Salt Sensitivity in Humans Is Associated With Abnormal Acid-Base Regulation

Arya M. Sharma, Andreas Kribben, Sabine Schattenfroh, Claudia Cetto, and Armin Distler

Metabolic acidosis has recently been observed in rat models of salt-sensitive genetic hypertension. To test the hypothesis that salt sensitivity in humans may be associated with abnormal acid-base homeostasis, we performed arterial blood gas analyses in young (20–31 years old) normotensive subjects ($n=40$) who were placed on a low salt diet (20 mmol NaCl/day) for 2 weeks with either 200 mmol sodium chloride or placebo added to the low salt diet for 1 week each in a randomized, single-blind crossover order. Furthermore, a subset of the subjects (seven salt-sensitive and eight salt-resistant) received 200 mmol sodium/day as the citrate salt as a supplement to the low salt diet for a third week. During each regimen, blood pressure as well as arterial pH and bicarbonate levels were measured. Salt sensitivity was defined as a significant drop in mean arterial pressure greater than 3 mm Hg (mean of 30 readings taken during each diet, $p<0.05$) while the subject was on the low salt diet. According to this definition, 16 subjects were salt-sensitive and 24 salt-resistant. During the high sodium chloride regimen, arterial pH and bicarbonate levels were significantly lower in the salt-sensitive than in the salt-resistant group ($p<0.0001$). The increase in blood pressure caused by sodium chloride correlated inversely to the arterial pH ($r=-0.57$, $p=0.0002$) and bicarbonate levels ($r=-0.52$, $p=0.0007$) during the high salt diet. Sodium chloride increased mean arterial blood pressure in the salt-sensitive subjects; sodium citrate did not. Sodium citrate led to an increase in pH and bicarbonate levels in both groups. Our finding that a sodium chloride–induced rise in blood pressure is associated with lower arterial plasma pH and bicarbonate levels points to an abnormality in renal acid-base regulation in salt-sensitive subjects. (*Hypertension* 1990;16:407–413)

R ecent reports on abnormal parameters of acid-base balance in different animal models of salt-sensitive hypertension[1-3] suggest a possible role of disturbed acid-base regulation in genetic hypertension. The finding of an increased Na^+-H^+ antiporter activity in platelets of patients with essential hypertension[4,5] may also be compatible with the suggestion that an abnormality of acid-base homeostasis plays a role in hypertension.

Sodium salts such as sodium bicarbonate[6] and sodium citrate[7] that induce metabolic alkalosis do not raise blood pressure as effectively as sodium chloride in patients with essential hypertension. This finding has been interpreted as indicating a concomitant role of chloride in the pressor effect of sodium chloride. The theoretical possibility that sodium bicarbonate or citrate may have failed to raise blood

pressure because of an effect on acid-base homeostasis has not been considered thus far.

To examine the relation between acid-base status and salt sensitivity, we conducted arterial blood gas and blood pressure measurements in normotensive subjects during sodium chloride depletion and during normal sodium chloride intake. In addition, we investigated the effect of an alkalinizing nonchloride sodium salt on blood pressure as related to acid-base status by administering sodium citrate to a subset of our subjects. We selected normotensive subjects for our studies because normotensive salt-sensitive subjects offer the unique opportunity of studying pathogenic mechanisms believed to be related to hypertension without the confounding presence of overt hypertension and its sequelae.

Our data show that a relative metabolic acidosis is present in salt-sensitive subjects during normal salt intake and that plasma pH levels are inversely correlated to the rise in blood pressure induced by salt intake.

Methods

The protocol of the study was approved by the ethical committee of our hospital. All participants

gave their informed consent. The study was performed in an ambulatory setting. All diets were prepared in the hospital kitchen.

Subjects

Forty-five healthy men (range 20–31 years of age) volunteered for the study. Before entering the study, routine physical and laboratory parameters were examined to ensure that none had hypertension, hyperlipidemia, diabetes mellitus, or hepatic or renal disease. Only subjects with a diastolic blood pressure below 85 mm Hg and a systolic pressure below 140 mm Hg were included. Parental histories on hypertension were obtained by direct personal communication with the family physicians. Subjects with at least one parent under treatment for hypertension were regarded as having a positive familial history of hypertension. Twenty subjects had positive familial histories of hypertension, whereas 25 subjects had negative familial histories.

Assessment of Salt Sensitivity

We have previously shown in normotensive individuals that salt sensitivity as defined below is a well reproducible phenomenon.[8] The same methods and definitions have been used in the current study. Subjects were given a standardized diet containing 20 mmol sodium as the chloride salt, 60 mmol potassium, and 20 mmol calcium per day for 14 days. Total caloric intake was estimated so as to keep body weight constant. The subjects were advised to drink about 2 l water/day. In a randomized, single-blind crossover protocol a daily supplement of 40 capsules containing either a placebo (dextrose, 0.45 g/capsule) or sodium chloride (5 mmol/capsule) was administered for 7 days each. The resulting daily salt intake of 220 mmol during the high salt period exceeds the average sodium intake in Western European cultures by roughly 25%[9] but is still within the normal range. On the morning of the seventh day of each period, after a 30-minute resting period, blood pressure was measured in the recumbent subject over 1 hour at 2-minute intervals with an automatic device (Tonoprint, Speidel and Keller, Jungingen, FRG). The standard error of the mean for a single 60-minute period ranged between 0.54 and 0.95 mm Hg. Salt sensitivity was defined as a significant drop in mean arterial pressure greater than 3 mm Hg,[8,10] calculated as the difference between the average of the 30 blood pressure readings under the high and low salt periods ($p<0.05$).

Blood Gas Analysis

After the blood pressure measurements, a heparinized arterial blood sample was drawn from the radial artery under anaerobic conditions by an experienced physician using a 22 gauge needle. All arterial blood samples were immediately placed in ice water, and pH, bicarbonate, and the partial pressures of oxygen and carbon dioxide were measured within 15 minutes

of collection using the ABL-300 acid-base laboratory (Radiometer, Copenhagen, Denmark) located on an adjacent laboratory bench. A venous blood sample was drawn from an antecubital vein for measurement of sodium, chloride, and potassium by standard laboratory techniques. Throughout the study, compliance was assessed by measurement of daily 24-hour urinary sodium, chloride, and potassium excretion with standard laboratory methods. Subjects were considered compliant when sodium and chloride excretion was below 35 mmol/24 hr during the last 3 days of the low salt period and above 180 mmol/24 hr during the last 3 days of the high salt period.

Sodium Citrate Study

In addition to the above regimen, 15 arbitrarily selected subjects also received a daily supplement of 200 mmol sodium as the citrate salt for a third week in addition to the low salt diet. The sequence of the three regimens (placebo, sodium chloride, and sodium citrate) was randomized according to a latin-square design. Blood pressure measurements, blood sampling procedures, and urine collection were conducted as described above. In these subjects, plasma aldosterone and renin activity were also measured under each regimen as described by Oelkers et al.[11] In addition to the criteria defined above, subjects were required to have a 24-hour urinary sodium excretion greater than 180 mmol and a chloride excretion lower than 35 mmol during the last 3 days of the sodium citrate regimen period to be considered compliant.

Statistics

Statistical analysis was performed using the SPSS/ PC+ software package (SPSS Inc., Chicago, Ill.). For testing the salt sensitivity of the individual subject, the independent t test was used to examine whether the 30 blood pressure readings taken during the high salt diet were significantly different from those taken during the low salt diet. Subsequently, the means of the 30 blood pressure readings as well as all other variables under the different regimens were compared within each group by the two-tailed t test for paired samples, whereby in the sodium citrate study the significance level was reduced to $p<0.016$ to compensate for multiple comparisons (placebo versus sodium chloride, placebo versus sodium citrate, and sodium chloride versus sodium citrate). The two-tailed t test for independent samples was used for comparisons between the salt-sensitive and salt-resistant groups. The Pearson correlation coefficient was used to test the relation between pH or bicarbonate and blood pressure change and between aldosterone and pH. Results are presented as mean±SEM.

Results

Five subjects were excluded from analysis because of poor compliance as assessed by urinary sodium and chloride excretion. Of the remaining subjects, 16

TABLE 1. Physical, Blood, and Urine Variables in Salt-Resistant and Salt-Sensitive Normotensive Subjects During Low and High Sodium Chloride Intake

Measurements	Salt-resistant (n=24)		Salt-sensitive (n=16)	
	Low salt	High salt	Low salt	High salt
Physical variables				
Systolic BP (mm Hg)	111.3±1.6	111.2±1.8	109.5±2.4	115.0±2.6*
Diastolic BP (mm Hg)	68.1±1.4	68.0±1.3	67.4±1.8	75.4±2.3†
MABP (mm Hg)	82.6±1.4	82.4±1.2	81.5±1.8	88.6±1.8‡
Heart rate (beats/min)	61.5±1.4	60.9±1.4	61.1±2.0	61.2±1.8
Weight (kg)	73.0±1.5	74.9±1.8§	72.6±1.2	73.7±1.2§
Arterial blood gas analysis				
pH	7.441±0.005	7.435±0.003	7.427±0.006 ‖	7.413±0.003¶
HCO₃ (mmol/l)	25.8±0.4	25.2±0.2	25.4±0.3	23.9±0.2#
pO₂ (mm Hg)	98.2±1.7	99.4±1.3	98.0±2.5	100.0±3.1
pCO₂ (mm Hg)	41.4±0.7	40.7±0.5	42.3±0.6	41.4±0.6
Plasma variables				
Sodium (mmol/l)	136.9±0.8	139.9±0.7**	138.6±0.8	139.5±0.5
Chloride (mmol/l)	98.6±0.6	102.9±0.5**	101.1±0.8††	104.3±0.8‡‡
Potassium (mmol/l)	4.0±0.1	4.0±0.1	4.2±0.1	4.2±0.1
Urine variables				
Volume (ml/24 hr)	2,038±177	2,198±181	1,840±207	2,348±174
Sodium (mmol/24 hr)	24.8±3.4	240±17§§	24.6±4.3	238±15§§
Chloride (mmol/24 hr)	21.7±4.3	236±17§§	24.8±3.8	247±37§§
Potassium (mmol/24 hr)	59.7±4.4	64.3±4.3	69.3±4.7	70.0±5.6

Values are mean±SEM. BP, blood pressure; MABP, mean arterial blood pressure.
*p=0.002 versus low salt diet.
†p=0.01 versus salt-resistant group and p<0.0001 versus low salt died.
‡p=0.018 versus salt-resistant group and p<0.0001 versus low salt diet.
§p=0.001 versus low salt diet.
‖p=0.076 versus salt-resistant group.
¶p<0.0001 versus salt-resistant group and p=0.057 versus low salt diet.
#p<0.0001 versus salt-resistant group and p=0.001 versus low salt diet.
**p<0.0001 versus low salt diet.
††p=0.016 versus salt-resistant group.
‡‡p=0.003 versus low salt diet.
§§p<0.0001 versus low salt diet.

were salt-sensitive and 24 were salt-resistant according to the predefined criteria. Although 13 of the 16 salt-sensitive subjects had positive familial histories of hypertension, this was the case with only five of the 24 salt-resistant subjects. There was no difference in mean age between the salt-sensitive (24.7±0.5 years) and salt-resistant (25.2±0.4 years) subjects. Physical, plasma, and urinary variables are shown in Table 1. There was no difference in the urinary excretion of sodium and chloride between the two groups under the different regimens. Although blood pressure was higher when subjects were under the high salt diet than under the placebo regimen in the salt-sensitive group, blood pressure was not affected in the salt-resistant group. Arterial pH and plasma bicarbonate were significantly lower in the salt-sensitive subjects during the high salt regimen (p<0.0001) compared with the salt-resistant group (Figure 1). There was a significant inverse correlation between salt sensitivity (expressed as the difference in mean arterial pressure between the high and low salt regimens) and both arterial pH levels (r=−0.57, p=0.0002) and plasma

bicarbonate (r=−0.52, p=0.0007) during the high salt diet (Figure 2). In the salt-sensitive group, the high salt intake led to a significant reduction in bicarbonate (p=0.001) compared with the low salt diet, whereas bicarbonate was not affected in the salt-resistant group (Figure 1). Under the low salt diet, plasma chloride was slightly higher in the salt-sensitive group than in the salt-resistant group (p=0.016). Under the high salt diet, plasma chloride increased significantly in both groups compared with the low salt regimen (p<0.005).

Sodium Citrate Study

Of the 15 subjects who participated in this part of the study, seven were salt-sensitive and eight were salt-resistant. All the salt-sensitive subjects had positive familial histories of hypertension, and all the salt-resistant subjects had negative familial histories. The data of this part of the study are summarized in Table 2. Addition of sodium chloride led to a rise in diastolic and mean arterial pressure in the salt-sensitive subjects (p<0.005 versus placebo), but
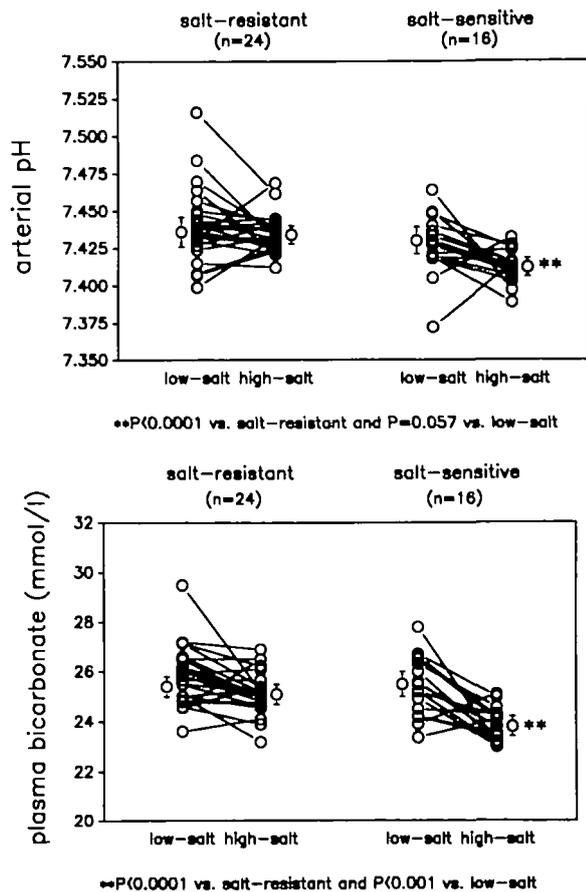
FIGURE 1.   *Plottings of arterial pH* (top panel) *and bicarbonate* (bottom panel) *levels in salt-resistant (n=24) and salt-sensitive (n=16) normotensive subjects during low (20 mmol/day) and high (220 mmol/day) sodium chloride intake.*

FIGURE 2.   *Scatterplots showing relation between sodium chloride-induced change in mean arterial blood pressure (MABP) and arterial pH* (top panel) *and bicarbonate* (bottom panel) *levels under high salt diet in normotensive salt-resistant* (○) *(n=24) and salt-sensitive* (●) *(n=16) subjects. Dotted line indicates 3 mm Hg rise in MABP arbitrarily selected to define salt sensitivity.*

sodium citrate did not. The different regimens had no effect on blood pressure in the salt-resistant group. During both the placebo ($p=0.004$) and sodium chloride ($p=0.03$) regimens, arterial pH was significantly lower in the salt-sensitive group than in the salt-resistant group. Plasma bicarbonate was lower in the salt-sensitive than in the salt-resistant subjects during the high salt diet ($p=0.021$). During the sodium citrate regimen, bicarbonate was significantly elevated in both groups ($p<0.005$ versus sodium chloride) and there was no difference in bicarbonate levels between the two groups under this regimen. There was an inverse correlation between the difference in mean arterial blood pressure between the high and low sodium chloride regimens and the arterial pH during the high sodium chloride diet ($r=-0.68$, $p<0.005$). Plasma potassium was slightly higher in the salt-sensitive subjects during the placebo ($p<0.005$) and the sodium chloride (not significant) periods. Plasma chloride was lower during both the placebo ($p<0.016$) and the sodium citrate ($p<0.005$) periods compared with the sodium chloride period in the salt-resistant group. Plasma chloride was lower in the salt-sensitive group during the sodium citrate than during the sodium chloride
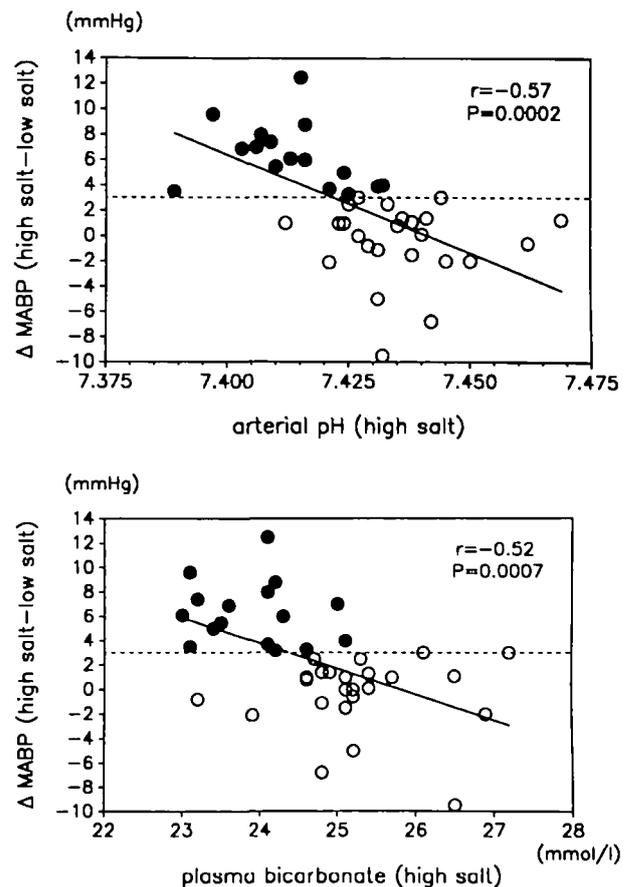
($p<0.016$) periods. Mean plasma levels of aldosterone and renin activity were slightly lower in the salt-sensitive than in the salt-resistant subjects during all regimens; the difference, however, was not statistically significant. There was a significant correlation between plasma aldosterone levels and blood pH in subjects during the high salt regimen ($r=0.63$, $p=0.015$) when the two groups were combined.

Discussion

Several authors have reported that salt sensitivity can be demonstrated in normotensive individuals[12,13] and that this sensitivity is related to a familial history of hypertension.[8,10] Salt sensitivity in normotensive subjects has been described to be associated with haptoglobin 1-1 phenotype,[14] and an increased prevalence of certain HLA antigens,[10] enhanced sympathetic responsiveness,[10] and enhanced upregulation of the α_2/β_2-adrenergic receptor ratio[15] suggests that salt-sensitive subjects might be genetically predisposed to the later development of hypertension.[10] We have previously shown that salt sensitivity can be

TABLE 2. Physical, Blood, and Urine Variables in Salt-Resistant and Salt-Sensitive Normotensive Subjects During Administration of Placebo, Sodium Chloride, and Sodium Citrate as Supplement to Low Salt Diet

	Salt-resistant ($n=8$)			Salt-sensitive ($n=7$)		
	Placebo	Sodium chloride	Sodium citrate	Placebo	Sodium chloride	Sodium citrate
Physical variables						
Systolic BP (mm Hg)	108.2±2.9	105.9±3.5	106.1±3.0	102.7±3.3	107.2±3.0	105.3±2.9
Diastolic BP (mm Hg)	64.3±2.9	65.5±2.2	65.2±3.0	65.0±2.9	71.4±2.7*	68.5±2.0
MABP (mm Hg)	79.1±2.6	79.0±2.3	78.9±2.0	77.6±2.7	83.2±2.2*	80.7±1.8
Heart rate (beats/min)	58.0±2.7	57.5±1.7	58.0±2.8	60.1±1.2	57.5±1.4	58.3±1.1
Weight (kg)	75.3±3.6	76.0±3.5	75.6±3.7	72.0±1.2	72.4±1.3	73.0±1.2
Arterial blood gas analysis						
pH	7.450±0.011	7.436±0.006	7.461±0.013	7.422±0.005†	7.415±0.007‡	7.444±0.009
HCO₃ (mmol/l)	26.5±1.0	25.3±0.3	27.6±0.5§	25.2±0.4	24.0±0.4‡	27.1±0.4§ ‖
pO₂ (mm Hg)	97.2±2.4	100.2±1.8	97.7±2.2	102.4±2.6	109.4±4.0	100.3±3.2
pCO₂ (mm Hg)	42.3±1.7	41.4±0.9	43.4±1.2	43.5±1.0	41.8±1.1	44.6±0.9
Plasma variables						
Sodium (mmol/l)	139.0±0.7	141.1±1.0	141.9±1.7	140.0±0.6	141.2±0.7	141.3±0.9
Chloride (mmol/l)	98.1±1.3	102.8±0.8 ‖	99.5±0.7¶	101.3±1.3	102.9±0.8	99.6±0.6#
Potassium (mmol/l)	3.9±0.1	4.1±0.1	3.8±0.1	4.4±0.1†	4.5±0.2	4.0±0.1
Renin activity (ng/ml/hr)	6.0±1.4	1.9±0.5*	2.2±0.4*	5.7±1.3	1.4±0.6*	1.2±0.2*
Aldosterone (nmol/l)	0.91±0.13	0.18±0.02*	0.24±0.07*	0.89±0.21	0.14±0.02*	0.16±0.04*
Urine variables						
Volume (ml/24 hr)	1,500±218	1,850±119	1,812±121	1,614±352	1,921±298	1,771±253
Sodium (mmol/24 hr)	21.5±4.9	216.5±15.4*	192.9±12.6*	19.9±5.8	222.4±10.2*	195.9±22.0*
Chloride (mmol/24 hr)	23.8±3.4	214.6±18.3*	21.1±4.1§	23.0±4.3	247.3±15.3*	20.7±2.3§
Potassium (mmol/24 hr)	49.6±3.3	58.9±6.2	48.9±2.2	52.1±4.9	51.1±3.5	44.7±3.2

Values are mean±SEM. BP, blood pressure; MABP, mean arterial blood pressure.
*$p<0.005$ versus placebo.
†$p<0.005$ versus salt-resistant group.
‡$p<0.05$ versus salt-resistant group.
§$p<0.005$ versus sodium chloride.
‖$p<0.01$ versus placebo.
¶$p<0.01$ versus sodium chloride.
#$p<0.016$ versus sodium chloride.

assessed in normotensive individuals in a well reproducible manner.[8]

In the present study, which examines the relation between salt sensitivity and acid-base status in normotensive subjects, arterial pH and plasma bicarbonate levels were found to be lower in the salt-sensitive group compared with the salt-resistant group under high salt intake. The inverse correlation found between the reaction of blood pressure to high salt intake and the pH and bicarbonate levels (Figure 2) demonstrates that there is no sharp dividing line in either pH or bicarbonate levels between salt-sensitive and salt-resistant subjects. Rather, the reaction of blood pressure to high salt intake as related to pH or bicarbonate appears to form a continuum.

The finding of lower pH and bicarbonate levels in salt-sensitive subjects is compatible with the observation of a relative metabolic acidosis made in various animal models of salt-sensitive hypertension. According to Lucas et al,[1,2] arterial plasma pH and bicarbonate levels are lower in spontaneously hypertensive rats (SHR) and Milan strain hypertensive rats compared with Wistar-Kyoto (WKY) rats and Milan strain normotensive rats, respectively. Reduced plasma bicarbonate levels were noted in young SHR before the development of hypertension.[2] Lower plasma bicarbonate levels have also been reported in the stroke-prone SHR.[3]

Little is known about acid-base status in patients with essential hypertension. We are aware of only two reports on venous pH measurements in patients with essential hypertension. In a study by Shore et al[16] dealing with the effects of storage on ionized calcium in blood samples, patients with essential hypertension were noted to have higher venous pH levels compared with normotensive controls. Unfortunately, blood gas data that would have served to rule out hyperventilation in their hypertensive subjects were not reported in that study. Resnick et al[17] observed a lower intracellular pH in erythrocytes of patients with essential hypertension compared with normal controls. Venous pH measured in their study was not different between the two groups. The major limitation of the latter studies lies in the fact that, although venous pH may suffice for the detection of acid-base abnormalities in the clinical setting, it is significantly affected by peripheral tissue metabolites and therefore may not be suitable for detecting small

pH differences of 0.05 units as can be expected from the animal studies mentioned above. Therefore, in this study, blood gas analysis was performed in arterial blood.

The differences in pH and bicarbonate between salt-sensitive and salt-resistant subjects observed in our study are extremely small and to our knowledge there are no reports suggesting that such minor changes can per se influence blood pressure. Although it is therefore unlikely that the mild acidosis observed is primarily responsible for the salt-induced rise in blood pressure, the acidosis could nevertheless point to a major homeostatic disturbance somehow linked to blood pressure regulation. Considering that acid-base equilibrium is carefully maintained by a variety of factors such as plasma and cellular buffer capacity, renal and respiratory factors, even the smallest change in pH may reflect major changes in factors normally serving to keep acid-base equilibrium constant.

An explanation for the relative acidosis found in the salt-sensitive group can be no more than conjectural at this stage. In view of the normal arterial carbon dioxide and oxygen tensions, the young age of our subjects, and the lower bicarbonate levels, it would be reasonable to assume that the acidosis observed was not a consequence of a respiratory abnormality. Assuming therefore a metabolic cause for the relative acidosis, one may have to look for some impairment of renal acid-base regulation in subjects with a predisposition to salt-sensitive hypertension. So far, no studies on renal acid-base disposition as related to blood pressure regulation have been reported in humans. However, in a recent animal study conducted by Lucas et al,[18] intraperitoneal administration of $NaHCO_3$ resulted in enhanced excretion of urinary bicarbonate in SHR compared with WKY rats, pointing to reduced tubular reabsorption of bicarbonate in this model of salt-sensitive hypertension. Also, an increased Na^+ uptake by renal brush border membrane vesicles isolated from Milan hypertensive rats,[19] decreased Na^+ excretion in young SHR,[20] and indirect evidence for enhanced proximal tubular Na^+ reabsorption in salt-sensitive normotensive subjects[10] and in normotensive subjects with positive familial histories of hypertension[21] point to some renal defect that could account for both the blood pressure increase and the relative acidosis during high salt intake. Clearly, more studies investigating the relation between renal sodium and acid-base homeostasis in salt-sensitive hypertension are warranted.

Because proton secretion in the distal renal tubule is stimulated by aldosterone,[22] a decreased secretion of or hyporesponsiveness to aldosterone in salt-sensitive subjects could lead to reduced distal tubular proton secretion as observed in some forms of distal tubular acidosis (type IV).[23] Although some authors have observed lower aldosterone levels in salt-sensitive subjects,[10,24] we and others[12] have not. Nevertheless, our finding of a significant correlation between plasma aldosterone and

pH during the high salt diet could indicate a role of aldosterone for the metabolic acidosis found in the salt-sensitive subjects.

Whether the relative acidosis observed in the salt-sensitive subjects is somehow related to reduced intracellular pH as found in erythrocytes of patients with essential hypertension[17] or to enhanced Na^+-H^+ antiport activity as described in platelets of patients with essential hypertension[4,5] and lymphocytes of SHR[25] remains unclear.

During the sodium citrate period, which failed to raise blood pressure in the salt-sensitive group, plasma pH and bicarbonate were not significantly different in the two groups. Alkalinization could thus have prevented a rise in blood pressure resulting from sodium administration in the salt-sensitive group. However, the finding that nonalkalinizing nonchloride sodium salts such as sodium phosphate also fail to raise blood pressure[26] makes the lack of the chloride anion a more likely factor accounting for the failure of sodium citrate to raise blood pressure in salt-sensitive subjects.[27,28]

In conclusion, we found that arterial pH and plasma bicarbonate levels are lower in salt-sensitive than in salt-resistant individuals. The degree of relative metabolic acidosis correlated to the rise in blood pressure during the high salt diet. Thus, salt sensitivity in normotensive humans and therefore the predisposition to salt-sensitive essential hypertension appears to be associated with an abnormality in (possibly renal) acid-base regulation. At present, it is not clear whether the acidosis by itself contributes to the development of salt-sensitive hypertension or is merely a marker for some underlying defect related to salt sensitivity. Further studies examining the renal acid-base disposition in patients with salt-sensitive essential hypertension and in normotensive salt-sensitive subjects as well as its relation to blood pressure regulation will be required.

References

1. Lucas PA, Lacour B, McCarron DA, Drüeke T: Disturbance of acid-base balance in the young spontaneously hypertensive rat. *Clin Sci* 1987;73:211–215
2. Lucas PA, Lacour B, Comte L, Drüeke T: Abnormal parameters of acid-base balance in genetic hypertension. *Kidney Int* 1988;34(suppl 25):S19–S22
3. Luft FC, Steinberg H, Ganten U, Meyer D, Gless KH, Lang RE, Fineberg NS, Rascher W, Unger T, Ganten D: Effect of sodium chloride and sodium bicarbonate on blood pressure in

stroke-prone spontaneously hypertensive rats. *Clin Sci* 1988; 74:577–585

4. Livne A, Veitch R, Grinstein S, Balfe JW, Marquez-Julio A, Rothstein A: Increased platelet Na^+/H^+ exchange rates in essential hypertension: Application of a novel test. *Lancet* 1987;1:533–536

5. Schmouder RL, Weder AB: Platelet sodium-proton exchange is increased in essential hypertension. *J Hypertens* 1989; 7:325–330

6. Morgan TO: The effect of potassium and bicarbonate ions on the rise in blood pressure caused by sodium chloride. *Clin Sci* 1982;63:407s–409s

7. Kurtz TW, Al-Bander HA, Morris RC: "Salt-sensitive" essential hypertension in men—Is the sodium ion alone important? *N Engl J Med* 1987;317:1043–1048

8. Sharma AM, Schattenfroh S, Kribben A, Distler A: Reliability of salt-sensitivity testing in normotensive subjects. *Klin Wochenschr* 1987;67:632–634

9. Intersalt Cooperative Research Group: Intersalt: An international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *Br Med J* 1988;297:319–328

10. Skrabal F, Herholz H, Neumayr M: Salt sensitivity in humans is linked to enhanced sympathetic responsiveness and to enhanced proximal tubular resorption. *Hypertension* 1984; 6:152–158

11. Oelkers W, Schoeneshoefer M, Bluemel A: Effect of progesterone and four synthetic progestagens on sodium balance and renin-aldosterone system in man. *J Clin Endocrinol Metab* 1974;39:882–890

12. 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–II-134

13. Luft FC, Miller JZ, Weinberger MH, Christian JC, Skrabal F: Genetic influences on the response to dietary salt reduction, acute salt loading, or salt depletion in humans. *J Cardiovasc Pharmacol* 1988;12(suppl 3):S49–S55

14. Weinberger MH, Miller JZ, Fineberg NS, Luft FC, Grim CE, Christian JC: Association of haptoglobin with sodium sensitivity and resistance of blood pressure. *Hypertension* 1987; 10:443–446

15. Skrabal F, Kotanko P, Meister B, Doll P, Gruber G: Up regulation of α-2 adrenoceptors and down regulation of β-2 adrenoceptors by high salt diet in normotensives: Enhanced up regulation of "operative (α-2/β-2) adrenoceptor ratio" predicts salt-sensitivity. *J Hypertens* 1986;4(suppl 4):S196–S199

16. Shore AC, Booker J, Sagnella GA, Markandu ND, MacGregor GA: Serum ionized calcium and pH: Effects of blood storage, some physiological influences and a comparison between normotensive and hypertensive subjects. *J Hypertens* 1987;5:499–505

17. Resnick LM, Gupta RK, Sosa RE, Corbett ML: Intracellular pH in human and experimental hypertension. *Proc Natl Acad Sci USA* 1987;84:7663–7666

18. Lucas PA, Lacour B, Comte L, Drücke T: Pathogenesis of abnormal acid-base balance in the young spontaneously hypertensive rat. *Clin Sci* 1988;75:29–34

19. Parenti P, Hanozet GM, Bianchi G: Sodium and glucose transport across renal brush border membranes of Milan hypertensive rats. *Hypertension* 1986;8:932–939

20. Beierwaltes WH, Arndshorst WJ, Klemmer PJ: Electrolyte and water balance in young spontaneously hypertensive rats. *Hypertension* 1982;4:908–915

21. Weder AB: Red-cell lithium-sodium countertransport and renal lithium clearance in hypertension. *N Engl J Med* 1986; 314:198–201

22. Koeppen BM, Giebisch G: Segmental hydrogen ion transport, in Seldin DW, Giebisch G (eds): *The Regulation of Acid-Base Balance.* New York, Raven Press, Publishers, 1989, chap 8

23. Batlle DC: Renal tubular acidosis, in Seldin DW, Giebisch G (eds): *The Regulation of Acid-Base Balance.* New York, Raven Press, Publishers, 1989, chap 15

24. Sullivan JM, Prewitt RL, Ratts TE: Sodium sensitivity in normotensive and borderline hypertensive humans. *Am J Med Sci* 1988;295:370–377

25. Batlle DC, Saleh A, Rombola G: Reduced intracellular pH in lymphocytes from the spontaneously hypertensive rat. *Hypertension* 1990;15:97–103

26. Shore AC, Markander ND, MacGregor GA: A randomized crossover study to compare the blood pressure response to sodium loading with or without chloride in patients with essential hypertension. *J Hypertens* 1988;6:613–617

27. Weinberger MH: Sodium chloride and blood pressure. *N Engl J Med* 1987;317:1084–1086

28. Boegehold MA, Kotchen TA: Relative contributions of dietary Na^+ and Cl^- to salt-sensitive hypertension. *Hypertension* 1989; 14:579–583

KEY WORDS • salt-sensitive hypertension • acid-base equilibrium • acidosis

Hypertension

American
Heart
Association.

Salt sensitivity in humans is associated with abnormal acid-base regulation.
A M Sharma, A Kribben, S Schattenfroh, C Cetto and A Distler

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/16/4/407