Pressor Reactivity to Norepinephrine and Angiotensin in Salt-Sensitive Hypertensive Patients

Vito M. Campese, Frederick Karubian, Indira Chervu, Mario Parise, Nadim Sarkies, and Roberto Bigazzi

The mechanisms responsible for increased blood pressure in response to a high dietary sodium intake in salt-sensitive patients with essential hypertension are only partially understood. The possibility that increased reactivity to pressor hormones might contribute to hypertension in these patients has not been adequately investigated. We studied 11 salt-sensitive and 15 salt-resistant patients with essential hypertension while they were ingesting a diet with 20 meq/day sodium for 9 days or one with 200 meq/day sodium for 14 days. During the last 4 days of each dietary regimen, they received 30 mg/day of slow-release nifedipine. Blood pressure response to increasing doses of norepinephrine and angiotensin II (Ang II) was studied at the end of each of four phases of the study. Salt-sensitive patients exhibited a greater blood pressure response to norepinephrine than salt-resistant patients, irrespective of the dietary sodium intake and whether we took into account the dose infused or the actual plasma levels of norepinephrine achieved during the infusion. The blood pressure response to Ang II, on the other hand, was greater in salt-sensitive than salt-resistant patients during low but not during high sodium intake. The blood levels of norepinephrine achieved during the infusion of this hormone were lower in salt-sensitive than in salt-resistant patients. These studies indicate that an increased reactivity to the pressor action of norepinephrine might contribute to the maintenance of hypertension in salt-sensitive patients. The increased reactivity appears to be specific for norepinephrine. In fact, we observed increased reactivity to Ang II during low but not during high sodium intake. Because salt-sensitive patients usually display suppressed levels of renin, the greater pressor response to Ang II during low sodium diet could be due to upregulation of Ang II receptors. Our studies also point to substantial differences in norepinephrine metabolism between salt-sensitive and salt-resistant patients with essential hypertension. (Hypertension 1993;21:301-307)

KEY WORDS • hypertension, sodium-dependent • kinetics

Patients with essential hypertension display a great variability in their blood pressure response to a sodium load. Kawasaki et al were the first to classify patients with essential hypertension as salt sensitive (SS) or salt resistant (SR) based on their blood pressure response to a sodium load, a finding confirmed by several other laboratories. However, because the blood pressure changes in response to high sodium (Na⁺) intake follow a Gaussian distribution, any subdivision of hypertensive patients according to this criterion is arbitrary. Nonetheless, pathophysiological and clinical considerations still justify a classification of SS and SR hypertensive patients. We have classified as SS those patients who display a rise in blood pressure of at least 10 mm Hg during a 200-meq/day Na⁺ diet, in comparison with a diet containing only 10-20 meq of Na⁺ per day.

Weinberger et al studied the blood pressure response to rapid volume expansion and contraction in 192 hypertensive patients and in more than 300 normal subjects and found that 51% of patients with hypertension were SS, 16% were SR, and the remaining had an intermediate response. In addition, salt sensitivity was more frequent in black and older patients than in white or younger patients. Using a different protocol and different criteria for classification, we have observed that approximately 50% of patients with essential hypertension are SS.

Several laboratories have studied the mechanisms responsible for the varied blood pressure response to dietary sodium in essential hypertension. One hypothesis proposes that salt sensitivity may be related to an inborn reduced ability of the kidneys to excrete a sodium load and to the consequent volume expansion. Williams and Hollenberg have suggested that salt sensitivity may be due to a defect of modulation of renin release and renal vascular tone, but they exclu...
TABLE 1. Clinical Characteristics of Salt-Sensitive and Salt-Resistant Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Salt-resistant</th>
<th>Salt-sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52±2.6</td>
<td>47±3.0</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>9/6</td>
<td>10/1</td>
</tr>
<tr>
<td>Race</td>
<td>9W/6B</td>
<td>11B</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>83±4.0</td>
<td>89±4.7</td>
</tr>
</tbody>
</table>

W, white; B, black.

sively evaluated patients with normal to increased plasma renin activity. Extensive evidence also suggests that sodium retention and hypertension in SS patients may be related to increased activity of the sympathetic nervous system or to an increase in the norepinephrine-to-dopamine secretion ratio.\(^{21,24}\)

The possibility that an abnormal response to pressor agonists might contribute to salt sensitivity has not been properly investigated. In the present study, we evaluated the blood pressure response to norepinephrine and to angiotensin II (Ang II) in SS and SR patients with essential hypertension during low and high Na\(^+\) intake and after the administration of a calcium channel blocker, nifedipine. The reason for choosing a calcium channel blocker was that some have proposed the sodium-linked calcium channels is unclear. In the latter case, a calcium blocker should interfere with the sodium-linked cellular calcium transport and revert the hemodynamic and hormonal abnormalities observed in SS patients with hypertension.\(^{15}\)

Indeed, in a recent study, we have shown that high Na\(^+\) intake increased arterial pressure and [Ca\(^{2+}\)] in lymphocytes of SS patients, an effect that was completely reverted by nifedipine.\(^{16}\)

Methods

Thirty-one patients with essential hypertension and normal renal function were included in these studies; demographic characteristics of 26 of the patients are shown in Table 1.

Exclusion criteria included patients with a creatinine clearance less than 80 mL/min; a history of myocardial infarction, congestive heart failure, stroke, diabetes mellitus, or liver disease; women with childbearing potential or on birth control pills; and patients known to abuse drugs or alcohol. Patients were considered to be hypertensive if, after discontinuation of antihypertensive medications for at least 2 weeks, they manifested blood pressure values equal to or greater than 140/90 mm Hg during three subsequent clinic visits to the Outpatient Clinic. A diagnosis of secondary hypertension was adequately ruled out by the findings of normal SMA-19, urinalysis, and chest x-rays. These studies were previously approved by the Human Research Committee of the University of Southern California.

After the nature and purpose of the study were explained and informed consent obtained, all patients were admitted to the Clinical Research Center of the Los Angeles County–University of Southern California Medical Center for a period of 23 days. Throughout the study, the subjects ingested the same basic diet containing constant amounts of protein (1.3 g/kg body wt), calories (30 kcal/kg body wt), calcium (800 mg per 24 hours), and potassium (80 meq/day), while their Na\(^+\) intake varied.

During the first 9 days, patients received 20 meq/day Na\(^+\), and during the remaining 14 days, they received 200 meq/day Na\(^+\). During the first 5 days of the low Na\(^+\) diet (phase 1) and the first 10 days of the high Na\(^+\) diet (phase 3), patients received a placebo; during the last 4 days of the low phase (phase 2) and high phase (phase 4) Na\(^+\) diet, they received nifedipine GITS (Gastrointestinal Transport System, Pfizer Laboratories, New York). The duration of phase 3 was extended to 10 days to avoid the possibility that residual nifedipine effect from phase 2 might influence the hemodynamic response to high Na\(^+\) intake.

An additional five black patients, four men and one woman, were included in the study to compare blood pressure response between SS and SR patients. All these patients received a low Na\(^+\) diet for 6 days and a high Na\(^+\) diet for 6 more days, but did not receive nifedipine, and were SR.

All subjects were weighed daily at 8 AM, after they had voided and before they had eaten breakfast. Twenty-four-hour urine collections were obtained daily for measurement of creatinine, sodium, and potassium excretion.

Infusions of Ang II and norepinephrine were performed on the last day of each phase of the study. Patients assumed the recumbent position between 7 and 8 AM, and a venous catheter was inserted into a vein in both forearms, one vein being used for blood collection and the other for infusion of norepinephrine and Ang II. One hour later, a blood sample was obtained for the determination of serum sodium, potassium, and creatinine levels and hematocrit, and measurements of blood pressure and heart rate were performed at 2-minute intervals. After baseline measurements, norepinephrine was infused at incremental doses of 10, 20, 50, and 100 ng/kg body wt per minute, each dose given for 10 minutes, and blood was drawn for measurement of plasma norepinephrine at baseline and at the end of the administration of 20 and 100 ng/kg per minute. Thirty minutes after the end of norepinephrine infusion, Ang II was administered at stepwise incremental doses of 0.5, 1, 3, and 6 ng/kg body wt per minute, each dose given for 10 minutes. Norepinephrine and Ang II pressor doses were calculated from the dose–response curves as the doses that increased mean arterial pressure by 20 mm Hg.

Blood pressure was measured with an automatic recorder (Omega 1000 In Vivo Research Laboratories, Inc., Tulsa, Okla.), and each recorded value represents the mean of at least three consecutive readings. Mean arterial pressure (MAP) was calculated as the sum of diastolic blood pressure and one third of pulse pressure. Sodium and potassium were determined by a flame photometer (Instrumentation Laboratories, Lexington, Mass.), creatinine by an autoanalyzer (Technicon Corp., Ardsley, N.Y.), and plasma catecholamines by high
performance liquid chromatography using an electrochemical detector (Shimadzu, Tokyo).

Statistical analysis of data was performed by analysis of variance for comparison between means, by Fisher’s exact test for multiple comparisons, and by linear regression analysis. Data are expressed as mean±SEM.

Results

Patients were divided into two distinct groups based on whether their MAP increased by 10 mm Hg or more on a high compared with a low dietary Na+ intake. The criterion of 10 mm Hg used to classify patients as SS and SR was based on our previous observation that during high Na+ intake, normal subjects without a predisposition to developing hypertension manifest an increase in MAP of less than 10 mm Hg.2 Based on this definition, 11 patients were classified as SS and 15 as SR.

The clinical characteristics of SS and SR patients have been previously published17 and are shown in Table 1. The mean age of SS patients was 47±3.0 years, not different from the mean age of SR patients (52±2.6 years). All SS patients were black, whereas nine SR patients were white and six were black.

During low dietary Na+ intake, SS and SR patients had a similar MAP (100±3.3 versus 102±2.7 mm Hg), but during high dietary Na+ intake, MAP increased to 114±3.6 mm Hg (p<0.01) in SS patients and remained unchanged in SR patients (98±2.0 mm Hg). In SS patients ingesting high Na+, nifedipine decreased MAP to levels comparable to those achieved during a low Na+ diet (from 114±3.6 to 103±3.2 mm Hg, p<0.01).

The blood pressure response to infused norepinephrine was greater in SS than in SR patients during each of the four phases of the study, the phases being low sodium, low sodium plus nifedipine, high sodium, and high sodium plus nifedipine (Figure 1).

The norepinephrine pressor dose, that is, the calculated dose that increased MAP by 20 mm Hg, was lower (p<0.05) in SS (82±11.1 ng/kg per minute) than in SR (180±39.6 ng/kg per minute) patients during low and high Na+ intake (50±8.4 and 76±17.1 ng/kg per minute, respectively) (Figure 2). In SS patients, nifedipine increased the norepinephrine pressor dose from 82±11.1 to 122±42.7 ng/kg per minute (p<0.05) during the low Na+ diet but not during the high Na+ diet (50±8.4 and 75±12.9 ng/kg per minute, respectively). In SR patients, nifedipine increased (p<0.05) the norepinephrine pressor dose from 180±39.6 to 277±41.9 during low and from 76±17.1 to 139±24.6 ng/kg per minute during high Na+ intake.

The plasma norepinephrine levels attained in SS patients after administration of 100 ng/kg body wt/per minute were significantly lower than those in SR patients during both low and high Na+ intake (Figure 3).

When blood levels of norepinephrine rather than infused doses were plotted against blood pressure response, SS patients again manifested significantly greater (p<0.05) blood pressure response to norepinephrine than SR patients during the four phases of the study (Figure 4).

The Ang II pressor dose was also lower (p<0.05) in SS than in SR patients during the low Na+ diet (2.9±0.42 and 7.8±3.1 ng/kg per minute, respectively) and during the low Na+ diet plus nifedipine (4.7±1.5 and 15.1±4.6 ng/kg per minute, respectively). However, during high Na+ intake, the Ang II pressor dose decreased in SR (from 7.8±3.1 to 3.8±1.0 ng/kg per minute, p<0.05) but not in SS patients (Figure 5), indicating increased vascular response to Ang II in SR but not in SS patients.

Pressor Reactivity in Black Patients

Because all 11 of the SS but only six of the SR patients were black, we had to rule out the possibility that the different blood pressure response in SS and SR patients was not due to different racial mix. For this purpose, we included five more SR patients (47±4.4 years of age; mean body weight, 86±2.7 kg). All these patients received a low and high Na+ diet for 6 days each but did not receive nifedipine.

The norepinephrine pressor dose in SS black patients was significantly lower (p<0.05) than in SR black patients during both the low (81±11.2 versus 162±37 ng/kg per minute) and the high (49±8 versus 95±21 ng/kg per minute) diets.
Norepinephrine Pressor Dose

FIGURE 2. Bar graph shows norepinephrine pressor doses; i.e., norepinephrine doses in nanograms per kilogram per minute that increased mean arterial pressure by 20 mm Hg in salt-sensitive (SS) and salt-resistant (SR) patients with essential hypertension during the four phases of the study. Nif, nifedipine. *p<0.05 vs. SR patients; #p<0.05 vs. low Na+ diet; @p<0.05 vs. high Na+ diet.

ng/kg per minute) Na+ intake. The Ang II pressor dose was also lower in SS than in SR black patients during the low Na+ diet (2.9±0.42 versus 9.5±4.1 ng/kg per minute). During the high Na+ diet, the Ang II pressor dose decreased in SR black patients from 9.5±4.1 to 3.5±1.3 ng/kg per minute but, as previously stated, did not change in SS black patients.

Discussion

These studies have shown that the blood pressure response to norepinephrine is increased in SS compared with SR patients with essential hypertension, irrespective of their dietary Na+ intake, whereas the blood pressure response to Ang II was greater in SS than in SR patients only during low Na+ intake. These studies also suggest that substantial differences in norepinephrine metabolism may exist between SS and SR patients with essential hypertension.

Hemodynamic differences have been described between SS and SR patients. Sullivan and Ratts18 showed greater forearm vascular resistance and lower venous capacitance in SS than in SR patients, irrespective of dietary sodium intake. Mark et al19 observed decreased forearm blood flow during sodium loading in patients with borderline hypertension, but they did not divide their patients according to salt sensitivity.

Several investigators have studied the blood pressure response to norepinephrine in patients with essential hypertension; some have shown increased sensitivity,20-25 whereas others have shown no difference26-29 between hypertensive and normotensive subjects. The

Plasma NE Pressor dose

FIGURE 3. Bar graphs show plasma levels of norepinephrine achieved in salt-resistant and salt-sensitive (SS) patients with essential hypertension during administration of 20 or 100 ng/kg per minute. Nif, nifedipine. *p<0.05 vs. SS patients; #p<0.05 vs. other phases of the study.

Plasma NE (NE) pressor dose; i.e., plasma concentration of norepinephrine achieved during infusion that increased mean arterial pressure by 20 mm Hg. SS, salt sensitive; SR, salt resistant; Nif, nifedipine. *p<0.05 vs. SR patients.

FIGURE 4. Bar graph shows plasma norepinephrine (NE) pressor dose; i.e., plasma concentration of norepinephrine achieved during infusion that increased mean arterial pressure by 20 mm Hg. SS, salt sensitive; SR, salt resistant; Nif, nifedipine. *p<0.05 vs. SR patients.
They also observed that a high Na+ diet caused a pressure response in hypertensive subjects; but the studies suggest that age, race, and dietary Na+ 

response to norepinephrine in patients with essential hypertension during the four phases of the study. Nif, nifedipine. *p<0.05 vs. SS patients; #p<0.05 vs. low Na+ diet.

reasons for these discrepancies are not clear; however, lack of homogeneity of the populations studied in relation to age, race, and dietary intake of Na+ may partially account for the contradictory data in the literature. Dimsdale et al30 evaluated the blood pressure response to infused norepinephrine in 34 normotensive and 21 hypertensive subjects and found a greater blood pressure response in hypertensive subjects; but the amount of that difference was consistent at all dose increments, and the slopes of the relation were not different between hypertensive and normotensive subjects. They also observed that a high Na+ diet caused a steeper slope of the dose-response curve to norepinephrine in older than in younger hypertensive patients and increased the pressor response to norepinephrine in black but not in white patients with hypertension. These studies suggest that age, race, and dietary Na+ intake must be taken into account when the pressor response to norepinephrine in patients with essential hypertension is being evaluated. Skrabal et al39 showed that the pressor response to norepinephrine was greater in SS than in SR patients independent of diet, but they did not measure blood levels of norepinephrine during the infusion nor did they correlate postinfusion blood levels with blood pressure response.

Ziegler et al31 have shown that plasma concentrations of norepinephrine achieved during stepwise infusions were lower in hypertensive than in normotensive subjects; moreover, they found an increase in pressor response to norepinephrine in hypertensive patients only when plasma norepinephrine levels rather than infusion rates were plotted against blood pressure.

Our studies have confirmed the existence of complex interrelations between Na+ intake and blood pressure response to agonists in hypertensive patients. SS patients displayed a greater blood pressure response to norepinephrine whether we took into account the dose infused or the actual plasma levels of norepinephrine achieved during the infusion. On the other hand, the increased blood pressure response to norepinephrine in SS patients appeared to be specific for this agonist and not due to a generalized and nonspecific hyperresponsiveness of the vasculature. In fact, blood pressure response to Ang II was increased in SS patients during the low but not during the high Na+ diet. The fact that SS patients manifest lower plasma renin activity than SR patients, particularly during a low Na+ diet, suggests that the greater pressor response to Ang II in SS patients during a low Na+ diet may be due to upregulation or decreased occupancy of Ang II receptors rather than to generalized hyperresponsiveness of the vasculature. Luft et al32 have shown a relation between changes in blood pressure response to a high dietary Na+ intake and changes in the ratio between α2/β2-receptor ratio in platelets of hypertensive subjects. They have suggested that the rise in blood pressure in response to high Na+ intake in predisposed patients may be due to enhanced vasosconstriction caused by increased α2/β2-receptor ratio in blood vessels and to enhanced sympathetically mediated renal Na+ reabsorption.

More recently, Sharma et al33 observed a greater pressor response to norepinephrine during a high rather than a low Na+ intake in young normotensive subjects. In addition, the blood pressure response was greater in SS than in SR subjects, findings consistent with our data. At variance with our studies, however, these investigators observed that SS subjects displayed an increase in blood pressure response to Ang II during both a low and high Na+ intake. The reason for this apparent discrepancy is unclear, but it may be due to the fact that our patients were older and hypertensive as opposed to those of Sharma et al, who were younger and normotensive. Renin secretion also may have differed between these two populations because of age and racial composition; most of our patients were black, whereas we presume that the majority, if not all, of the patients studied by Sharma et al were Caucasian.

Because all SS but only six SR patients were black, we compared separately the SR blacks with the SS patients and found no significant difference in norepinephrine pressor dose between SS and SR blacks, probably because of the small number of black SR patients.

Previous studies in the rat have shown that calcium channel blockers inhibit the systemic pressor response and intrarenal vasoconstriction caused by Ang II, norepinephrine, and vasopressin.34,35 Administration of calcium channel blockers also has been used to gain insights into the mechanism of vascular smooth muscle contraction in patients with essential hypertension. Robinson36 measured the effect of verapamil and nitroprusside on forearm vascular resistance in 35 hypertensive and 23 normotensive subjects and observed that the hypertensive subjects had a significant enhancement of the vasodilator response to verapamil but not to nitroprusside. This suggests that alterations in the potential-sensitive calcium channel rather than structural abnormalities contribute to the maintenance of increased vascular resistance in these patients. Vanhouthe37 suggested that the antihypertensive effect of calcium channel blockers is dependent on their inhibitory effect of α-adrenergic activation and of the inherent myogenic tone.

In our studies, nifedipine decreased the blood pressure response to norepinephrine; this inhibition was most evident when we evaluated the plasma norepinephrine.
norepinephrine pressor doses, that is, the plasma concentrations of norepinephrine that raised MAP by 20 mm Hg (Figure 4). Surprisingly, the inhibition appeared to be more pronounced in SR than in SS patients (Figures 3 and 4), and it was not influenced by dietary Na+ intake, suggesting that a greater contribution to the vascular tone of resistance vessels by the potential-sensitive system may be present in SR patients.

Plasma norepinephrine levels achieved during the infusion of this agonist were significantly lower in SS patients with essential hypertension, suggesting diversities in the norepinephrine metabolism between these two groups of patients that could be due to alteration of clearance or volume of distribution. Although no one, to our knowledge, has studied norepinephrine clearance in hypertensive patients classified according to their blood pressure sensitivity to salt, there is some evidence that norepinephrine clearance in hypertensive patients may be either normal48–50 or diminished.41 This makes it less likely that the lower norepinephrine levels in SS patients may be due to increased clearance. There is evidence, however, that the volume of norepinephrine distribution may be greater in hypertensive than in normotensive subjects.42

In previous studies, we observed that SS hypertensive patients manifest reduced suppressibility of plasma norepinephrine in response to high dietary sodium intake.2 Several other laboratories have confirmed both in humans and in SS animals with hypertension that the activity of the sympathetic nervous system is actually increased rather than suppressed in response to a high dietary sodium intake.5,43–46 The present study suggests that alterations of the metabolism or volume of distribution of catecholamines may be present in SS patients with essential hypertension. However, norepinephrine kinetic studies are needed to evaluate this problem further.

References


32. Luft FC, Miller JZ, Weinberger MH, Christian J, Skrabal F: Genetic influences on the response to dietary salt reduction, acute
Pressor reactivity to norepinephrine and angiotensin in salt-sensitive hypertensive patients.

V M Campese, F Karubian, I Chervu, M Parise, N Sarkies and R Bigazzi

Hypertension. 1993;21:301-307
doi: 10.1161/01.HYP.21.3.301

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/21/3/301