Association Between Salt Sensitivity and Target Organ Damage in Essential Hypertension

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Cardiovascular events occur more frequently in sodium-sensitive patients with essential hypertension; recently, sodium sensitivity was shown to be a cardiovascular risk factor independently of other classic factors such as blood pressure and cigarette smoking This study examined the relationship between salt sensitivity status and target organ damage in hypertensive patients. Ninety-six patients (35 men, 61 women) with moderate essential hypertension were studied for salt sensitivity status and the presence of target organ damage, including hypertensive retinopathy, serum creatinine, creatinine clearance, and urinary albumin excretion (UAE). Four different patterns of left ventricular anatomic adaptation were identified by categorizing patients according to the values of left ventricular mass index and relative wall thickness by the means of echocardiography. Forty-five (47%) patients were shown to be salt-sensitive, in contrast to 51 (53%) salt-resistant subjects. Serum creatinine and UAE were significantly higher in the group of salt-sensitive hypertensives ($P < .05$ and $P < .001$, respectively). Left ventricular mass index (LVMI), relative wall thickness (RWT), and left atrial index (LAI) were all significantly higher in the group of salt-sensitive hypertensive patients. Concentric hypertrophy was significantly more prevalent in the salt-sensitive group (37.8% *v* 11.8%; $P < .01$). The prevalence of hypertensive retinopathy in the salt-sensitive group was 84.4%, in contrast to 59.6% in the salt-resistant group ($P < .01$). Multivariate regression analysis revealed salt sensitivity as a significant predictor of LVMI, RWT, and UAE, independently of age, body mass index, and mean blood pressure. In conclusion, salt-sensitive hypertensive patients are more prone to develop severe hypertensive target organ damage that may enhance their risk of renal and cardiovascular morbidity. Am J Hypertens 2000;13:864–872

KEY WORDS: **Salt sensitivity, left ventricular hypertrophy, target organ damage, urinary albumin excretion, hypertensive retinopathy, left atrium, essential hypertension.**

Blood pressure is affected by dietary salt in many, but not all, normotensive and hypertensive subjects[1,2] and approximately half of hypertensive patients are shown to be salt sensitive.[2] The mechanisms responsible for the increase in blood pressure in response to high salt intake are only partially understood. A complex interaction between neuroendocrine factors and the kidney may underlie the propensity of such patients to retain salt and develop salt-dependent hypertension, and a potential role for several vasodilator and natriuretic agents, such as nitric oxide (NO), atrial natriuretic

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peptide (ANP), and kinin-kallikrein system, has been proposed.[3] An association between salt sensitivity and a greater propensity to develop renal failure has been described in certain groups of hypertensive patients, such as blacks, the elderly, and those with diabetes mellitus.[4] Recently, Morimoto et al have showed that cardiovascular events occurred more frequently in sodium-sensitive patients with essential hypertension and that sodium sensitivity is a cardiovascular risk factor independently of other classic factors such as blood pressure and cigarette smoking.[5] How sodium sensitivity increases the risk of cardiovascular events remains unknown. Clustering of several factors with well-known atherogenic potential, including hyperinsulinemia, hyperlipidemia, and microalbuminuria, in salt-sensitive hypertensives may explain in part the increased cardiovascular risk of these patients.[6] Only a few studies addressed an issue of the higher prevalence of hypertensive heart disease among salt-sensitive patients but a clear relationship has not yet been established.[7–9] We hypothesized that salt sensitivity in hypertension might be associated with substantial renal, hemodynamic, metabolic, and cardiac abnormalities that may enhance the risk for cardiovascular and renal morbidity. This study was designed to elucidate the prevalence of salt sensitivity among the group of untreated patients with moderate essential hypertension and its relationship to other hypertensive target organ damage including renal involvement, hypertensive retinopathy, and left ventricular geometric adaptation.

MATERIALS AND METHODS

Study Population Ninety-six consecutive patients (35 men, 61 women) with moderate essential hypertension (stage 1–2) according to JNC-VI report[10] were enrolled in the study. All study patients had never been treated with antihypertensive therapy at the time of their initial diagnostic evaluation.

Patients were defined as being hypertensive if they had diastolic pressure $\geq$ 90 mm Hg or systolic pressure $\geq$ 140 mm Hg in the sitting position (average of two separate measurements) on three successive outpatient visits before entering the study. Patients with secondary hypertension, preexisting cardiac disease, or other apparent disease were excluded by clinical and laboratory evaluation. The normality of carbohydrate metabolism was confirmed by the following criteria: fasting glucose levels $<$ 120 mg/dL (6.7 mmol/L), normal glucose response to oral glucose load (75 g), HbA1C $<$ 6%, and absence of glycosuria. The patients with unsatisfactory transthoracic echocardiograms were also excluded from analysis.

Each patient underwent an evaluation including previous medical history, physical examination, and appropriate laboratory evaluation. Hypertensive heredity was defined as the presence of at least one first-degree relative affected by essential hypertension before the age of 50 years. Informed consent was obtained from all subjects. The study protocol was approved by the ethical committee of Marmara University School of Medicine.

Study Protocol After being included in the study, patients were placed on a regular NaCl diet (120 mmol/day) for 1 week. Throughout the study, the patients ingested a constant amount of K^+ (2000 mg/day), Ca^{2+} (500 mg/day), and calories (40 kcal/kg). Compliance to diet throughout the study was assessed by measuring the 24-h urinary sodium excretion on days 3 to 4. The patients were considered compliant when the sodium excretion was between 80 and 130 mmol/day. On the last morning of the first week of study period, after fasting, patients were kept in the supine position for 60 min, blood pressure was determined, and venous blood for determination of plasma active renin (PAR), plasma aldosterone concentration (PAC), serum creatinine, electrolytes, glucose, cholesterol, triglyceride, and uric acid levels was drawn. Echocardiographic examination as well as fundoscopic examination were also performed at the end of the first week of study period.

Twenty-four–hour samples of urine for measurement of urinary albumin excretion (UAE) were taken on three different occasions after negative urine cultures were obtained to exclude for the presence of urinary infection. If at least two of three measurements of albumin excretion were between 30 mg/day and 300 mg/day, the patient qualified as having microalbuminuria. During the second and third week of the study period, patients were evaluated for salt sensitivity.

Sodium-Sensitivity Assessment The response to salt was assessed by comparing the blood pressure measurements on the seventh day of a low salt intake period (20 mmol/day for 1 week) with that on the seventh day of a high salt intake period (220 mmol/day for 1 week dispensed by us in the form of cachets).[11] All of the participants were instructed not to alter their physical activity and energy intake between the two tests. Patients were considered compliant when Na^+ excretion was $>$ 200 and $<$ 30 mmol/24 h in urine collections obtained during the high- and the low-Na^+ intake, respectively.

On the last morning of both low-salt and high-salt intake periods, after fasting, patients were kept in the supine position for 30 min and subsequently, blood pressure was measured for 1 h at 5-min intervals. The average of all obtained measurements was used to calculate mean blood pressure (MBP) as a diastolic blood pressure + 1/3 pulse pressure. Salt sensitivity was defined as a significant drop in MBP $\geq$ 10% (the

10% criterion)[12] under the low-salt diet, calculated as a difference between the average of the readings during the high- and low-salt periods. The reproducibility of this approach was confirmed previously.[13]

Measurements Microalbuminuria was assayed by turbidimetric method (Urinpak, Bayer, Germany). Serum creatinine, glucose, cholesterol, triglyceride, and uric acid levels were determined photometrically. Urinary and serum electrolyte levels were measured by spectrophotometry. Active renin concentration was measured by immunoradiometric assay using a commercial kit (Nichols Institute Diagnostics, CA) and the results were expressed as microunits per milliliter. The plasma aldosterone concentration was measured using an aldosterone radioimmunoassay kit (DPC, Los Angeles, CA) and the results were expressed as picograms per milliliter. The fundoscopic examinations were performed by a single observer (ophthalmologist) who was blinded with respect to the diagnosis of the subject.

Echocardiographic Methods Two-dimensional guided M-mode echocardiography was performed by standard methods using an ultrasound system (Ultramark 9, Advanced Technology Laboratories, Bothell, WA) with a 2.25-MHZ transducer by the same cardiologist for all patients. Color Doppler examination was performed to exclude the presence of mitral regurgitation. Left ventricular internal dimension (LVID), as well as septal (IVST) and posterior wall thickness (PWT) were measured at end-diastole according to the American Society of Echocardiography guidelines.[14] Left ventricular mass (LVM) was calculated at end-diastole by using the Penn convention formula ($LVM = 1.04\ [(LVIDd + IVSTd + PWTd)^3 - LVIDd^3] - 13.6$ g).[15] Left ventricular mass index (LVMI) was calculated as a ratio of left ventricular mass to body surface area. Relative wall thickness (RWT) was measured at end-diastole as the ratio of $2 \times PWT/LVID$.[16]

Four different patterns of left ventricular anatomic adaptation to sustained hypertension were identified by categorizing patients according to the values of left ventricular mass index and relative wall thickness.[17] Upper normal limits for LVMI accepted (estimated as the mean ± 2SD value of normotensive control subjects) were 134 and 110 g/m^2 in men and women, respectively.[18] A partition value of 0.44 for relative wall thickness, representing the 99th percentile value in normotensive control subjects, was used both for men and women.[17] Patients with increased LVMI and increased RWT were considered to have concentric hypertrophy, and those with increased LVMI and normal RWT were considered to have eccentric hypertrophy. Those with normal LVMI and increased RWT were considered to have concentric remodeling, whereas those with normal LVMI and RWT were accepted to have a normal left ventricle.[17]

Left atrial size was determined in accordance with the American Society of Echocardiography guidelines,[14] and was indexed by body surface area (left atrial index, LAI); LAI of 2.2 cm/m^2 was used as partition value for left atrial enlargement.[17] The intraobserver variability for the measurements of LA size, LV wall thickness, and LV dimensions were 1.6%, 4.2%, and 2.7%, respectively.

Statistical Analysis All values are expressed as mean ± SD, with the exception of urinary albumin excretion, urinary sodium excretion, serum triglyceride, and active plasma renin levels, which are expressed as median value with 25th and 75th percentiles given in brackets. The differences in baseline characteristics that were continuous between salt-sensitive and salt-resistant groups were tested with unpaired t test and Mann-Whitney test when indicated. χ^2 analyses were used when the baseline characteristics were categorical. In addition, serum creatinine, LVMI, RWT, and LAI were assessed by ANCOVA, with age, gender, BMI, and MBP as covariates to adjust for the differences in age, gender, BMI, and MBP that existed between the two groups. Multivariate regression analyses were employed when evaluating the effect(s) of a continuous or categorical covariate(s) on LVMI, RWT, UAE, and serum creatinine used as dependent variables. $P < .05$ was considered statistically significant. The statistical analyses were performed by SPSS version 6.0 for Windows.

RESULTS

Among the 96 patients, there was total of 45 (47%) who were shown to be salt sensitive, in contrast to 51 (53%) salt-resistant subjects. The baseline clinical characteristics of the salt-sensitive and salt-resistant hypertensive patients measured during the regular NaCl diet (120 mmol/day) are presented in Table 1. The average age of patients in the salt-sensitive group (50 ± 9.1 years) was significantly higher than in the group of salt-resistant subjects (44.2 ± 11.7 years, $P < .01$). There were also significantly more women in this group than in the salt-resistant group ($P < .01$, Table 1). The subjects shown to be salt sensitive had an average body mass index of 28.5 ± 0.7 kg/m^2, which was significantly higher than in the group of salt-resistant subjects (25.6 ± 0.6 kg/m^2, $P < .001$). There was no difference between the groups in the duration of hypertension or hypertensive heredity. Serum creatinine was significantly higher in the salt-sensitive group and this difference was preserved after adjustment for age, BMI, gender, and mean blood pressure. Urinary albumin excretion was significantly higher in the group of salt-sensitive hypertensives, with a me-

TABLE 1. BASELINE CHARACTERISTICS OF THE SALT-SENSITIVE AND SALT-RESISTANT GROUPS OF 96 PATIENTS WITH ESSENTIAL HYPERTENSION

	Salt-Sensitive Patients (n = 45)	Salt-Resistant Patients (n = 51)
Age (years)	50.0 ± 9.1*	44.2 ± 11.7
Gender (male/female) (%)	25/75*	37/63
Body mass index (kg/m^2)	28.5 ± 4.2†	25.6 ± 3.8
Body surface area (m^2)	1.77 ± 0.22	1.78 ± 0.16
Creatinine (mg/dL)		
Unadjusted	0.95 ± 0.21‡	0.86 ± 0.22
Adjusted¶	0.949 ± 0.205‡	0.861 ± 0.215
Blood urea nitrogen (BUN) (mg/dL)	13.8 ± 4.0	13.8 ± 2.8
Creatinine clearance (mL/min)	97.6 ± 21.4	98.0 ± 23.4
Urinary albumin excretion (mg/day)	38.0 (22.9–67.0)†	20.3 (12.6–26.0)
Urinary sodium excretion (mmol/L)§	88.5 (50.1–140.8)	75.5 (51.3–104.8)
Total serum cholesterol level (mg/dL)	246.4 ± 54.5*	216.9 ± 41.9
HDL cholesterol (mg/dL)	45.8 ± 11.4	45.5 ± 10.9
Triglyceride level (mg/dL)	170 ± 90	150 ± 86
LDL cholesterol (mg/dL)	166.9 ± 53.0‡	143.4 ± 38.5
Uric acid (mg/dL)	4.7 ± 1.3	4.8 ± 1.4
Active renin (μU/mL)§	15.5 (10.4–22.2)	19.6 (12.8–31.1)‡
Plasma aldosterone (pg/mL)	15.6 ± 7.5	15.2 ± 9.81
Family history of HT (%)		
No	45.45	33.33
One relative	29.54	39.58
Two or more relatives	25.01	27.09
Duration of HT (years)	2.08 ± 1.18	2.11 ± 1.45
Hypertensive retinopathy (%)	84.4 (OR 3.68)†	59.6
Hypertensive retinopathy (%)		
Normal	15.6 (OR 0.20)‡	40.4
Grade 1	33.3 (OR 2.05)	21.3
Grade 2	48.9 (OR 2.09)‡	34.0
Grade 3	2.2 (OR 0.55)	4.3

LDL cholesterol = low-density lipoprotein cholesterol; HDL cholesterol = high-density lipoprotein cholesterol; OR = odds ratio; HT = hypertension. Values are expressed as mean ± SD.

* P < .01; † P < .001; ‡ P < .05.

¶ *Serum creatinine level is adjusted for age, gender, body mass index, and mean blood pressure (see Materials and Methods).*

§ *Values are expressed as mean (25th–75th percentile).*

dian level of 38 mg/day, in contrast to 20.3 mg/day in the group of salt-resistant subjects ($P < .001$). Active renin level was significantly higher in the group of salt-resistant subjects (median value, 19.6 *v* 15.5 μU/mL), $P < .05$), but there was no difference in plasma aldosterone levels between the two groups. Urinary sodium excretion in the group of salt-sensitive subjects was significantly higher than in the other group (median level, 88.5 *v* 75.5 mmol/L, $P < 0.05$).

Systolic (SBP) and diastolic blood pressure (DBP) were significantly higher in the group of salt-sensitive subjects ($P < .01$ and $P < .001$, respectively; Table 2). Mean blood pressures after the normal-sodium diet as well as after the high-sodium diet were significantly higher in the group of salt-sensitive subjects (114.5 ± 8.6 and 115.9 ± 9.9 *v* 109.2 ± 6.7 and 104.9 ± 11.0, respectively; $P < .001$). The MBP during the low-sodium diet was not different between the two groups (Table 2).

The echocardiographic characteristics of the groups are summarized in Table 2. Left ventricular mass index, PWT, RWT, left atrial dimension, and LAI were all significantly higher in the group of salt-sensitive hypertensive patients in contrast to the salt-resistant group. The difference in LVMI and RWT between the two groups was not changed after eliminating any impact of age, gender, BMI, and MBP by employing ANCOVA analysis. Although LAI was still higher in the salt-sensitive group after adjustment for age, gender, BMI and MBP, the difference was not statistically significant (Table 2). There were also significant differences in the prevalences of different patterns of left ventricular geometry between the two groups; con-

TABLE 2. BLOOD PRESSURE VALUES AND ECHOCARDIOGRAPHIC CHARACTERISTICS OF THE SALT-SENSITIVE AND SALT-RESISTANT GROUPS OF 96 PATIENTS WITH ESSENTIAL HYPERTENSION

	Salt-Sensitive Patients (n = 45)	Salt-Resistant Patients (n = 51)
Office systolic blood pressure (mm Hg)	150.7 ± 13.1*	142.9 ± 10.7
Office diastolic blood pressure (mm Hg)	97.6 ± 6.8†	93.2 ± 4.3
Mean arterial blood pressure (mm Hg)		
Normal Na^+ intake	114.5 ± 8.6*	109.2 ± 6.7
Low Na^+ intake	104.0 ± 8.9	105.6 ± 10.8
High Na^+ intake	115.9 ± 9.9†	104.9 ± 11.0
Left ventricular mass index (g/m^2)		
Unadjusted	126.3 ± 28.2*	107.9 ± 26.6
Adjusted¶	124.84 ± 25.74*	109.35 ± 28.12
Left ventricular end-diastolic diameter (cm)	4.7 ± 0.3	4.8 ± 0.4
Posterior wall thickness (cm)	1.03 ± 0.14*	0.96 ± 0.14
Relative wall thickness		
Unadjusted	0.44 ± 0.06†	0.40 ± 0.05
Adjusted¶	0.436 ± 0.046†	0.403 ± 0.063
Left atrial dimension (mm)	39 ± 4.6‡	37.2 ± 4.5
Left atrial index (cm/m^2)		
Unadjusted	2.18 ± 0.27‡	2.06 ± 0.28
Adjusted¶	2.169 ± 0.269	2.078 ± 0.285
Left ventricular geometric patterns (%):		
Concentric hypertrophy	37.8 (OR 4.55)*	11.8
Eccentric hypertrophy	17.8 (OR 0.70)	23.5
Concentric remodeling	11.1 (OR 0.78)	13.7
Normal left ventricle	33.3 (OR 0.48)‡	51.0

OR = odds ratio.

* $P < .01$; † $P < .001$; ‡ $P < .05$.

Values are expressed as mean ± SD.

Values are adjusted for age, gender, body mass index, and mean blood pressure.

centric hypertrophy was significantly more prevalent in the salt-sensitive group (37.8% *v* 11.8% in the salt-resistant group, odds ratio [OR] 4.45; $P < .01$) (Table 2) (Fig. 1).

The prevalence of hypertensive retinopathy in the salt-sensitive group was 84.4% in contrast to 59.6% in the salt-resistant group (OR 3.68, $P < .01$, Table 1, Fig. 2). There was a significant difference between the prevalence of retinopathy between the two groups ($P < .01$) when comparing both for the total number of individuals with retinopathy or for particular grades of retinopathy. When stepwise multivariate regression analysis was performed diastolic blood pressure, left atrial dimension, relative wall thickness, and age appeared as the most significant, although weak, predictors of fundoscopic grade, accounting for 20% of its variance ($F = 5.84$, $P < .0001$).

Table 3 summarizes the results of multivariate regression analysis performed for the LVMI, RWT, and UAE as dependent variables. The presence of salt-sensitive status in hypertensive subjects was an independent predictor of these variables and was statistically associated with an increase in LVMI, RWT, and UAE, with a parameter estimate of 22.68 g/m^2 ($P < .0004$), 0.05 ($P = .0001$), and 3.26 mg/day ($P = .05$), respectively. Age, gender, body mass index, and mean blood pressure did not contribute to these associations. Mean blood pressure appeared not to be an important predictor of LVMI, RWT, or UAE ($P = .17$, $P = .1$, and $P = .9$, respectively).

The model that best predicted serum creatinine level, on the other hand, included left ventricular mass, relative wall thickness, left atrial dimension (mm), UAE, and serum uric acid level and accounted for 42% of its variance ($F = 12.1$, $P < .0001$).

DISCUSSION

Our study demonstrated that hypertensive target organ damage is more severe among the group of salt-sensitive hypertensive subjects. In addition to greater urinary albumin excretion and higher serum creatinine, salt-sensitive subjects were shown to have more severe fundoscopic changes and more severe cardiac involvement, determinated by the presence and magnitude of the left ventricular hypertrophy.

The results of this study also demonstrate that salt sensitivity is associated with older age, which is the finding consistently reported in several studies.[2,19] In

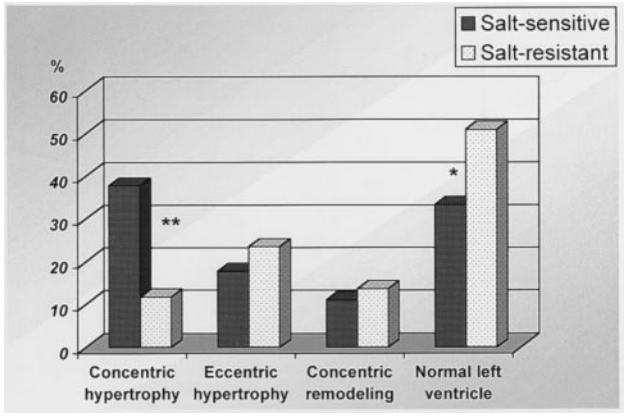

FIG. 1. *Prevalence of different patterns of left ventricular geometric adaptation in the groups of salt-sensitive and salt-resistant patients.* *P $<$ .05; **P $<$ .01.

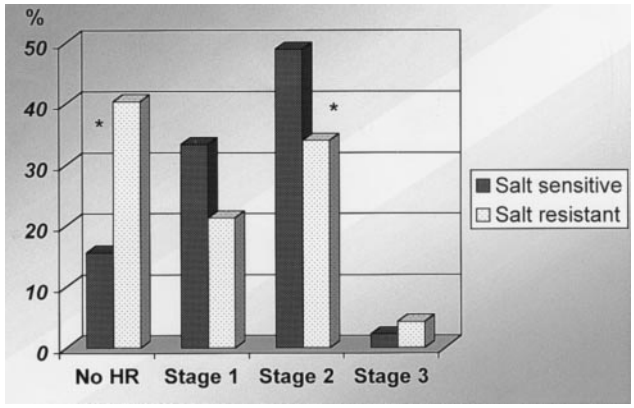

FIG. 2. *Prevalence of hypertensive retinopathy in the groups of salt-sensitive and salt-resistant essential hypertensive patients.* *P $<$ .05.

our population of hypertensive subjects, women tended to be more salt sensitive than men. Although this finding has been reported before,[19,20] it has not been confirmed by all investigators.[21] The higher prevalence of women in our study population may be the potential explanation for such an association. Our results support the correlation between salt sensitivity and obesity reported by several other investigators.[22,23] Significantly higher systolic and diastolic pressures[7,22] also characterized the group of salt-sensitive subjects.

Several studies have demonstrated that salt sensitivity can be a marker for increased cardiovascular risk in patients with essential hypertension, as it is associated with the cluster of well-known risks for atherosclerotic cardiovascular disease, including hyperlipidemia, hyperinsulinemia, and microalbuminuria.[6] Our results support this finding by demonstrating that salt-sensitive subjects tended to have higher serum levels of total and low-density lipoprotein cholesterol (LDL), as well as greater urinary albumin excretion. Nesovic et al have demonstrated that salt-sensitive hypertensive subjects manifest greater urinary albumin excretion than salt-resistant subjects and that this correlation is independent of the duration of hypertension.[22] Bigazzi et al also demonstrated that UAE was higher in salt-sensitive than salt-resistant subjects.[23] They found that during high sodium intake salt-sensitive subjects demonstrated a decrease in renal plasma flow and an increase in filtration fraction and intraglomerular pressure.[23] The increase in albumin excretion rate observed in salt-sensitive subjects during high sodium intake was significantly correlated with glomerular capillary pressure.[23] Moreover, the results of our study indicated that sodium sensitivity is also an important predictor of UAE independently of age, gender, blood pressure, and body mass index. More severe renal involvement in salt-sensitive hypertensive subjects is furthermore supported by our observation of the higher serum creatinine level in this group, which is present even after adjustment for age, BMI, gender, and mean blood pressure differences between the two groups. Microalbuminuria may reflect widespread endothelial dysfunction that permits increased penetration of atherogenic lipoprotein particles into the vessel wall[24] and prevents proper vasodilation of the renal vasculature among hypertensive patients.[24,25] This proposed endothelial dysfunction might underlie the link between an increased UAE and an elevated risk for cardiovascular disease.[25] Several studies have demonstrated that salt-sensitive patients display higher serum levels of low-density lipoprotein cholesterol and lipoprotein (a) and lower levels of high-density lipoprotein cholesterol than salt-resistant patients.[6,8,23,26] Salt-sensitivity is also directly correlated with insulin sensitivity and fasting serum insulin.[6,26] The clustering of these renal and metabolic derangements in salt-sensitive subjects could ultimately lead to a worse renal and cardiovascular prognosis observed in this group of patients with essential hypertension.

Hypertensive retinopathy was present among 84.4% of salt-sensitive patients in our study, compared with 59.6% of salt-resistant subjects, and hypertensive retinopathy is 3.56 times more likely to occur in salt-sensitive subjects. To the best of our knowledge this is the first report that identifies the association between hypertensive retinopathy and salt sensitivity.

On the other hand, just a few studies have addressed the issue of the link between left ventricular hypertrophy and salt-sensitivity status. Heimann et al demonstrated that the left ventricular mass as well as left ventricular end-diastolic diameter were higher in salt-sensitive than in salt-resistant patients.[7] De la Si-

TABLE 3. MULTIVARIATE REGRESSION ANALYSIS

Variable	Left Ventricular Mass Index				Relative Wall Thickness				Urinary Albumin Excretion			
	Estimate (g/m^2)	Lower CI	Upper CI	*P*	Estimate (cm)	Lower CI	Upper CI	*P*	Estimate (mg/day)	Lower CI	Upper CI	*P*
Intercept	−6.3764	−104.775	92.0225	.89	0.1830	−0.0212	0.3873	.07	−25.6684	−59.3223	7.9855	.1
SS status	22.6872	10.5855	34.7888	.0004	0.0511	0.0261	0.0762	.0001	3.2644	−1.5786	8.1075	.05
MBP (mm Hg)	0.5010	−0.2260	1.2281	.17	0.0010	−0.0045	0.0025	.1	−0.0038	−0.2681	0.2604	.9
Age (years)	0.0857	−0.4735	0.6451	.76	0.0016	−0.0091	0.0013	.7	0.0298	−0.1638	0.2234	.7
Gender	−12.6294	−26.0258	0.7669	.06	0.0103	−0.0173	0.0380	.4	−1.2827	−6.1356	3.5701	.6
Creatinine	40.6873	8.7876	72.5870	.01	0.0873	0.0215	0.1532	.009	7.6204	−4.3953	19.6363	.02
(mg/dL)	0.0522	0.0130	0.0391	.33	0.0015	−0.0133	0.0164	.3				
UAE (mg/day)	20.1225	1.1052	41.3503	.06	0.0014	−0.0425	0.0455	.8				
LAI (cm/m^2)												
LVMI (g/m^2)									0.0340	−0.0456	0.1137	.3
RWT (cm)									56.1485	16.3027	95.9942	.006
	$R^2 = 0.42$				$R^2 = 0.34$				$R^2 = 0.32$			
	$F = 7.76$, $P < .0001$				$F = 5.93$, $P < .0001$				$F = 5.64$, $P < .0001$			

SS = salt sensitivity; MBP = mean blood pressure; UAE = urinary albumin excretion; LAI = left atrial index; LVMI = left ventricular mass index; RWT = relative wall thickness; CI = confidence interval.

erra et al studied 50 patients with essential hypertension and showed that LVMI, and septal and posterior wall thickness were significantly higher in a group of salt-sensitive subjects.[8] Gerdts et al were unable to demonstrate a difference in LVM and RWT between salt-sensitive and salt-resistant subjects but the results of this study are limited because of the small number of patients included (eight salt-sensitive and 22 salt-resistant hypertensives).[9] Our study demonstrated that left ventricular mass index, and posterior and relative wall thickness were significantly higher among the salt-sensitive subjects independently of age, gender, body mass index, and mean blood pressure. Furthermore, when we analyzed the prevalence of different types of left ventricular geometric adaptation among the salt-sensitive and salt-resistant subjects, concentric hypertrophy was shown to be significantly more prevalent among the salt-sensitive subjects and salt-sensitive subjects had a fourfold higher risk of developing concentric hypertrophy than salt-resistant subjects. Salt sensitivity is also shown to be a significant predictor of both LVM and relative wall thickness independently of age, gender, and blood pressure. Hypertensive heart disease manifested by the development of left ventricular hypertrophy provides a major risk factor for premature cardiovascular morbidity and mortality[27] and results of the Framingham Heart Study have demonstrated that subjects with concentric hypertrophy have the worst prognosis among hypertensive subjects with LVH.[28]

Although the mechanism underlying this relationship is not clear, it has long been recognized that salt intake is directly correlated with left ventricular mass and hypertrophy.[29] Schmieder et al reported that among patients with essential hypertension dietary salt intake assessed by sodium excretion over 24 h was a powerful determinant of posterior wall thickness, relative wall thickness, and left ventricular mass.[29] Du Cailar et al found that in both normotensive and hypertensive subjects LVM was directly correlated with urinary sodium and this relationship was independent of gender, age, and body weight in both groups.[30] In the group of normotensives the correlation with urinary sodium was the result of an increase in the end-diastolic diameter without a change in PWT, whereas in hypertensive patients it was the consequence of an increase in wall thickness without a modification of left ventricular diameter.[30] Several potential underlying mechanisms of how salt intake modulated myocardial structure have been proposed, including the influence of sodium on left ventricular mass via raised preload, the increased activity of the sympathetic nervous system acting as a mediator,[31] and an abnormality in the renin-angiotensin-aldosterone system.[32] Animal studies performed in Dahl salt-sensitive rats that were used as a model for studying salt-sensitive hypertensive subjects have demonstrated that impaired aortic endothelium-dependent relaxation and decreased aortic compliance positively contributed to left ventricular hypertrophy in addition to but independently of systolic blood pressure.[33] Furthermore, comparative studies of spontaneously hypertensive rats and hypertensive Dahl salt-sensitive rats suggested a link between reduced NOS activity, vascular remodeling, and end-organ damage.[33,34] Accordingly, Ferri et al showed that human salt-sensitive hypertension is associated with increased levels of two markers

of endothelial damage, endothelin-1 and von Willebrand factor, as well as with the augmented ET-1 response to glucose loading.[35] They proposed that endothelial dysfunction may explain the increased risk to develop hypertension-related vascular complications among salt-sensitive subjects.[35]

Another interesting finding of our study is that left atrial index was higher among the salt-sensitive hypertensive subjects. Recently, Simek et al pointed out that in patients with essential hypertension and normal left ventricular systolic function, left atrial size correlates with left ventricular wall thickness and may provide a simple noninvasive assessment of the degree of left ventricular diastolic dysfunction.[36] In our preliminary study we have shown that a significant association exists between the presence of LA enlargement and target-organ damage in hypertensive subjects, including LVH and hypertensive retinopathy, and that the coexistence of left atrial enlargement and left ventricular hypertrophy was remarkable for the group of hypertensive patients with the most severe target organ damage.[37] Obviously, further studies are necessary to elucidate potential pathophysiologic mechanisms involved in the development of particular patterns of left ventricular geometry as well as other cardiac morphofunctional changes in salt-sensitive hypertensive subjects.

The blood pressure changes in response to a high NaCl intake follow a Gaussian distribution.[38] Although salt-sensitive subjects do not represent a discrete, well-defined subset of patients, substantial hemodynamic and hormonal differences have been identified between these two subgroups to justify this subdivision. Several studies have also shown that salt sensitivity defined according to rigid protocols that employ periods of very low salt intake (20 mmol/day) followed by a high salt intake period (220 mmol/day) is highly reproducible even in normotensive subjects[39,40]; this observation furthermore speaks against the possibility of a random effect of NaCl intake on blood pressure. On the other hand, one can argue that the increased age and level of blood pressure might themselves contribute to the observed results despite the independence of salt sensitivity from these factors when analyzed statistically. A prospective, longitudinal study with the individuals carefully matched for the potential contributing variables, including age and blood pressure levels, should eventually resolve this question.

In conclusion, our study demonstrated that salt-sensitive hypertensive patients are more likely to have severe hypertensive target organ damage. More severe cardiac involvement, tendency for the clustering of atherogenic factors such as hyperinsulinemia, hyperlipidemia, and microalbuminuria, and underlying endothelial dysfunction may explain, at least in part, the increased risk of cardiovascular and renal morbidity among salt-sensitive hypertensive patients.

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