Sodium Depresses Arterial Baroreceptor Reflex Function in Normotensive Humans

Mark A. Creager, Mary-Anne Roddy, Kathleen M. Holland, Alan T. Hirsch, and Victor J. Dzau

Sodium may contribute to the pathogenesis of hypertension by impairing arterial baroreceptor reflex function. The objectives of this study were to 1) determine whether a high sodium diet depresses arterial baroreceptor reflex function in normotensive humans, and 2) determine whether alterations in baroreceptor reflex function are related to changes in arterial compliance. Seventeen normotensive men, aged 30±2 years, received 10 and 200 meq sodium per day diets, each for 5 days, in a randomized crossover trial. Carotid baroreceptor reflex function was assessed by measuring the blood pressure response to sequential neck suction (0, −10, −20, and −30 mm Hg) and neck pressure (0, +10, +20, and +30 mm Hg). Forearm vascular resistance was determined by venous occlusion plethysmography. Arterial compliance was evaluated by calculating the quotient of the diastolic blood pressure decay time constant and forearm vascular resistance. Blood pressure averaged 124±3/62±2 mm Hg on the low sodium diet and 122±3/60±2 mm Hg on the high sodium diet (p=NS). Baroreceptor reflex slopes representing the systolic and diastolic blood pressure responses to changes in neck chamber pressure were steeper in the subjects when randomly assigned to low sodium diet than to high sodium diet. Diastolic blood pressure decay time and forearm arterial compliance were similar during low and high sodium intake. We conclude that short-term exposure to a high sodium diet depresses carotid baroreceptor reflex function in normotensive humans. This observation cannot be attributed to changes in the arterial compliance. (Hypertension 1991;17:989–996)

Large population-based studies have implicated sodium in the pathogenesis of hypertension.1–3 Furthermore, sodium depletion by dietary sodium restriction or via the administration of diuretic agents results in a fall in blood pressure.4–6 Arterial baroreceptor reflex dysfunction is known to occur in salt-sensitive animal models of hypertension and also in patients with hypertension.7–14 Accordingly, we hypothesized that increased dietary sodium intake impairs arterial baroreceptor reflex function in humans and thereby may contribute to the development of hypertension.

The primary objective of this study was to determine whether a high sodium diet depresses arterial baroreceptor reflex function in normotensive humans. Only normotensive subjects were included to avoid the confounding effects of hypertension on arterial baroreceptors. One explanation for sodium-mediated depression of baroreceptor function is that sodium alters vascular wall properties and decreases arterial compliance.15,16 A greater transmural pressure would be required to stimulate the baroreceptors of a less distensible vessel, thereby raising baroreceptor threshold and decreasing sensitivity.17 Thus, the secondary objective was to determine whether alterations in baroreceptor reflex function are related to changes in arterial compliance.

Methods

Subjects

Seventeen normotensive men participated in this study. Their ages ranged from 21 to 62 years and averaged 30±2 years (mean±SD). Each subject underwent a complete history and physical examination as well as screening laboratory analysis to exclude hematologic, renal, or hepatic dysfunction. The research protocol was approved by the Committee for the Protection of Human Research of the Brigham and Women’s Hospital, and each volunteer gave written informed consent.
Arterial Baroreceptor Reflex Function

Arterial baroreceptor reflex function was assessed by measuring the blood pressure response to perturbations in carotid sinus pressure. A custom-built chamber, formed of sheet lead and ribboned with sponge rubber (University of Iowa, Medical Instrument Department, Iowa City), was placed comfortably around each subject's neck. The carotid baroreceptors were stimulated by applying negative pressure (suction) and were unloaded by applying positive pressure to the neck chamber. Initially, neck suction was applied at levels of 0, −10, −20, and −30 mm Hg, each for approximately 8–10 seconds during end-expiratory apnea. Blood pressure was measured at each level of negative pressure. This sequence was repeated at least five times in each subject, and the blood pressure responses at each level of pressure were averaged to generate a dose–response curve relating chamber pressure to arterial pressure. Thereafter, neck positive pressure was applied in a comparable manner at levels of 0, +10, +20, and +30 mm Hg, each for approximately 8–10 seconds during end-expiratory apnea. This sequence was repeated five times, and the blood pressure responses were averaged.

Hemodynamic Measurements

Brachial artery pressure was measured via an indwelling arterial cannula. The cannula was attached to a pressure transducer (model P23, Gould Inc., Cleveland, Ohio), and the phasic pressure measurements were displayed on a physiological recorder (model 4600, Gould Inc.). Heart rate was calculated from the R-R interval of a simultaneously obtained electrocardiographic signal. Forearm blood flow was determined by venous occlusion strain-gauge plethysmography, as described previously. Forearm vascular resistance (FVR) was calculated as the ratio of mean blood pressure to forearm blood flow and is expressed as resistance units (mm Hg/ml·100 ml⁻¹·min⁻¹).

Arterial compliance was determined by examining the blood pressure waveform during diastole. This method, as applied by Simon et al., models the arterial system as a simple first-order exponential that exhibits a diastolic decay profile according to the formula

\[ P = R \cdot Q - (R + Q - P_0) \cdot e^{-t/T} \cdot C \]

where \( P \) is pressure, \( P_0 \) is pressure at the onset of the diastolic blood pressure decay, \( Q \) is flow during diastole, \( R \) is resistance, \( C \) is arterial compliance, and \( t \) is time during diastole. In this model, therefore, the product of compliance and resistance is equal to the reciprocal of the semilogarithmic linear slope of the exponential decline in pressure, referred to as the diastolic pressure decay time constant (T). Thus, \( T = C \cdot R \). Forearm arterial compliance (FAC) can be calculated according to the formula:

\[ FAC = T / FVR \]

Hormonal Assays

Blood samples for hormonal assays were placed immediately on ice when collected, centrifuged at 4°C, and stored at −70°C. Plasma norepinephrine concentration was determined by a modified radioenzymatic assay. Plasma renin activity was determined by radioimmunoassay of angiotensin I generation. Plasma angiotensin II and plasma vasopressin concentrations were determined by radioimmunoassays.

Experimental Protocol

Each subject was hospitalized in the Clinical Research Center for 12–14 days. Subjects were studied after receiving a diet containing 10 meq sodium/day for at least 5 days and also after receiving a diet containing 200 meq sodium/day for at least 5 days. The order of diet assignment was randomly chosen. By using this crossover design, each subject served as his own control. Sodium balance was confirmed by daily 24-hour collections of urine. When sodium balance was achieved, arterial baroreceptor reflex function and arterial compliance were measured. Caloric intake was individualized for each subject and determined by a dietician based on the subject's size and usual daily activity. Potassium intake was maintained at 80 meq daily, and calcium intake was 800 mg daily during both sodium diets.

Hemodynamic Measurements

Each study was conducted in the morning in a temperature-controlled 22°C vascular research laboratory. Each subject was studied in the postabsorptive state. Blood for hormonal assays was withdrawn from a venous cannula without the use of a tourniquet. Thereafter, the arterial pressure tracing was recorded and forearm blood flow measurements were made. This procedure was repeated until stability of measurements was achieved. Each subject then underwent sequential application of neck negative and positive pressure, as described above.

Statistical Analysis

The experimental results are presented as mean±SEM. Statistical analysis employed analysis of variance with multifactor repeated measures to evaluate the effects of neck positive and negative pressure during low and high sodium intake. Slopes representing the blood pressure response to neck suction and pressure were then constructed by linear regression analysis. The Student's \( t \) test was used to compare forearm hemodynamic measurements and neurohormonal concentrations during each diet. Statistical significance was accepted at the 95% confidence level (\( p \leq 0.05 \)).

Results

The effects of each sodium diet on blood pressure, heart rate, body weight, and urinary sodium excretion are displayed in Table 1. Blood pressure, heart rate, and body weight were not affected by dietary sodium intake. As anticipated from the experimental design, urinary sodium excretion was...
Table 1. Effect of Dietary Sodium Intake on Blood Pressure, Body Weight, and Urinary Sodium Excretion

<table>
<thead>
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<th>10 meq sodium diet</th>
<th>200 meq sodium diet</th>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>124±3</td>
<td>122±3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>62±2</td>
<td>60±2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>58±2</td>
<td>55±2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73±2</td>
<td>74±2</td>
</tr>
<tr>
<td>Sodium excretion (meq/day)</td>
<td>11±2</td>
<td>179±9*</td>
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*p<0.001, between 10 and 200 meq sodium diets.

significantly higher during the high sodium diet than during the low sodium diet.

Carotid Baroreceptor Reflex Function

Application of neck negative pressure stimulated carotid sinus baroreceptors and reduced systolic and diastolic blood pressure during each sodium diet. The fall in systolic blood pressure was greater at each level of neck suction during the 10 meq sodium diet than during the 200 meq sodium diet (Figures 1A and 1B). The change in diastolic blood pressure was greater at -20 and -30 mm Hg of neck suction. Neck positive pressure was used to unload carotid sinus baroreceptors. The change in systolic blood pressure during incremental neck positive pressure was similar on both diets (Figures 2A and 2B). Diastolic blood pressure, however, increased to a greater extent at +30 mm Hg neck positive pressure during low sodium as compared with high sodium intake.

To assess overall baroreceptor reflex sensitivity, slopes representing the blood pressure responses to both neck pressure and neck suction were constructed (Figure 3). The baroreceptor reflex slopes representing the systolic (0.29±0.03 versus 0.23±0.03 mm Hg/mm Hg, p<0.05) and diastolic (0.28±0.03 versus 0.23±0.02 mm Hg/mm Hg, p<0.05) blood pressure responses to changes in neck chamber pressure were steeper in the subjects when randomized to a low sodium diet than to a high sodium diet (Figure 3).

Forearm Vascular Resistance and Arterial Compliance

Forearm blood flow and forearm vascular resistance were similar during high and low sodium diets (Table 2). Similarly, the diastolic blood pressure decay time constant was similar during both diets. As a result, the...
calculated forearm arterial compliance was not significantly different during high and low sodium intake.

**Hormonal Responses to Dietary Sodium Intake**

Plasma renin activity and plasma angiotensin II concentration were higher during the 10 meq sodium diet than during the 200 meq sodium diet (Table 3). Plasma norepinephrine and arginine vasopressin concentrations were not significantly altered by dietary sodium intake.

**Discussion**

The purpose of this study was to examine the relation between sodium intake and arterial baroreceptor reflex function in normotensive humans. We reasoned that sodium may interfere with arterial baroreceptor reflex function even before the development of hypertension, and thereby may contribute to the pathogenesis of this disorder. The important new observation in this study is that arterial baroreceptor reflex function, as discerned by measuring the systemic blood pressure response to perturbations in carotid sinus pressure, is depressed in normotensive humans when ingesting a diet containing 200 meq sodium/day compared with one consisting of 10 meq sodium/day.

These observations are consistent with some animal studies that have examined the relation between sodium and arterial baroreceptor reflex function. High sodium intake increases aortic baroreceptor

<table>
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<th>Hemodynamic measurement</th>
<th>10 meq sodium diet</th>
<th>200 meq sodium diet</th>
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<tr>
<td>Forearm blood flow (ml/100 ml tissue·min⁻¹)</td>
<td>2.5±0.2</td>
<td>2.4±0.3</td>
</tr>
<tr>
<td>Forearm vascular resistance (mm Hg/ml·100 ml·min⁻¹)</td>
<td>39±4</td>
<td>39±3</td>
</tr>
<tr>
<td>Diastolic decay time constant (mm Hg/sec)</td>
<td>2.0±0.1</td>
<td>1.9±0.1</td>
</tr>
<tr>
<td>Forearm arterial compliance (mm Hg/sec·mm Hg/ml·100 ml·min⁻¹)</td>
<td>0.06±0.01</td>
<td>0.06±0.01</td>
</tr>
</tbody>
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pressure threshold in normal Sprague-Dawley rats in vitro and depletes arterial baroreceptor reflex function in normotensive rats and rabbits in vivo.25,26 Furthermore, the pressor response to carotid occlusion is potentiated in sodium-depleted dogs after vagotomy.27 In the Dahl salt-sensitive rat, however, high sodium intake does not alter arterial baroreceptor function, even when hypertension is prevented by chemical sympathectomy.28 Our findings are not consistent with a previous study in normotensive humans in which sodium loading did not affect baroreceptor reflex sensitivity as determined from the heart rate response to a phenylephrine bolus.29

There are multiple mechanisms whereby sodium may affect the arterial baroreceptor reflex loop. Sodium may alter local factors that regulate baroreceptor function, influence central integration of afferent neuronal impulses, modulate sympathetic efferent traffic, or modulate vascular responsiveness to sympathetic stimuli. In addition, sodium may affect levels of circulating hormones, such as angiotensin II, arginine vasopressin, atrial natriuretic peptide, prostaglandins, and the ouabainlike factor, thereby affecting baroreceptor reflex function indirectly. The following discussion examines the mechanisms that may explain the findings of this study.

**Local Factors Affecting Baroreceptor Function**

Arterial baroreceptors are stimulated when pressure changes deform or strain the vessel walls in which they are located.17 Sodium could interfere with baroreceptor function by decreasing vascular distensibility. Indeed, arterial distensibility improves in normotensive subjects who ingest a low sodium diet for an average of 2 years.16 In our study, however, short-term exposure to diets of both low and high sodium intake did not affect the diastolic blood pressure decay time constant or forearm arterial compliance. Measurements of forearm arterial compliance, however, may not reflect local vascular changes at arterial baroreceptors. Nonetheless, our data are consistent with in vitro studies of aortic arch preparations from rats in which aortic distensibility was not altered by sodium intake.9,28 Accordingly, it is unlikely that decreased arterial distensibility accounts for depressed arterial baroreceptor reflex function during high sodium intake in humans.

Increases in flow may sensitize arterial baroreceptors.30 Thus, changes in carotid blood flow during the different diets may have affected baroreceptor sensitivity. While others have reported that sodium loading increases cardiac output and forearm blood flow, in this study, forearm blood flow was similar during high and low salt diets.31,32 Furthermore, an increase in carotid blood flow during sodium loading would have favored augmentation, not depression, of carotid baroreceptor reflex function.

Dietary sodium intake also may affect baroreceptor function by inducing changes in the ionic environment of the baroreceptors. A small reduction in sodium concentration may affect the sensitivity of mechanoreceptors by altering the equilibrium potential for sodium.33,34 In the presence of a decreased extracellular concentration of sodium, the carotid and aortic baroreceptor threshold is increased and sensitivity is decreased.35–37 This possibility cannot be discounted from our data.

**Central and Sympathetic Efferent Effects**

Sodium may have influenced central integration of afferent neuronal impulses.38 It is difficult to study
central mechanisms directly in humans. It has been reported, however, that lower body negative pressure reduces central venous pressure and augments the forearm vasoconstrictive response to carotid neck pressure, an observation that underscores the synergistic interaction between cardiopulmonary and carotid baroreceptor reflexes. Central venous pressure is lower during sodium depletion than during sodium loading, creating a situation similar to that which occurs during lower body negative pressure. Thus, sodium depletion may unload cardiopulmonary baroreceptors and augment the vasopressor response to carotid sinus unloading. This mechanism may explain, in part, the mild augmentation in the pressor response to neck pressure that occurred during sodium depletion.

Sympathetic efferent activity may be modulated by sodium. In Dahl salt-sensitive rats, the vasoconstrictive response to sympathetic nerve stimulation is increased during sodium loading and reduced during sodium depletion. Sodium loading impairs the ability of the nerve terminal to bind and store norepinephrine; thus, augmented release of norepinephrine during sympathetic nerve stimulation may explain the potentiated vasoconstrictive response. Consistent with this hypothesis is the observation that the pressor response to tyramine is attenuated in sodium-depleted dogs, suggesting that the release of norepinephrine is decreased. One cannot, therefore, invoke the interaction of sodium with sympathetic efferent activity to explain the observation that high sodium intake blunts the blood pressure response to carotid sinus unloading.

**Effect of Sodium on Vascular Responsiveness**

Sodium may modify baroreceptor reflex function by altering vascular responsiveness to vasoactive stimuli. In normotensive humans, sodium loading potentiates the forearm vasoconstrictive response to intra-arterial norepinephrine. An augmented vasoconstrictor response to sodium loading could not account for the attenuated diastolic blood pressure response to carotid sinus unloading observed during the 200 meq sodium diet in our subjects. Other studies have suggested that sodium loading impairs vasodilation in hypertension, but there is very little information regarding the effect of sodium on vasodilator responsiveness in normotensive individuals. It is conceivable, therefore, that the reduced vasodepressor response to carotid sinus stimulation was a consequence of impaired vasodilator function.

**Hormonal Changes in Baroreceptor Reflex Function**

A variety of hormonal changes occurred during sodium loading that may have impacted on arterial baroreceptor reflex function. Plasma renin activity and angiotensin II concentration were higher during sodium depletion than during sodium loading. Angiotensin II has been shown to attenuate baroreceptor reflex function at a central level. In addition, angiotensin II may increase the vascular response to sympathetic stimuli by facilitating the release of norepinephrine. Thus, the increased levels of plasma angiotensin II concentration during sodium depletion would not explain the increased baroreceptor reflex sensitivity to neck suction, but they could contribute to the pressor response during neck pressure. Previous studies have shown that arginine vasopressin augments arterial baroreceptor reflex sensitivity. However, there was no significant difference in plasma arginine vasopressin concentration between low and high sodium diets in our study.

**Clinical Significance**

The observation that high sodium intake depresses arterial baroreceptor reflex sensitivity in humans may provide additional insight regarding the relationship between sodium and high blood pressure. Our data do not imply that sodium-mediated baroreceptor reflex function causes hypertension directly. Indeed, there was no significant difference in blood pressure between the low and high sodium diets. Impaired baroreceptor function, however, may not adequately buffer the other hemodynamic effects of sodium loading that contribute to hypertension, such as increased cardiac output and heightened vascular responsiveness to sympathetic stimulation, particularly after prolonged exposure to a high sodium diet.

**Limitations of Study**

Several technical limitations preclude a more detailed evaluation of the mechanisms contributing to sodium-mediated arterial baroreceptor reflex dysfunction. First, we only examined carotid baroreceptor reflex function. It is difficult to examine aortic baroreceptor reflex function in humans, and the results may not be identical. Nonetheless, our findings are supported by in vitro studies that use isolated aortic arch–aortic nerve preparations. Second, we did not determine the precise location in the baroreceptor reflex loop that is most affected by dietary sodium intake. It was not possible to record afferent or central neural impulses in our volunteers. Additional studies, however, could examine sympathetic efferent activity as well as vascular responsiveness. Third, carotid distensibility was not measured directly in this study. Thus, it may not be appropriate to extrapolate our measurements of forearm arterial compliance to the carotid artery. A more direct approach to assessing carotid artery compliance would be useful in future studies.

The data from this study enable us to conclude that short-term exposure to a high sodium diet depresses carotid baroreceptor reflex function in normotensive humans. The specific mechanisms must still be defined, however; potential candidates include factors localized to the baroreceptors, such as the ionic milieu, central integration of afferent stimuli, and reduced vasodilator responsiveness. These findings provide insight into the pathogenesis of hypertension in populations exposed to sodium enriched diets.
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