Salt-sensitivity in essential hypertension: diagnosis, pathophysiology and associated cardiovascular risk

A. de la Sierra, E. Bragulat, V. Giner, M.T. Aguilera, C. Sierra, E. Gómez-Angelats, M.T. Antonio, A. Coca.
Hypertension Unit. Department of Internal Medicine. Hospital Clínic. 170-Villarroel. 08036-Barcelona, SPAIN.

1. INTRODUCTION

Several epidemiological and interventional studies have demonstrated a close relationship between salt intake and hypertension, although the blood pressure response to an excessive salt intake is heterogeneous in both hypertensive and normotensive subjects. Salt-sensitivity is clearly established in experimental hypertension, but the studies on salt-sensitivity conducted in humans have brought up several problems regarding definition and methods.

The underlying mechanisms involved in the pathogenesis of salt-sensitivity are not well established. Several mechanisms have been proposed to explain the blood pressure elevation in salt-sensitive individuals, such as an increase in sodium retention during high-salt intake with a rightward shift of the pressure natriuresis curve, an increase in sympathetic nervous system activity, an enhanced blood vessel response to vasoconstrictor agonists and an insufficient decrease in the renin-angiotensin-aldosterone axis during high-salt intake. Finally, it has been suggested that salt-sensitive hypertensive subjects might have an increased risk in terms of cardiovascular morbidity.

The aims of the present study were: 1) the assessment of salt-sensitivity in essential hypertension using reproducible definition criteria, 2) a more comprehensive knowledge of the underlying mechanisms of salt-sensitivity at hormonal and cellular level, and 3) the evaluation of distinctive clinical features in patients with salt-sensitive hypertension.

2. DESIGN AND METHODS

Fifty essential hypertensive patients (23men, 27 women), aged 25 to 72 years (mean 52 years) were placed on low-salt diet (20 mmol Na/day), supplemented by placebo and NaCl tablets (240 mmolNa/day) one week each. Baseline evaluations included biochemical measurements and left ventricular mass index (LVMI) determination by echocardiography. At the end of both low salt and high-salt period, all patients underwent 24-hour ambulatory blood pressure monitoring (ABPM), 24-hour urinary sodium, biochemical measurements, plasma hormones including plasma renin activity (PRA), aldosterone, noradrenaline and atrial natriuretic peptide (ANP), intraplatelet pH and calcium concentration and maximal rates of erythrocyte Na/K ATPase, Na/K/Cl cotransport, Na/Li countertransport and Na-dependent Cl/HCO_3 exchange. Salt sensitive hypertension was diagnosed when 24-hour mean blood pressure significantly increased ($p<0.05$; >4 mmHg) when patients switched form the low to the high salt intake.

3. RESULTS

3.1. Blood pressure changes and prevalence of salt sensitive hypertension

Twenty-two essential hypertensive patients (44%) showed a significant increase ($p<0.05$) in 24-h mean BP from low to high salt intake and were diagnosed of salt-sensitive (SS). Conversely, 28 hypertensives did not modify their BP values and were considered as having salt resistant hypertension (SR). Table 1 shows mean systolic (SBP) and diastolic (DBP) BP values during low and high salt intake in SS and SR.

3.2. Clinical differences between salt-sensitive and salt-resistant hypertensives

Compared with SR hypertensives, SS patients exhibited lower values of HDL-cholesterol (1.1±0.1 vs. 1.3±0.1 mmol/L; $p<0.05$), higher total cholesterol/HDL-cholesterol ratio (5.9±0.4 vs. 4.7±0.3; $p<0.01$). As shown in table 2, left ventricular parameters were significantly different between groups and, consequently, the proportion of patients with left ventricular hypertrophy was significantly higher ($p<0.05$) in SS (96%), compared with SR patients (61%).

Table 1. Blood pressure during low (LS) and high salt (HS) intakes

24-h BP	Salt-sensitive (n=22)		Salt-resistant (n=28)	
	LS	HS	LS	HS
SBP	145±3	154±4*	147±3	147±4
MBP	110±3	116±3*	110±2	110±3
DBP	91±2	95±2*	90±2	88±2

All values in mmHg; *p<0.001

Table 2. Left ventricular parameters in salt-sensitive and salt-resistant patients

Parameter	Salt-sensitive (n=22)	Salt-resistant (n=28)
PWT (mm)	12.0±0.4	10.4±0.3*
IST(mm)	12.7±0.4	11.1±0.3*
LVEDD (mm)	51.5±1.1	51.4±1.6
LVMI (g/m^2)	164±8	138±6#
WTR	0.5±0.02	0.4±0.02#

*p<0.01; #p<0.05

3.3. Differences in hormonal adaptations between salt-sensitive and salt-resitant hypertensive patients

High salt intake induced a significant decrease in PRA, aldosterone, and ANP in the whole group of essential hypertensive patients. However, the response of the renin-aldosterone axis to high salt was blunted in SS patients. As shown in Table 3, the decrease in plasma aldosterone was significantly more pronounced in SR, compared with SS patients. Likewise, SS presented an increase in plasma noradrenaline when exposed to high salt intake, whereas mean values of this neurohormone decreased in SR patients.

3.4. Erythrocyte sodium transport systems and intraplatelet pH and calcium concentration

In the whole group of patients studied, high salt intake induced a significant increase in the maximal rate of erythrocyte Na/Li countertransport and Na-dependent HCO_3/Cl exchanger. Likewise, intraplatelet and calcium significantly increased with high salt intake in the whole group of hypertensives.

As shown in table 4, high salt intake promoted opposing changes in some of the transport systems studied, depending on salt sensitivity. Compared with SR patients, SS hypertensives significantly increased maximal rates of Na/K ATPase, Na/K/Cl cotransport and Na/Li countertransport with high salt intake.

Table 3. Values of vasoactive hormones during low (LS) and high salt (HS) intakes

	SS (n=22)		SR (n=28)	
	LS	HS	LS	HS
PRA	0.2±0.1	0.1±0.1	0.5±0.2	0.2±0.1
ALDO	485±76	364±83	446±35	226±35*
ANP	15±2	24±3*	15±2	24±4*
NOR	1.2±0.1	1.6±0.1*	1.5±0.1	1.1±0.1*#

PRA: plasma renin activity in pmol/mL/h; ALDO: serum aldosterone in pmol/L; ANP: atrial natriuretic peptide in fmol/L, NOR: norepinephrine in nmol/L; *p<0.05 comparing low vs. high salt intake, #p<0.05 comparing SS vs. SR patients.

Table 4. Erythrocyte sodium transport systems, intraplatelet pH, and calcium content during low (LS) and high salt (HS) intakes

	SS (n=22)		SR (n=28)	
	LS	HS	LS	HS
Pump	7.0±0.4	8.8±0.4*#	8.0±0.4	6.9±0.3*
CO	416±37#	612±41*#	578±53	481±43*
CT	248±20	389±17*#	289±29	275±26
EX	1.0±0.1	1.2±0.1	0.9±0.1	1.2±0.1
pH	7.1±0.2#	7.2±0.3	7.2±0.2	7.2±0.2
Ca	47±2.5	58±4	50±2.3	57±2.9

Pump: Na/K ATPase in mmol/L.cells/h; CO: Na/K/Cl cotransport; CT: Na/Li countertransport, both in µmol/L.cells/h; EX: HCO_3/Cl exchanger in mmol/L.cells/h; pH: intraplatelet pH; Ca: intraplatelet calcium concentration in nmol/L. ; *p<0.05 comparing low vs. high salt intake, #p<0.05 comparing SS vs. SR patients.

4. CONCLUSION

Only less than one half of essential hypertensive patients exhibit sensitivity to the pressor effect of high salt intake. Salt sensitive patients tend to have other cardiovascular risk factors, as left ventricular hypertrophy and a worse lipid profile. From a pathophysiological point of view, salt-sensitivity is characterized by misadaptations of the renin-angiotensin system, the sympathetic nervous system and the transmembranous sodium transport systems.

REFERENCES

1. De la Sierra A, Lluch MM, Coca A, et al. Am J Hypertens 1995; 8: 970-977.
2. De la Sierra A, Lluch MM, Paré JC, et al. J Human Hypertens 1996; 10: 795-799.
3. De la Sierra A, Lluch MM, Coca A, et al. Clin Sci 1996; 91: 155-161.
4. Lluch MM, De la Sierra A, Poch E, et al. Hypertension 1996; 27: 919-925.