Definition and Prevalence of Salt Sensitivity and Salt-sensitive Hypertension

Seung-Jae Joo

Department of Internal Medicine, Jeju National University School of Medicine, Jeju, Korea

(Received December 7, 2012: Revised December 14, 2012: Accepted December 21, 2012)

Abstract

High salt intake is associated with significantly increased risk of stroke and total cardiovascular disease. Reduction in habitual dietary salt intake of 6 g/day decreases systolic and diastolic BP, but not in all hypertensive subjects. Salt sensitivity is defined as the tendency for BP to fall during dietary salt restriction and rise during salt supplementation. Salt sensitivity is diagnosed by a low and high salt diet protocol or a rapid sodium, volume expansion and contraction protocol. Prevalence of salt sensitivity ranged from 30 to 60% in hypertensive subjects and from 15 to 46% in normotensive subjects. Salt sensitivity is more frequently found in hypertensive subjects, blacks, aged people, and women. (J Med Life Sci 2012;9(2):123-127)

Key Words : Salt, Sensitivity, Hypertension, Prevalence

Introduction

All guidelines for hypertension management recommends dietary salt intake less than 5-6 g per day. Although the criticism still exists, the causal relation between dietary salt intake and blood pressure (BP) has been established through experimental, epidemiological, and intervention studies. The INTERSALT study assessed the relationship between BP and sodium intake, which was measured by 24-hour urinary sodium excretion, in a very large sample (almost 11,000) of men and women aged 20-59 years from 52 centers in 39 countries (Fig. 1).[1,2] Within centers, sodium excretion was significantly related to BP in individual subjects. Cross center analyses of sodium excretion and median BP showed a weak, but significant positive relationship when all 52 centers were included. A meta-analysis of randomized controlled trials of salt reduction and BP revealed that a reduction in habitual dietary salt intake of 6 g a day would be associated with reductions in systolic/diastolic BP of 7/4 mmHg in people with hypertension and 4/2 mmHg in those without hypertension.[3] However, not all individuals have demonstrable changes in BP after high or low sodium intake. Some individuals manifest large BP changes in response to acute or chronic salt depletion or repletion, and are termed "salt sensitive". Salt sensitivity is defined as the tendency for BP to fall during salt reduction and rise during salt repletion/supplementation. Salt sensitivity or resistance is associated with genetic factors, race/ethnicity, sex, age, and associated disease such as hypertension.

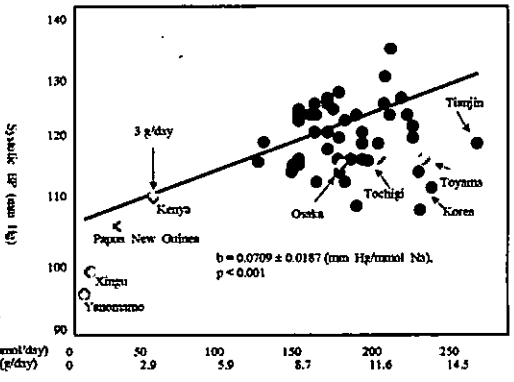

Figure 1. Relationship between salt intake and systolic blood pressure (BP). The INTERSALT study[1,2]

1. Definition of salt sensitivity

The concept of heterogeneity of BP responsiveness to alterations in dietary sodium intake was first suggested by Kawasaki et al.[4] They measured BP after a normal (109 mmol/day), low (9 mmol/day), and then high (249 mmol/day) sodium intake in 19 hypertensive subjects. BP fell significantly with dietary salt restriction and increased significantly back to baseline levels after the high salt intake. They arbitrarily separated the subjects into two groups; salt sensitive (n=9; 47%), those who demonstrated at least a 10% increase in mean arterial pressure, and non-salt sensitive (n=10; 53%), those having smaller increases in

Address for correspondence : Seung-Jae Joo
Department of Internal Medicine, Jeju National University Hospital, 15 Aran 13-gil, Jeju City, Jeju Special Self-governing Province, Korea, 690-767
E-mail : sejjoo@jejunu.ac.kr

BP when the low and high salt pressures were compared. This heterogeneous BP response in hypertensive subjects were also observed in the normotensive population. In a study of 16 normotensive young men, BP was measured after a 7-day period of 10 mmol/day sodium and then successive 3-day periods of 300, 600 or 800, and 1200 or 1500 mmol/day. BP inclined significantly from the lowest to the highest salt intake. However, the individual responses were variable and ranged from an increase of 1.5% to 34%.[5] Weinberg et al.[6] arbitrarily defined salt sensitivity in normotensive subjects as a decrease in mean arterial pressure of at least 3 mmHg following the period of dietary salt restriction and defined salt resistance as an increase of the same magnitude. Those demonstrating changes between these levels were considered indeterminate with respect to classification. Using these criteria, they found that 42% of these normotensive subjects were salt sensitive and 18% were salt resistant, with the remainder indeterminate.

Many investigators have reported the results of studies in normotensive and hypertensive subjects using alterations in dietary sodium content and classifying the subsequent BP responses. The criteria for the definition of salt "sensitivity," "non-sensitivity," "resistance," and "counter regulation" of BP have varied markedly. To make the classification of salt sensitivity easier, an acute intravenous saline challenge coupled with salt reduction plus diuretic treatment to achieve volume depletion has been developed. Weinberger et al.[7] utilized these techniques to characterize the salt sensitivity of BP in 378 normotensive and 198 hypertensive volunteers. Antihypertensive medications were discontinued 2 weeks before the study. The protocol began with the intravenous administration of 2 L normal saline (0.9%) over 4 hours in the morning. BP was measured at the completion of the infusion at noon. On the following day, sodium and volume depletion was induced by a 10 mmol sodium diet and three doses of oral furosemide (40 mg each). BP was again measured on the following morning. The responses were heterogeneous and formed a normal distribution in both normotensive and hypertensive groups. They arbitrarily classified salt sensitivity as a decrease in mean arterial pressure $\geq$10 mmHg and salt resistance as a decrease less than <5 mmHg when the two BP measurements were compared. Those with a decrease in blood pressure between 5 and 9 mmHg were considered indeterminate. The reproducibility of this method was examined in the follow up study.[8] Normal and hypertensive subjects (n=28) were studied twice within a year. A reproducible (r=0.56, p<0.002) response was observed among these 28 subjects. Four subjects changed categories on restudy (1 from resistant on initial study to sensitive and 3 who were initially defined as salt-sensitive had resistant responses on repeat study). Six subjects changed to the indeterminate category on restudy after initial classification as salt-sensitive (3) or salt-resistant (3).

Comparison of two methods for defining salt sensitivity was also performed in hypertensive subjects. Significant congruent BP responses between the rapid sodium, volume expansion and contraction protocol and a dietary protocol with sodium intake $\geq$200 mmol/day for 5 days followed by 7 days of sodium intake $\leq$15 mmol/day was observed.[9] The Italian Society of Hypertension also examined the reproducibility of BP responses of the most commonly used rapid technique and a carefully controlled manipulation of dietary sodium intake in a large group of hypertensive subjects.[10] They showed the responses to repetition of the techniques and the responses to the two different approaches were significantly correlated. They also found no misclassification of subjects as salt-sensitive or salt-resistant on repeated testing.

2. Prevalence of salt sensitivity

Prevalence of salt sensitivity depends on the methods and definition used. It ranged from 30 to 60% in hypertensive subjects and from 15 to 46% in normotensive subjects (Table 1).[11]

Hypertensive patients were significantly more salt sensitive than the normotensive individuals. The first study using the rapid sodium and volume expansion and contraction protocol reported that 26% of the normotensive subjects were salt sensitive and 58% were salt resistant; in the hypertensive group, 51% were sensitive and 33% were resistant.[7] Despite differences in the methods and definitions used in the evaluation of salt sensitivity, several consistent demographic factors have emerged. Blacks have been consistently shown to have a greater frequency of salt sensitivity than whites. In one study, 73% of black hypertensive patients were salt sensitive compared with 56% of a white hypertensive group, but in the normotensive population, the frequency of salt sensitivity among blacks (36%) was similar to that seen among whites (29%).[7] A similar finding of a greater frequency of salt sensitivity among blacks in hypertensives (50% vs. 29% in white) and in normotensives (27% vs. 15% in white) has been reported in another study.[11] A large population-based study of salt sensitivity using a low and high salt diet protocol was

performed in 1,906 Chinese people.[12] If an absolute change of mean arterial pressure ≥5 mmHg was used to define sodium-sensitivity, 33.9% during low-salt intervention and 32.4% during high-salt intervention were salt-sensitive. If a proportional change of mean arterial pressure ≥5% was used, 38.7% during low-salt intervention and 39.2% during high-salt intervention were salt-sensitive (Fig. 2).

Age was also found to be related to salt sensitivity of BP. Increasing salt sensitivity has been noted with increasing age in several such studies. This relationship appears to be stronger in hypertensive than in normotensive individuals (Table 2).[8] In a 10-year follow up study after the initial classification of salt sensitivity, BP of salt-sensitive individuals increased greater than salt resistant subjects.[8]

Table 1. Definition and prevalence of salt sensitivity. Modified from reference 11).

	Protocol	Criteria	Prevalence	
			NT	HT
Kawasaki, 1978	Diet	△ mean BP ≥10%		50%
Sullivan, 1980	Diet	△ mean BP ≥5%	15%	29%
Fujita, 1980	Diet	△ mean BP ≥10%		50%
Takeshita, 1982	Diet	△ mean BP ≥10%		47%
Campese, 1982	Diet	△ mean BP ≥10%		60%
Koolen, 1983	Diet	△ mean BP ≥10 mmHg		32%
Weinberger,1986	Rapid	△ mean BP ≥10 mmHg	26%	51%
Sharma, 1989	Diet	△ mean BP ≥3 mmHg	46%	

Table 2. Age and salt sensitivity of blood pressure. Modified from reference 8).

	Salt-sensitive or indeterminated	Salt-resistant
Normotensive		
<30 years	35%	65%
≥50 years	77%	23%
Hypertensive		
<30 years	50%	50%
≥50 years	85%	15%

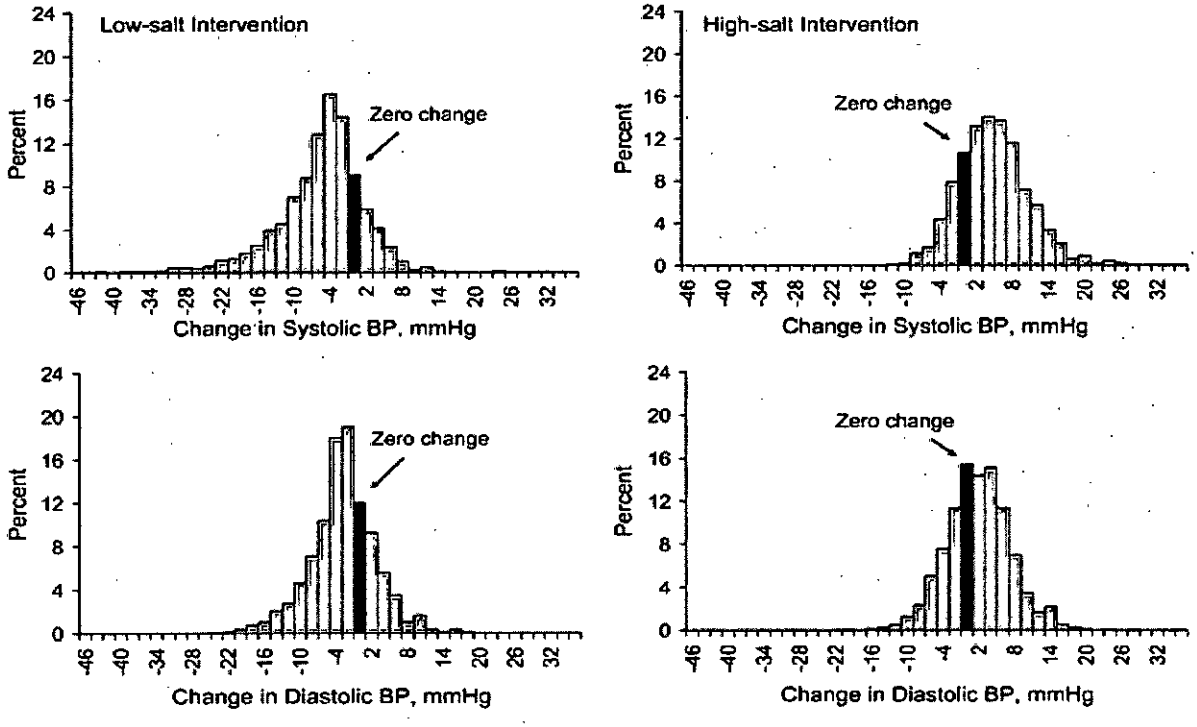

Figure 2. Distribution of systolic (upper panels) and diastolic (low panels) BP responses to low-salt intervention (left panels) and high-salt intervention (right panels) in Chinese populations. The Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study. BP response to low sodium=BP on low-sodium diet -BP at baseline and BP response to high-sodium=BP on high-sodium diet - BP on low-sodium diet.[12]

Sex was suggested to influence the salt sensitivity. In a dietary feeding study of a 7-day low-salt intervention (51.3 mmol sodium/day) and a 7-day high-salt intervention (307.8 mmol sodium/day), BP responses to low-sodium intervention were significantly greater in women than in men (-8.1 vs. -7.0 mmHg for systolic and -4.5 vs. -3.4 mmHg for diastolic). BP responses to high-sodium interventions were also significantly greater in women than in men (6.4 vs. 5.2 mmHg for systolic and 3.1 vs. 1.7 mmHg for diastolic).[13]

Recently characteristics of salt sensitivity in Korean populations were reported.[14] One week of low-sodium diet (100 mM) followed by one week of high-sodium diet (300 mM) protocol was used to classify salt sensitivity in 101 subjects. Salt sensitivity was defined as an increase of mean arterial pressure of ambulatory BP monitoring >4 mmHg in response to high-sodium diet. The prevalence of salt sensitivity was 27.7%, but much higher in hypertensives (51.6%) than non-hypertensives (17.1%) (Table 3). There was no gender difference of the prevalence of salt sensitivity.

Table 3. Characteristics of salt sensitivity in Korean populations. Modified from reference 14).

Parameters	Sodium-sensitive	Sodium-resistant	*P* value
All			
Number (%)	28 (27.7)	73 (72.3)	
Age(years)	54.4±12.9	42.8±16.9	<0.001
Gender, male(%)	11 (39.9)	40 (54.8)	0.163
Hypertension(%)	16 (57.1)	15 (20.5)	<0.001
Non-hypertensives			
Number (%)	12 (17.1)	58 (82.9)	
Age(years)	48.8±16.2	39.2±16.2	0.064
Gender, male(%)	3 (25.0)	30 (51.7)	0.091
Hypertensives			
Number (%)	16 (51.6)	15 (48.4)	
Age (years)	58.6±8.0	57.7±11.7	0.613
Gender, male(%)	8 (50.0)	10 (66.7)	0.347

High salt intake is associated with significantly increased risk of stroke and total cardiovascular disease.[15] Despite the skeptics about the concept, the methods used, the criteria of BP response of a normal Gaussian distribution to define salt sensitivity, hypertensives who need the test, and its clinical significance, salt sensitivity is important to understand the pathogenesis or genetics of essential hypertension. However, because of methodological difficulties to define salt sensitivity, it has not been widely studied in Korean. Salt sensitivity is an old concept, but a new one in Korea.

참 고 문 헌

1) INTERSALT Cooperative Research Group: INTERSALT Study: an international study of electrolyte excretion and blood pressure: Results for 24-hour urinary sodium and potassium excretion. BMJ 297:319-28, 1988.
2) Kawano Y. Salt, hypertension, and cardiovascular diseases. J Korean Soc Hypertens 2012;18:53-62.
3) He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. J Hum Hypertens 2002;16:761-70.
4) Kawasaki T, Delea CS, Bartter FC, Smith H. The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. Am J Med 1978;64:193-198.
5) Luft FC, Rankin LI, Bloch R, Weyman AE, Willis LR, Murray RH, Grim CE, Weinberger MH. Cardiovascular and humoral responses to extremes of sodium intake in normal black and white men. Circulation 1979;60:697-706.
6) Weinberger MH. Salt sensitivity of blood pressure in humans. Hypertension 1996;27:481-90.
7) Weinberger MH, Miller JZ, Luft FC, Grim CE, Fineberg NS. Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertension 1986;8(suppl II):II-127-34.
8) Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure: age and pressure change over time. Hypertension 1991;18:67-71.
9) Weinberger MH, Stegner JE, Fineberg NS. A comparison of two tests for the assessment of blood pressure responses to sodium. Am J Hypertens 1993;6:179-84.
10) Strazzullo P, Galletti F, Dessì-Fulgheri P, Ferri C, Glorioso N, Malatino L, Mantero F, Manunta P, Semplicini A, Ghiadoni L, Zoccali C. Prediction and consistency of blood pressure salt-sensitivity as assessed by a rapid volume expansion and contraction protocol. J Nephrol 2000;13:46-53.
11) Sullivan JM. Salt sensitivity: definition, conception, methodology, and long-term issues. Hypertension 1991;17(suppl I):I-61-8.
12) Chen J. Sodium-sensitivity of Blood Pressure in Chinese

Populations. Curr Hypertens Rep 2010;12:127-34.
13) He J, Gu D, Chen J, Jaquish CE, Rao DC, Hixson JE, Chen JC, Duan X, Huang JF, Chen CS, Kelly TN, Bazzano LA, Whelton PK; GenSalt Collaborative Research Group. Gender difference in blood pressure responses to dietary sodium intervention in the GenSalt study. J Hypertens 2009;27:48-54.
14) Shin SJ, Lim CY, Rhee MY, Oh SW, Na SH, Park Y, Kim CI, Kim SY, Kim JW, Park HK. Characteristics of sodium sensitivity in Korean populations. J Korean Med Sci 2011; 26:1061-7.
15) Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovasculardisease: meta-analysis of prospective studies. BMJ 2009;339:b4567.