Abnormal Renal Hemodynamics in Salt-Sensitive Patients with Essential Hypertension

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Thirty hypertensive patients were studied during a low-sodium diet for three days and a high-sodium diet for six days. They were classified as "salt-sensitive" (SS) ($n = 10$) or "non-salt-sensitive" (NSS) ($n = 20$) based on the increase in mean blood pressure (BP) with changes in sodium intake from 25 mEq/day to 250 mEq/day ($14.7 \pm 1.3\%$ versus $4.0 \pm 0.8\%$, $p < 0.001$). With the high-sodium diet, the SS patients had a greater increase in cardiac output ($p < 0.001$), and the increment in mean BP with the salt loading significantly correlated to that in cardiac output ($r = 0.672$, $p < 0.01$). Thus, the increase in BP during short-term salt loading may be attributed to the increase in cardiac output. The role of renal hemodynamics in the increment of BP with salt loading after sodium restriction was evaluated in six SS and 14 NSS patients. Although the glomerular filtration rate was not different in the two groups, the renal vascular resistance was greater ($p < 0.05$) in the SS patients than in the NSS ones. Moreover, renal vascular resistance positively correlated to the increment in mean BP with salt loading ($r = 0.612$, $p < 0.01$). Thus, it is suggested that renal vasoconstriction may be an important factor influencing "salt-sensitivity" in essential hypertension, possibly via the impaired renal sodium excretion.

EXCESSIVE sodium intake is believed to play a role in the development of hypertension in man,¹ and the loss of salt produced by diuretics is often associated with a decrease of blood pressure (BP) in hypertensive patients.^{2,3} It has been proposed that the expansion of extracellular fluid volume is an important initial event,⁴⁻⁶ although the precise mechanisms by which salt intake increases BP in hypertensive humans is still unknown.

In previous studies,⁷⁻⁹ patients with essential hypertension were classified as "salt-sensitive" (SS) or "non-salt-sensitive" (NSS) as estimated from the BP rise with increase in sodium intake. On a high-salt diet, the SS hypertensive patients retained more sodium and gained more weight,

with greater increase in BP, than did the NSS patients. There were no significant differences between the two groups in plasma electrolyte concentrations or in glomerular filtration rate (GFR). Fujita et al^{8,9} demonstrated that pressor and depressor substances may be involved in the impaired sodium excretion and the resultant higher BP with sodium load in the SS patients. In the previous studies, however, the renal factors responsible for excessive sodium retention in the SS patients and their relationship to BP have not been evaluated.

It is well known that renal hemodynamics, such as GFR and renal blood flow (RBF), play an important role in the control of renal sodium excretion. Many investigators¹⁰⁻¹³ reported that in some patients with mild to moderate essential hypertension, RBF was decreased despite normal level of GFR. Thus, an increased filtration fraction may enhance the renal sodium reabsorption,¹⁴ and may cause sodium retention in

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TABLE I DATA IN SYSTEMIC AND RENAL HEMODYNAMICS

	Salt-Sensitive		Non-Salt-Sensitive	
	Low-Na	High-Na	Low-Na	High-Na
Mean BP (mmHg)	99.4 ± 2.6	113.8 ± 2.5*	102.9 ± 2.0	106.8 ± 1.9
Difference (%)	14.7 ± 1.3**		4.0 ± 0.8	
Heart Rate (/min)	69.6 ± 2.0	69.5 ± 2.7	71.0 ± 2.0	66.3 ± 1.5
Difference (%)	-0.2 ± 2.3		-6.1 ± 1.9	
Cardiac Index (L/min/m ²)	3.19 ± 0.37	3.84 ± 0.41	3.16 ± 0.15	3.40 ± 0.14
Difference (%)	26.3 ± 4.3**		8.3 ± 1.5	
SVR (dynes·sec·cm ⁻⁵ ·m ²)	2804 ± 231	2531 ± 184	2786 ± 148	2667 ± 133
Difference (%)	-8.8 ± 2.8		-3.3 ± 2.0	
RBF (ml/min/1.73 m ²)	735.1 ± 60.8	753.9 ± 40.6	854.2 ± 45.5	876.2 ± 40.1
Difference (%)	5.3 ± 7.9		4.4 ± 4.8	
RVR (units)	12.26 ± 0.88*	12.49 ± 0.79**	9.99 ± 0.56	9.65 ± 0.57
Difference (%)	3.8 ± 7.2		-2.0 ± 4.3	
Creatinine Clearance (ml/min/1.73 m ²)	110.9 ± 7.0	116.3 ± 5.2	116.7 ± 5.5	120.6 ± 3.4
Difference (%)	7.1 ± 4.8		6.8 ± 4.6	

Low-Na = the 3rd day of the low-sodium diet; High-Na = the 6th day of the high-sodium diet.

**p* < 0.05, versus Non-Salt-Sensitive

***p* < 0.01.

TABLE II CORRELATION TO % CHANGE IN MEAN BP WITH SALT LOADING

	Basal Value	% Change with Salt Loading
Cardiac Index	<i>r</i> = -0.126 (N.S.)	<i>r</i> = 0.672 (<i>p</i> < 0.01)
SVR	<i>r</i> = 0.141 (N.S.)	<i>r</i> = -0.273 (N.S.)
RBF	<i>r</i> = -0.466 (<i>p</i> < 0.05)	<i>r</i> = -0.037 (N.S.)
RVR	<i>r</i> = 0.612 (<i>p</i> < 0.01)	<i>r</i> = 0.081 (N.S.)
Creatinine Clearance	<i>r</i> = -0.325 (N.S.)	<i>r</i> = 0.143 (N.S.)

some patients with essential hypertension. Therefore, an elevated renal vascular resistance (RVR) may be a possible candidate to cause an increased "salt-sensitivity".

In order to examine whether the RVR in the SS patients is increased or not, and how any increased RVR may participate in the BP rise with sodium loading, the association between renal circulation and the increase in BP with sodium loading after salt restriction was studied in the SS patients with essential hypertension.

MATERIALS AND METHODS

Thirty patients with essential hypertension (23 men, seven women) were studied. These patients had mild to moderate hypertension, with casual (morning) clinic BP from 150 to 180 mmHg systolic and 90 to 115 mmHg diastolic.

The patients underwent the usual evaluation for hypertension, including serum electrolytes, urinalysis, electrocardiography, and intravenous pyelography. All subjects gave informed consent prior to the study.

All antihypertensive medications were discontinued for at least 2 weeks before admission. Each subject was maintained on a regimen of constant activity and on a daily diet containing 25 mEq of sodium and 50 mEq of potassium ("low-sodium diet").¹⁵ Patients were studied for 3 days with this diet to which 140 mEq of sodium chloride (NaCl) was added each day ("normal-sodium diet"). Then, the low-sodium diet alone was given for 3 days, followed by 6 days of the low-sodium diet to which 225 mEq of NaCl was added each day ("high-sodium diet"). On the first day of the low-sodium diet, 40 mg of furosemide was injected intravenously.

Fig. 1. Renal vascular resistance in the SS and NSS patients.

Throughout the study BP was measured by sphygmomanometer every 4 hours, after the patients had been supine for 5 minutes or longer.¹⁵ For statistical comparison of the effects of dietary sodium on BP, mean BP was calculated for every 4-hour reading as diastolic pressure plus one-third of the pulse pressure, for the third day of the normal- and low-sodium diet and the 6th day of the high-sodium diet.

The hemodynamic study was performed on the third day of the low-sodium diet and on the 6th day of the high-sodium diet. Cardiac output (CO) was determined by dye dilution (indocyanine green).^{15,16} The measurements were made in the morning after the patients had rested supine for at least 30 minutes. Systemic vascular resistance (SVR) was calculated as the ratio of mean BP to CO, expressed in dynes·sec·cm⁻⁵·m².

Renal blood flow (RBF) was determined by the single injection clearance of ¹³¹Iodine para-amino hippurate (¹³¹I-PAH)¹⁷ on the basis of the model proposed by Sapirstein et al.¹⁸ The fasting patients were recumbent for 30 minutes prior to ¹³¹I-PAH injection. Sixty μ Ci/1.73 m² of ¹³¹I-PAH were injected intravenously and then heparinized 5-ml blood samples were drawn at 5, 10, 15, 20, 30, 40, 50, 60 minutes after injection. Renal plasma flow was calculated as proposed by Sapirstein.¹⁸ This value was corrected for hematocrit and body surface area. Renal vascular resistance (RVR) was calculated as the ratio of mean BP to RBF, expressed in

unit of dynes·sec·cm⁻⁵·(1.73 m²).

Numerical results are expressed as means $\pm$ standard errors of the mean. Statistical analysis of the data was performed using Student's paired- and unpaired-t test and regression analysis according to standard procedure. Differences at a 5% level ($p < 0.05$) were considered significant.

RESULTS

Ten patients were categorized as SS, and 20 as NSS by the criteria previously proposed.⁸ There was no significant difference in age, sex distribution, or body weight. Also there was no significant difference in known duration of hypertension, or in either systolic and diastolic BP, or in secondary effects of hypertension, as revealed by the incidence of left ventricular hypertrophy, creatinine clearance, or the concentrations of either electrolytes.

The average mean BPs for the SS group taking the normal-sodium diet, the low-sodium diet, the high-sodium diet were 109.4 ± 2.3 , 99.4 ± 2.6 , 113.8 ± 2.5 mmHg, respectively (Table I). Corresponding averages of mean BP value for the NSS group were 107.3 ± 2.2 , 102.9 ± 2.0 , 106.8 ± 1.9 mmHg, respectively. The mean BP values during the normal- or low-sodium diet did not differ in the groups, but during the high-sodium diet the value was significantly ($p < 0.05$) higher in the SS patients than in the NSS ones. The mean decrease in mean BP between the normal-sodium and low-sodium diets was significantly ($p < 0.01$) greater in the SS patients than in the NSS ones ($-9.2 \pm 1.5\%$ versus $-4.3 \pm 0.9\%$). Also, the mean increment in mean BP with the sodium loading differed significantly ($p < 0.001$) between the SS and NSS groups ($14.7 \pm 1.3\%$ versus $4.0 \pm 0.8\%$; Table I).

Urinary sodium during the normal-sodium diet was not significantly different in either group (175.2 ± 10.0 mEq/day versus 170.9 ± 9.7 mEq/day, N.S.). On the 3rd day of sodium restriction, urinary sodium was decreased equally in both groups (25.3 ± 6.4 mEq/day versus 29.5 ± 2.8 mEq/day, N.S.). On the last day of the high-sodium diet, urinary sodium was quite close between the SS and NSS patients (253.6 ± 14.3 mEq/day versus 262.2 ± 8.9 mEq/day, N.S.), despite the significantly ($p < 0.05$) higher level of BP in the SS patients (113.8 ± 2.5 mmHg versus 106.8 ± 1.9 mmHg).

As shown in Table I, the average level of CO

on the third day of the low-sodium diet did not differ in the two groups. However, the increase in CO with sodium loading was significantly ($p < 0.001$) greater in the SS patients than in the NSS ones ($26.3 \pm 4.3\%$ versus $8.3 \pm 1.5\%$). Moreover, the increment in CO was significantly ($r = 0.672$, $p < 0.01$) correlated to that in mean BP with sodium loading (Table II). However, the change in SVR did not differ between the groups, nor did correlate to the increment of BP.

RBF was measured in six SS and 14 NSS patients. The SS patients had slightly lower RBF than did the NSS ones, but the difference was not significant (Table I). However, RBF was significantly ($r = -0.466$, $p < 0.05$) correlated to the increase in BP with sodium loading. In the SS patients RBF remained unchanged with salt loading in spite of markedly greater increase in CO.

Although SVR was not different in the groups, RVR was significantly ($p < 0.05$) higher in the SS patients than in the NSS ones (12.26 ± 0.88 units versus 9.99 ± 0.56 units; Table I, Fig. 1). Moreover, RVR during the low-sodium diet was significantly ($r = 0.612$, $p < 0.01$) correlated to the increment in mean BP with sodium loading (Table II).

DISCUSSION

In order to study the related valuables, we have divided hypertensive patients into two groups according to the response of BP to the salt loading;^{8,9} those with a response of 10% or more are termed "salt-sensitive" (SS) and those with a response less than 10% are termed "non-salt-sensitive" (NSS). We found that the extent of increase in CO with salt loading was significantly greater in the SS patients than in the NSS ones, which is similar our to previous observation.⁸ In all patients, the increment in BP positively correlated to that in CO. Thus, the increase in BP with salt loading in the SS patients may be attributed to the concomitant increase in cardiac output, probably via excessive sodium retention.^{7,8} Thereafter, several investigators have reported that the increased BP was associated with increased cardiac output^{8,19-21} increased peripheral resistance^{20,22,23} and/or decreased venous distensibility²⁴; and then the hemodynamic mechanisms for the BP rise with salt loading may be more complicated. However, the effect of the sodium retention may be most

important as a basic initial event of BP rise with salt loading. Therefore, an impaired renal sodium excretion seems to be the central cause of the BP rise with salt loading in the SS patients.

The renal abnormalities to shift the pressure-natriuresis relationship toward the development of high BP are mainly following; decreased glomerular filtration rate or increased renal vascular resistance.²⁵ It is unlikely that the alteration in GFR causes the increased BP with sodium loading in the SS patients, since creatinine clearance did not differ between the groups, as previously reported.^{8,9} On the other hand, RVR was significantly higher in the SS patients than in the NSS ones. Moreover, there is the highly significant correlation between RVR and the increase in BP. Thus, the increase in the renal vascular resistance in the SS patients can induce the impaired renal sodium excretion leading to the increase in BP with sodium loading, and the filtration fraction may be increased as a result of increased RVR without concomitant decrease in GFR. The increased oncotic pressure of plasma in the peritubular hydrostatic pressure in the peritubular capillaries may therefore, enhance sodium reabsorption.¹⁴

The question arises whether the elevated RVR in the SS patients might be a secondary effect of high BP. However, the evidence dose not oncotic pressure of plasma and the decreased of systolic and diastolic BP and the variances (67.6 versus 80.0 , $F = 1.18$, N.S.) were quite close between the SS and NSS patients. In addition, there was no significant correlation between mean BP and RVR ($r = 0.022$, N.S.). However, many investigators^{10,12,13} have reported that there was a decrease in RBF and an increase in RVR with increasing BP. These previous studies included a wide range of BP levels from normotensive to severe hypertensive. In patients with benign essential hypertension (without normotension or malignant hypertension), there was no correlation between BP and RBF.¹² Thus, the increased RVR in some patients with benign hypertension did not appear to be a consequence of hypertension.

A lot of evidence suggests that the increase in RVR that characterizes the patients with essential hypertension is due to functional rather than morphological change. The RVR response to nonspecific vasodilators was heightened in patients with essential hypertension, and the potentiated flow response was often associated with a reversal of the abnormalities seen in the

renal arteriogram.²⁶ In addition, patients with essential hypertension had a two- to three-fold larger variation in RBF when compared with normal subjects.^{27,28} Biopsies from some patients with established hypertension may often show normal histology or only minor changes suggestive of arteriolar spasm.^{29,30}

In the present study, the SS patients had the greater RVR in spite of the similar level of systemic vascular resistance when compared with the NSS patients, indicating that the vasoconstriction in the kidney may occur on the selective basis. Also, during sodium loading, the SS patients showed an insignificant change in RBF despite the markedly greater increase in CO. Thus, the possibility exists that the increased renal vascular resistance in the SS patients may be a functional abnormality.

Many extrarenal factors may regulate renal vascular tone. For example, renal vascular beds have the exquisite sensitivity to angiotensin II.³¹ Angiotensin II may constrict the efferent arterioles of the kidney, resulting in enhanced renal sodium reabsorption.²⁵ On the other hand, it has been demonstrated that the sympathetic nervous system influences renal sodium excretion.³² Although the renal arteriole showed almost the same sensitivity to the circulating norepinephrine as other vascular beds,³¹ the sympathetic vasoconstrictor fibers exert maximal effects in the kidney when compared with other vasculature.³³ Moreover, the long-term stimulation of the sympathetic nerve to the kidney^{25,34} and intrarenal infusion of norepinephrine³⁵ caused the development of hypertension. In addition, vasodilator substances, such as prostaglandin³⁶ and kinin,³⁷ may influence renal vascular tone, so that the control mechanism for renal vascular resistance is more complex. Further studies are necessary to clarify the cause of the disturbance to the regulation of renal hemodynamics and the rise in BP with salt loading.

In summary, the data suggest that the greater increase in BP with salt loading in the SS patients can be attributed to an increase in cardiac output, possibly resulting from a greater sodium retention. The mechanism for impaired renal sodium excretion in the SS patients may be mainly due to the increase in the renal vascular resistance.

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