elevated arterial pressure levels is unsettled (Watson *et al.*, 1979). Evidence against such a relationship has included reports that hypertensives and normals did not differ in norepinephrine levels (Lake and Ziegler, 1978; Lake *et al.*, 1977). On the other hand, evidence for a link between the SNS and chronic hypertension is as follows.

(1) Signs of sympathetic overactivity and increased production or excretion of catecholamines have characterized various hypertensive states (Axelrod and Weinshilboum, 1972), such as pheochromocytoma, thyrotoxicosis, and drug overdose.

(2) Certain investigators have indicated either an enhanced production (DeChamplain *et al.*, 1976) or decreased degradation (Dollery, 1979) of SNS mediators in essential hypertension.

(3) Early essential hypertension is often characterized by increased heart rate and cardiac output (Dustan *et al.*, 1976; Frohlich, 1974).

(4) Blood pressure and plasma norepinephrine levels both increase linearly with age (Ziegler *et al.*, 1976).

(5) Log plasma norepinephrine levels have correlated with the systolic blood pressure of essential hypertensives in a dynamic fashion (Watson *et al.*, 1979).

(6) Both the capacitance vessels (Guyton *et al.*, 1975; Takeshita and Mark, 1979) and renal vessels (Lowenstein *et al.*, 1967) show phentolamine-reversible increased vascular resistance in essential hypertension, suggesting the tonic influence of increased sympathetic tone (or increased susceptibility to normal sympathetic tone).

(7) Sympatholytic drugs working at many different sites have been used successfully without diuretics in the treatment of hypertension. Taken en masse, these data strongly support a role for the SNS in hypertension.

If indeed sympathetic outflow is involved in the pathogenesis of hypertension, it is also possible that nonsympatholytic therapy of essential hypertension (such as rigid sodium restriction) might be limited by compensatory increases in SNS activity. Volume depletion by furosemide has previously been noted to increase plasma norepinephrine levels in both normal patients and hypertensives. In our investigation of the value of short-term sodium restriction in essential hypertension and its effects on SNS activity, we found a relatively modest pressure decrement despite rigorous control of sodium intake (urinary $Na^+$ 35 mEq/24 h). An appreciable blood pressure decrease was in fact achieved merely through a control period of bed rest alone. The fact that arterial pressure had stabilized before dietary manipulation argues against additional bed rest effects during subsequent changes in sodium balance. Moreover, it is generally conceded that most of the effects of bed rest on blood pressure occur within 48–72 h of its imposition.

During the low-salt study, heart rate and the urinary excretion of catecholamines, metanephrines, and vanillylmandelic acid all increased significantly as blood pressure and blood volume fell. Assuming the unlikely case that patients were able to maintain this degree of salt restriction over many months or years, the pressure decrement at best would be small. Aside from questionable compliance, the limitations of such a program could well involve compensatory sympathetic overdrive.

Changes in sympathetic nervous function which occur in response to volume manipulations have been the focus of several recent publications. Luft *et al.* (1979) reported an inverse relationship between urinary sodium and urinary norepinephrine excretion over a wide range of salt intakes in normal volunteers. Similarly, Romoff *et al.* (1979) found plasma epinephrine and norepinephrine levels to vary inversely with urinary sodium excretion in normal subjects. These findings are in agreement with our data from hypertensives, suggesting that the sympathetic response to volume manipulation is qualitatively similar in both the normal and hypertensive populations. In contrast, Nicholls *et al.* (1980) reported a biphasic response of plasma norepinephrine to salt loading in healthy men. As dietary sodium was increased from "low" to "normal" levels, plasma norepinephrine indeed decreased; however, during further increments of sodium intake to "high" levels, plasma norepinephrine levels increased. This curious norepinephrine "rebound" remains unexplained, but may be related to a stress phenomenon associated with massive volume expansion.

The importance of salt and water overload in hypertension has been extensively emphasized in recent years (Freis, 1976). Yet, disenchantment with diuretics as the first pharmacotherapeutic maneuver in essential hypertension has appeared because such agents increase plasma lipids; primarily diuretic-treated essential hypertensive patients in the Framingham study showed no decrease in coronary events (Veterans Administration Cooperative Study Group, 1970); and such a decrease in coronary sequelae was shown by European investigators who began treatment with a sympatholytic agent (Berglund *et al.*, 1978). Even the assumption that diuretics (thiazides or low-dose furosemide) exert their hypotensive effects primarily through volume depletion has been questioned recently (O'Connor *et al.*, 1979). Moreover, sympatholytic agents which have little propensity to foster volume expansion are available. Our findings have a bearing on choice of first antihypertensive therapy and support the following conclusions.

(1) Drugless therapy of essential hypertension (salt restriction) is of unproven ultimate value and in the short-term setting appears to result in only modest decrements of mean arterial pressure.

(2) The antihypertensive effect of hospitalization and bed rest *per se* complements that of sodium deprivation; the mechanism for this is unknown, but the phenomenon persists despite sodium ingestion and could be due to a reduction in sympathetic outflow. Thus, simple hospitalization is a therapeutic antihypertensive maneuver which is not wholly dependent on sodium balance.

(3) The hypotensive effect of salt restriction may be limited by activation of sympathetic nervous outflow.

(4) Support is offered for the rationale of sympatholytic drug therapy as an initial step in the management of hypertensive patients requiring arterial pressure reductions greater than those afforded by diet alone.

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