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Salt Restriction Lowers Resting Blood Pressure but not 24-H Ambulatory Blood Pressure

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Dietary salt restriction is the most common therapeutic recommendation given to hypertensives, but past studies have assessed the effect of salt restriction using *resting* blood pressure (BP) measurements not with the newer technique of 24-h ambulatory BP monitoring. We compared the effect of high (250 mEq Na/day) and low (10 mEq Na/day) salt diets on resting versus ambulatory BP in 12 normal and 15 hypertensive subjects. Each diet was given for 7 days. Ambulatory BP was monitored from day 6 to day 7 of each diet; resting supine BP was measured on the morning of day 8. In normal subjects, neither resting nor ambulatory BP changed with sodium restriction. In hypertensives, resting BP fell $14 \pm 3/6 \pm 2$ mm Hg (systolic/diastolic; $P < .01$ for both) with sodium restriction while ambulatory BP fell only $4 \pm 2/2 \pm 2$ (P = NS). The resting BP fall was significantly greater than the ambulatory BP fall ($P < .05$) for both systolic and diastolic pressure. Ambulatory heart rates were also significantly greater during sodium restriction, suggesting that the low salt diet activated the sympathetic nervous system. This may, in turn, have partially offset the hypotensive effect of sodium restriction. We conclude that using resting BP to assess the effect of sodium restriction may overestimate the efficacy of this therapy. Ambulatory BP monitoring should be employed in future studies of sodium restriction.
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KEY WORDS: Dietary salt restriction, blood pressure, ambulatory monitoring.

The connection between dietary salt intake and blood pressure has been extensively investigated. Early epidemiological studies indicated a correlation between a society's level of salt intake and the prevalence of hypertension.[1-6] These studies were followed by direct, intervention trials, assessing the effect of high and low salt diets in hypertensive subjects.[7-10] From these trials we have learned that approximately half of the essential hypertensive population are sensitive to salt intake: a high salt diet increasing and a low salt diet decreasing blood pressure.

One feature shared by all past studies of salt restriction is that they quantitated the response to salt restriction using *resting* blood pressure measurements. To date, the newer technique of 24-h ambulatory blood pressure monitoring has not been used to study the effect of salt restriction. Ambulatory blood pressure monitoring (ABP) may offer advantages over isolated, office readings. First, the multiple measurements provided by ABP offer an integrated value for blood pressure over an entire day, and thus may provide a more representative index of the level of blood pressure. In support of this notion, the level of blood pressure measured by ambulatory monitoring has been reported to be a better "predictor" of hypertensive cardiac damage than is resting blood pressure.[11-15] Second, ABP offers round-the-clock measurements and may reveal greater or lesser

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antihypertensive efficacy at different times of day, such as been seen in some trials of antihypertensive drugs.[16-18]

Therefore, we designed the present study to compare the effect of dietary salt restriction on resting versus 24-h ambulatory blood pressure in a group of normal and hypertensive subjects. To allow direct comparison of our results versus those of earlier studies, we employed the same sodium intakes used originally by Barter and colleagues: 10 and 250 mEq Na/day.[7,8]

METHODS

Effect of Sodium Restriction on Blood Pressure We studied 12 normotensive and 15 hypertensive subjects (Table 1). The hypertensives had diastolic blood pressure (BP) >90 mm Hg at 3 separate office visits before being included in this trial. Those who had been previously treated with antihypertensive agents were off those drugs for at least 3 weeks. Reversible causes of hypertension were ruled out with careful clinical evaluation and normal values for plasma cortisol, aldosterone, and catecholamines. Creatinine clearance was >80 mL/min in all subjects.

To allow comparison with previously published work, we used a study design very similar to that used in other studies of "salt-sensitivity."[7,8] All subjects ingested, as outpatients, a constant, calculated diet (provided by our metabolic kitchen) containing 225 to 250 mEq Na/day and 100 mEq K for 7 days, followed by sodium intake of 10 mEq Na and 100 mEq K/day for 7 days. The diets were given consecutively, without a break. From day 6 to day 7 of each diet, 24-h ambulatory blood pressure was measured. Subjects continued their usual daily activities until the evening of day 7 of each diet; patients were then admitted to the metabolic ward of our hospital overnight and, on the morning of day 8 (after being supine and fasting overnight), blood was drawn for hormone levels and resting blood pressure was measured. Compliance and appropriate sodium balance were assured using measurements of 24-h urinary creatinine, sodium, and potassium.

We used two automated, oscillometric devices for measuring ambulatory and resting blood pressure. Ambulatory pressure was measured with SpaceLabs Monitor #90202 (SpaceLabs Inc., Redmond, WA), measuring blood pressure every 30 min between 6:00 AM and midnight, and every 60 min between midnight and 6:00 AM. Resting blood pressure was measured with a Dinamap device (Critikon Inc., Tampa, FL) while subjects were supine after overnight fasting. Blood pressures were measured every 5 min for a 60 min period between 7:30 and 9:00 AM. Each of the devices measures systolic, diastolic, and mean arterial pressure. Blood pressure was measured with a mercury sphygmomanometer at the time each automatic device was placed to assure accuracy of the automatic readings.

Assessing the Reproducibility of Blood Pressure Measurements To determine whether ambulatory or resting BP, measured with our two devices, would change over the course of one week even without a change in sodium intake, we performed a pilot study measuring blood pressure in a group of subjects on two separate occasions, 6 to 7 days apart. All subjects were outpatients eating their usual, free-choice diets, but they were asked to make no modifications in their diets during the period of the study. (To assure that no major changes in sodium intake occurred, we measured sodium in overnight urine collections on the nights of monitoring in six of these subjects). The reproducibility of ambulatory BP measurement was tested in six subjects (4 normal, 2 hypertensives) and of resting blood pressure in 5 subjects (4 normal and 1 hypertensive). All measurements were performed on work days, thus assuring approximately equivalent activity levels and sleep/wake cycles during the periods of measuring. Resting blood pressure was measured with the Dinamap device in the supine position every 5 min for 60 min. Ambulatory blood pressure was measured every 30 min from 6:00 AM until midnight and hourly between midnight and 6:00 AM.

Assays Urinary sodium was measured by direct potentiometry with an ion-sensitive electrode (Nova Analyzer I, Nova Biomedical, Waltham, MA). Plasma renin activity and angiotensin II were measured using previously reported assays.[19] Plasma aldosterone was measured by the Coat-a-count assay kit (Diagnostic Products, Los Angeles, CA).

TABLE 1. CHARACTERISTICS OF SUBJECTS

	Normals	Hypertensives
Age (range)	29 ± 2 (22-39)	40 ± 3 (24-66)
Systolic BP (mm Hg) (prestudy, untreated)	109 ± 3	138 ± 3
Diastolic BP (mm Hg) (prestudy, untreated)	75 ± 2	96 ± 1
Gender (M:F)	7:5	5:10
Plasma renin activity (ng angiotensin I/mL/h)		
high salt	0.9 ± 0.1	0.9 ± 0.1
low salt	2.5 ± 0.5	2.1 ± 0.3
Angiotensin II (pg/mL)		
high salt	13 ± 2	15 ± 2
low salt	25 ± 3	23 ± 2
Aldosterone (ng/dL)		
high salt	7 ± 1	10 ± 2
low salt	32 ± 5	28 ± 5
Urinary sodium (mEq/24 h)		
high salt	177 ± 11	181 ± 11
low salt	4 ± 1	5 ± 1

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Statistics The effect of sodium intake on BP was calculated by subtracting the high-salt BP from the low-salt BP. The difference (ie, the fall in BP with sodium restriction) was used as an indicator of "salt-sensitivity." For a given subject, the BP on a diet was defined as the average of all measurements taken. Thus, 40 to 42 ambulatory readings or 12 supine, resting readings were averaged to give a single 24-h or resting BP value. These single representations of high-salt or low-salt BP were used in our statistical comparisons, using the paired or unpaired Student's *t* tests.

Data from the reproducibility pilot study were analyzed by standard regression relationships. The reproducibility of ABP or resting BP within a given subject was determined by intraclass correlation coefficients, defining each subject's pair of BP measurements as a "group" for analysis of variance. The intraclass correlation coefficient (r_I) was calculated by:

$$r_I = \frac{\text{between group mean squares} - \text{within group mean squares}}{\text{between group mean squares} + \text{within group mean squares}}$$

The null hypothesis was rejected if $P < .05$. Data are displayed as mean values ± SEM.

RESULTS

Reproducibility Pilot Study Overnight urinary sodium measurements in a subset of six subjects indicated similar sodium balance on both study days: 30 ± 7 mEq on the first study day and 30 ± 3 mEq on the second.

Both BP monitors provided very reproducible results (Figure 1). Intraclass correlation coefficients were > 0.95 for systolic, mean, and diastolic pressures with both the Dinamap and Spacelabs monitors. The y intercepts of the regression relationships for both devices suggested that a decline of 2 to 3 mm Hg might be expected at the time of a repeat determination in the absence of any change in sodium intake.

Salt Restriction Study The characteristics of our study subjects are shown in Table 1. The hypertensive subjects were older than the normal subjects ($P < .01$), but there was considerable overlap in the age ranges of the two groups. Urinary sodium excretion on day 7 of each diet indicated an appropriate balance and was not different in the two groups. As expected, the levels of plasma renin activity, angiotensin II, and aldosterone increased with salt restriction in both normal and hypertensive subjects, but there were no intergroup differences in the levels of any of these hormones.

In the normal subjects, salt restriction had no significant effect on blood pressure. Resting pressure was 111 ± 3/68 ± 2 mm Hg on the high salt intake and 111 ± 2/68 ± 1 mm Hg on low salt. Ambulatory pressure was 113 ± 3/70 ± 2 *v* 112 ± 3/71 ± 1 mm Hg on the two diets. Heart rate measured during resting BP monitoring was similar on both diets. Average heart rate during ABP was significantly faster during sodium restriction (78 ± 2 *v* 73 ± 3 beats/min; $P < .05$).

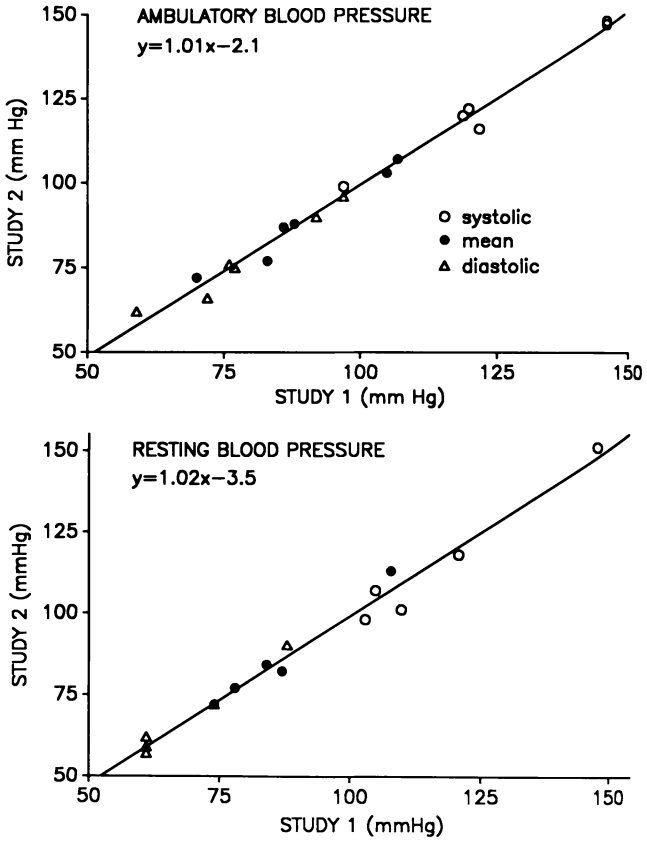

FIGURE 1. *Reproducibility of BP as measured by automatic, oscillometric devices in subjects monitored on two occasions (1 week apart) without a change in dietary sodium intake. Both the ambulatory monitor and the device used for resting BP provided good reproducibility for systolic, mean, and diastolic BP.*

In hypertensives, resting BP fell significantly during sodium restriction. This was true for systolic (falling from 145 ± 4 to 131 ± 3 mm Hg), diastolic (from 91 ± 2 to 85 ± 1 mm Hg), and mean pressure (from 108 ± 2 to 100 ± 1 mm Hg) (all $P < .01$; Figure 2). In contrast, 24-h ABP declined much less with sodium restriction. Systolic fell from 134 ± 2 to 130 ± 2 mm Hg, diastolic from 86 ± 2 to 84 ± 1 mm Hg, and mean pressure from 99 ± 2 to 96 ± 1 mm Hg (all P = NS; Figure 2). The fall in resting BP during salt restriction was significantly greater ($P < .05$) than the fall in ABP for all three measurements (systolic, diastolic, and mean). The degree of fall in ambulatory pressure was, in part, related to the time of day. During waking hours (7 AM to midnight), salt restriction reduced ambulatory mean pressure by only 2 ± 2 mm Hg. During sleep (midnight to 6 AM), mean pressure fell 4 ± 2 mm Hg ($P < .05$). From 7 AM til

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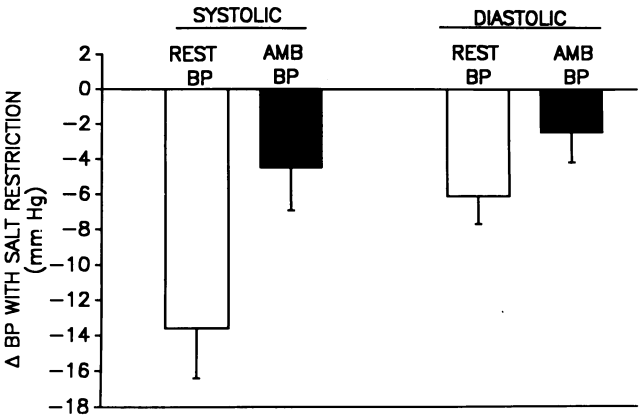

FIGURE 2. *Change in blood pressure during sodium restriction in hypertensive subjects. Resting BP fell significantly while ambulatory BP did not. The decline in resting pressure was significantly greater than ambulatory pressure for both systolic and diastolic pressure.*

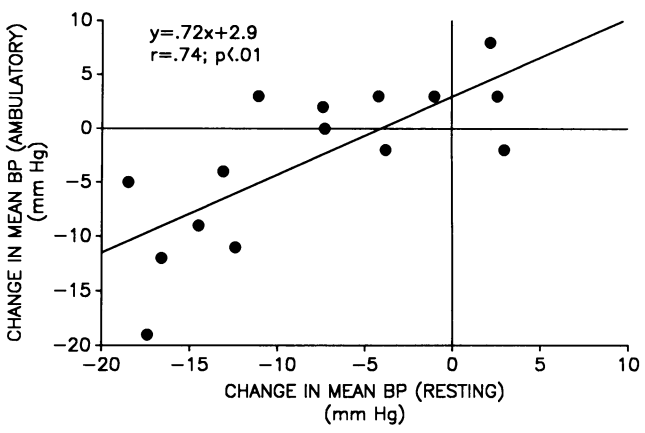

FIGURE 4. *Comparison of the effect of salt restriction on resting versus ambulatory mean BP in individual hypertensive subjects. Although salt restriction decreased resting more than ambulatory BP in 13 of 15 subjects, there was a significant correlation between salt restriction's effect on the two measurements.*

2 PM, the time of day when ambulatory BP is normally highest, the levels were almost identical on high and low salt intakes (Figure 3).

Although there was a difference in the extent of pressure reduction in resting versus ambulatory values, within a given subject there was a correlation between the effects of salt restriction on these two BP responses (Figure 4). This was true only in the hypertensive subjects; no correlation was observed in the normal subjects' responses. Using the definition of "salt-sensitive" hypertension originally proposed by Kawasaki, Bartter, et al[7] (ie, a salt-related change in mean pressure of >10%), 7 of our 15 hypertensives were salt-sensitive according to their resting pressures, but only 3 of 15 by ambulatory pressures.

As in the normotensives, hypertensives had equivalent resting heart rates on both diets (66 ± 3 *v* 67 ± 3 beats/min), but 24-h ambulatory heart rates were significantly faster during sodium restriction (84 ± 3 *v* 77 ± 2 beats/min; $P < .005$).

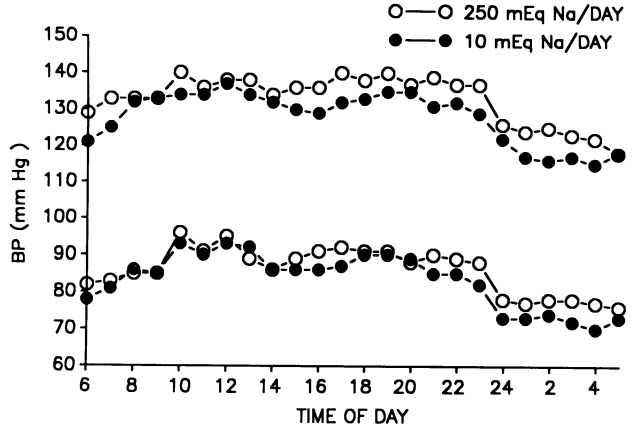

FIGURE 3. *Hourly ambulatory blood pressure in hypertensive subjects. There was no significant effect of salt restriction during waking hours, but BP did fall during sleep (11 PM till 6 AM; P < .05). From 7 AM till 2 PM, BP was nearly identical on the two diets.*

DISCUSSION

The effect of salt intake on resting BP in our subjects confirms what has been seen in most previous studies[7-10,20,21]: sodium restriction has little or no effect on the BP of normal subjects and a modest BP lowering effect in hypertensives. The new information contributed by our study is that sodium restriction has much less effect on ambulatory BP, lowering arterial pressure by only 4/2 mm Hg in hypertensives.

What accounts for the differences between resting and ambulatory BP responses to sodium restriction? There was no difference in salt balance on the days when ambulatory versus resting BP's were measured: the readings were taken on consecutive days and sequential 24-h urinary sodium levels indicated similar sodium balance during both studies. Likewise, the difference is not due to systematic differences in the reproducibility of BP measurements using these two devices. As seen in our pilot study, both devices yielded highly reproducible values when subjects were studied with no change in dietary sodium intake. In fact, BP reproducibility with the devices we used was better than that seen in previous studies.[22,23] We attribute this to the fact that we had standardized environmental factors known to affect BP on the two days of BP measurement (eg, salt intake, time of day, sleep/wake cycle, activity level, etc).

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Certainly there were no systematic differences in the reproducibility of the two devices which might explain the greater BP fall during rest than during ABP. Also, our study was not blinded. Both investigators and subjects were aware which phase was high or low salt. We avoided investigator bias by using automated devices to measure blood pressure. For the subjects, is it possible that the "placebo" effect of salt restriction could lower pressure? Our study design dealt with this issue by measuring pressure repeatedly (12 measurements over 1 h for resting pressure, 40 over 24 h for ABP). We think it unlikely that any placebo effect would lower pressure during these sustained and repeated observations.

We see two possible explanations for our findings. The first, and to us the most likely, explanation is that sodium restriction activates vasoconstrictor systems which, during activity, either minimize (as in hypertensives) or compensate for (normotensives) the BP lowering effect of sodium restriction. The higher angiotensin II levels during sodium restriction may mediate such compensatory vasoconstriction. The higher heart rates seen during sodium restriction suggest, in addition, an increase in sympathetic tone. Angiotensin II may also contribute directly to increased sympathetic tone via its effects on the central nervous system.[24] The fact that salt restriction lowered BP more during sleep than during waking hours suggests that these "compensatory" mechanisms are either more dominant during activity or perhaps have their own diurnal cycle and are inactive during sleep. In this regard, Bittle et al[25] measured BP every 30 min for 24 h in a group of hypertensives after one week each of high and low salt intakes (nearly identical to the design we used). However, all their subjects remained supine throughout the blood pressure measurement day, allowing dissociation of diurnal influences from activity influences. While heart rates are not reported, the average fall in mean blood pressure in Bittle's subjects was 5 mm Hg, an intermediate value compared with our 8 mm Hg fall in resting pressure and 3 mm Hg fall during our ambulatory monitoring. Our results, coupled with those of Bittle et al, suggest that salt restriction has less effect on round-the-clock blood pressure than on isolated, resting values and even less hypotensive effect in active, ambulatory subjects.

A second, converse explanation for our findings would be that salt loading increases resting BP but not ambulatory BP. In our hypertensives, high-salt ambulatory BP was similar to both resting and ambulatory BP on low salt diet, while resting BP on high salt diet is higher than all three other measurements. Previous studies comparing resting versus ambulatory blood pressure in hypertensives on normal salt intake have also shown that resting blood pressure is higher than ambulatory blood pressure. Our hypertensives' high salt resting versus ambulatory BP would therefore be consistent with what has been previously reported. As a possible explanation of this finding, Fujita et al[8] and more recently Gill et al[27] found that some hypertensive subjects fail to suppress sympathetic tone and plasma norepinephrine levels appropriately when sodium loaded, leading to an increase in blood pressure. While such an hypothesis might explain why hypertensives increase their blood pressure with sodium loading, it would not explain our finding that the hypertensive effect of sodium would be seen only in the resting condition and not during ambulatory BP monitoring. Furthermore, following Fujita's hypothesis, one might expect to see higher heart rates (reflecting increased sympathetic tone) during sodium loading in the hypertensive subjects. In our study, heart rates were higher during sodium restriction. For these reasons, we think that vasoconstriction during salt restriction is the more likely explanation for the lack of ABP response to low salt diet.

We urge caution in extrapolating from our results to a conclusion that sodium restriction is not clinically effective in lowering blood pressure. First, our period of sodium restriction was brief, only 7 days. Second, it is important to note that our low-salt diet (10 mEq Na/day) is an extreme degree of sodium restriction. We used this diet because it is a diet commonly employed in the research definition of salt-sensitivity in previous studies. It is possible that less extreme sodium restriction, such as is routinely employed in clinical practice, would not activate the putative vasoconstrictor compensatory mechanisms as intensely as our 10 mEq sodium diet did. Despite this caveat, our findings at least raise the concern that sodium restriction may be less effective at lowering ambulatory blood pressure than resting blood pressure. We feel that ambulatory blood pressure measurement should be included as a routine end point in any future studies of sodium restriction.

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