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## SODIUM-SELECTIVE SALT-SENSITIVITY: ITS OCCURRENCE IN BLACKS

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### Abstract

We tested the hypothesis that the  $\text{Na}^+$ -component of dietary NaCl can have a pressor effect apart from its capacity to complement the extracellular osmotic activity of  $\text{Cl}^-$  and thus expand plasma volume (PV). We studied 35 mostly normotensive blacks who ingested a low NaCl-diet, 30mmol/d, for three weeks, in the first and third of which  $\text{Na}^+$  was loaded orally with either  $\text{NaHCO}_3$  or NaCl, in random order, 250mmol/d. In subjects adjudged to be salt-sensitive (SS,  $n=18$ ;  $\Delta\text{MAP} \geq 5\text{mmHg}$  with NaCl-load) but not in salt-resistant subjects (SR,  $n=17$ ) loading with  $\text{NaHCO}_3$  also was pressor. The pressor effect of  $\text{NaHCO}_3$  was half that of NaCl: MAP (mmHg) increased significantly from 90 on low NaCl to 95 with  $\text{NaHCO}_3$  and to 101 with NaCl. The pressor effect of NaCl strongly predicted that of  $\text{NaHCO}_3$ . As judged by hematocrit decrease, PV expansion with NaCl was the same in SR and SS and twice that with  $\text{NaHCO}_3$ , irrespective of pressor effect. In SS, MAP varied directly with plasma  $\text{Na}^+$  concentration attained with all  $\text{Na}^+$ -loading. In SS but not SR,  $\text{NaHCO}_3$  and NaCl induced decreases in renal blood flow (RBF) and increases in renal vascular resistance (RVR); changes in RBF were not different with the two salts. Responses of RBF and RVR to  $\text{NaHCO}_3$  were strongly predicted by those to NaCl. In establishing the fact of “sodium-selective” salt-sensitivity, the current observations demonstrate that the  $\text{Na}^+$ -component of NaCl can have pressor and renal vasoconstrictive properties, apart from its capacity to complement  $\text{Cl}^-$  in PV expansion.

### Keywords

blood pressure physiopathology; sodium; chlorides; bicarbonates; renal circulation; African Americans

### Introduction

Blood pressure (BP) is said to be “salt-sensitive” when it varies directly with the dietary intake of NaCl. Salt-sensitivity characterizes “essential” human hypertension in perhaps half of those affected, and confers its own cardiovascular risks, including that of the occurrence of hypertension.<sup>1</sup> A pathophysiological mechanism for salt-sensitivity has not been defined, despite recent demonstrations that human salt-sensitive hypertension can be caused by single genetic alterations that abnormally enhance the renal tubular reclamation of  $\text{Na}^+$  and  $\text{Cl}^-$ .<sup>2</sup> These demonstrations comport with the formulation that an excessive renal retention of  $\text{Na}^+$  and  $\text{Cl}^-$  initiates all salt-sensitivity, and does so only by these ions’ joint osmotic expansion of extracellular fluid and thereby of plasma volume (PV).<sup>2–5</sup>  $\text{Na}^+$  and  $\text{Cl}^-$  are the only physiologic

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Conflicts of Interest

None

ions whose osmotic activities distribute throughout, and near exclusively to, extracellular fluid. Accordingly, in men selected only for salt-sensitive hypertension and rendered normotensive by NaCl-restriction, NaCl-loading induced within days both hypertension and a substantial expansion of PV, whereas Na-citrate-loading induced neither.<sup>6</sup> Such “selective” Na<sup>+</sup>-loading, i.e. without Cl<sup>-</sup>, has repeatedly failed to elicit a pressor effect in NaCl-sensitive hypertension.<sup>7</sup> Allegedly, “only NaCl causes an expansion of PV and a rise in BP.”<sup>8</sup> But selective Na<sup>+</sup>-loading appears not to have been investigated in salt-sensitive blacks. In them, compared to salt-sensitive whites, the pressor effect of dietary NaCl is on average greater,<sup>9</sup> and hence the pressor agency of NaCl might involve more than its ions’ joint mediation of PV expansion. We find that in the more severely salt-sensitive blacks, selective Na<sup>+</sup>-loading (as NaHCO<sub>3</sub>) induces an increase in BP that cannot be ascribed only to the concomitant increase in PV.

## Methods

### Participants and Setting

We studied 35 healthy blacks, ages 35 to 56, with screening BP <160/100 mmHg and body weight (BW) within 30% of ideal BW, as inpatients at the General Clinical Research Center (GCRC), University of California, San Francisco (UCSF). The study was approved by and conducted according to the guidelines of the UCSF Committee on Human Research. All participants gave written informed consent.

### Basal Diet

Throughout the study, participants ate a eucaloric basal metabolic diet providing, per 70 kg BW per day, 30 mmol Na<sup>+</sup> and 45 mmol K<sup>+</sup>. They drank water, 20 g/kg BW per day during Na<sup>+</sup>-restriction and 35 g/kg BW during Na<sup>+</sup>-loading, respectively.

### Intervention (Na<sup>+</sup>-Loading)

The study consisted of 3 consecutive 7-day periods: The 2 periods of oral Na<sup>+</sup>-loading were separated by a period of Na<sup>+</sup>-restriction. Na<sup>+</sup>, 250 mmol/70kg BW per day (but no more than 300mmol/d), was supplemented as NaCl during the 1<sup>st</sup> week and as NaHCO<sub>3</sub> during the 3<sup>rd</sup> week or vice versa. All participants received placebo tablets during the 2<sup>nd</sup> (low-salt) week. Participants and nurses performing BP measurements were not informed about the content of the tablets.

### Assessment of Na<sup>+</sup>-induced Pressor Effects

With an automated oscillometric device (Dinamap, Criticon Inc. Tampa, Florida) programmed to obtain 5 readings over a period of 5 minutes, BP was measured daily every 4 hours (between 6AM and 10PM) after 10 minutes of supine rest; an average daily BP was calculated. The first standardized BP measurements were obtained within about 2 hours of the subject’s arrival at the GCRC, at 2PM. The 2PM values of day 1 are reported as “initial” (baseline) BP in Table 1 and Figure 1. To determine the pressor effects of Na<sup>+</sup> salts, the average mean arterial pressure (MAP) of days 5 and 6 during Na<sup>+</sup>-restriction, was subtracted from the average MAP of days 5 and 6 during loading of either NaCl or NaHCO<sub>3</sub>. Salt sensitivity (SS) was defined as a NaCl-induced increase in MAP of ≥5 mmHg, salt-resistance (SR) as an increase of <5 mmHg.

### Metabolic Outcomes

We measured BW daily at 6AM. Spontaneously voided urine was collected daily over 24-hour periods and analyzed for Na<sup>+</sup>, Cl<sup>-</sup> and creatinine. During week 3 of the study we measured weekly cumulative Na<sup>+</sup> excretion (UVNaCum), corrected for creatinine excretion and adjusted for 70 kg of BW. On the last day of each 7-day period, between 9AM and noon, blood samples

were obtained with participants in supine position to determine levels of PRA, aldosterone, hematocrit, creatinine and serum electrolytes by standard techniques.

### Renal Hemodynamics

PAH clearance studies were performed in 31 participants (16 SS and 15 SR) on the last day of each 7-day period using standard methods.

### Data Analysis

We assessed the effects of Na<sup>+</sup>-loading as either NaCl or NaHCO<sub>3</sub> on BP using repeated measures ANOVA, followed by Newman-Keuls test. To assess whether the order by which the supplements were administered had an effect on outcome we included “supplement order” as a between-group factor in the comparison. To rule out NaHCO<sub>3</sub>- or NaCl-induced effects on serum K<sup>+</sup> or hematocrit as a major source of between-group differences in pressor effects we repeated between-group comparisons of pressor effects using changes in and final concentrations of serum K<sup>+</sup> and changes in hematocrit as covariates. We assessed the effects of NaCl or NaHCO<sub>3</sub> on BW, hematocrit, electrolytes and renal hemodynamics and the pressor effect in salt-sensitive subgroups using paired and unpaired t-tests, respectively, for within group and between-group comparisons. Non-parametric tests were used to assess the effect on PRA and aldosterone as these variables were not normally distributed. Linear regression and Spearman rank correlation analyses were used to explore the relationship between variables. Data is presented as mean and 95% C.I. The null hypothesis was rejected at p<0.05.

## Results

### Salt-Sensitivity

18 of 35 participants (51%; 17 males, 1 female) were salt-sensitive (SS), average NaCl-induced  $\Delta$ MAP 11±2 mmHg; 17 (49%; 15 males, 2 females) were salt-resistant (SR), average NaCl-induced  $\Delta$ MAP -1±2 mmHg (Figure 1, Figure 2A). In SS, but not in SR, Na<sup>+</sup>-restriction during week 2 induced a significant hypotensive effect compared to initial BP.

### Demographic Characteristics

SS subjects were slightly older than SR and had a significantly higher initial BP, higher serum Na<sup>+</sup> concentration and lower body mass index (BMI), Table 1. After adjusting for age and BMI, the difference remained significant for DBP and MAP but not for SBP.

### Pressor Effects of NaHCO<sub>3</sub>

In SS but not in SR, NaHCO<sub>3</sub>-loading, compared to Na<sup>+</sup>-restriction, induced a significant pressor effect (Figures 1, Figure 2A, Table 2). However, this pressor effect was significantly less than that of NaCl. The sequence in which Na<sup>+</sup>-salts were administered did not affect their pressor effect. ANOVA, summary of effects: SS vs SR (group), P=0.004; NaCl vs low-NaCl vs NaHCO<sub>3</sub> (intervention), P<0.0001; sequence (of Na<sup>+</sup>-salt), P=0.65; interaction of intervention by group, P<0.00001; interaction of intervention by sequence, P=0.58; interaction of sequence by group, P=0.27.

In 11 of 18 the SS the NaHCO<sub>3</sub>-induced increase in MAP was ≥5 mmHg. In these 11 “sodium-selective” salt-sensitive subjects (sNaS), the mean NaHCO<sub>3</sub>-induced increase in MAP was two thirds that induced by equimolar amounts of NaCl (Figure 2B, Table 2). In 7 of 18 the SS the NaHCO<sub>3</sub>-induced increase in MAP was <5 mmHg. In these “classic” salt-sensitive subjects (cSS) the mean NaCl-induced increase in MAP was significantly lower than that in sNaS. In fact, the pressor effect of NaHCO<sub>3</sub> in sNaS was similar to that of NaCl in cSS (Figure 2B,

Table 2). For all SS and SR subjects combined, changes in MAP induced by NaCl strongly predicted those induced by NaHCO<sub>3</sub> (Figure 3A).

Mean values of  $\Delta$ MAP adjusted for changes in serum K<sup>+</sup> or hematocrit were not different from unadjusted means.

### Effects of NaHCO<sub>3</sub> and NaCl on Renal Hemodynamics

In SS but not SR, both NaHCO<sub>3</sub> and NaCl induced significant decreases in RBF and increases in RVR (Figure 4). Changes in RBF did not differ significantly between SS subgroups. But average changes tended to be greater in (the more salt-sensitive) sNaS than in cSS. Since this study was designed to compare 2 groups only, SR and SS, subgroup analysis was not expected to achieve sufficient power to detect relevant differences. For all subjects combined, NaHCO<sub>3</sub>-induced changes in RBF and RVR, respectively, were strongly predicted by NaCl-induced changes (Figure 3B and C).

### Metabolic Effects of NaHCO<sub>3</sub> and NaCl

Both NaCl and NaHCO<sub>3</sub> induced significant increases in BW (Figure 2C and D and Table 2). Increases were similar in SR and SS as well as in SS sub-groups and tended to be larger with NaCl than with NaHCO<sub>3</sub>. Both NaCl and NaHCO<sub>3</sub> induced significant decreases in hematocrit values. Decreases were similar in SS and SR but were significantly larger with NaCl than with NaHCO<sub>3</sub> in both groups (Figures 2E and F and Table 2). Changes in BW and hematocrit were not predictive of pressor effects for either Na<sup>+</sup>-salt.

UVNaCum during loading of either NaCl or NaHCO<sub>3</sub> did not differ between SS and SR. For all subjects combined, UVNaCum was 17% greater with NaHCO<sub>3</sub> than with NaCl, P=0.07. During NaCl-loading UVNaCum was, mmol/mg creatinine per 70kg BW, 0.63±0.11 in SS (n=8) and 0.63±0.10 in SR (n=8) and during NaHCO<sub>3</sub>-loading it was 0.78±0.16 (n=9) and 0.69±0.08 (n=8) in SS and SR, respectively.

Changes in plasma aldosterone and PRA were similar with NaCl and NaHCO<sub>3</sub> and significant in both SR and SS (Table 2). The NaCl-induced decrease in PRA but not in aldosterone was slightly but significantly greater in SR than in SS. NaHCO<sub>3</sub>-induced changes did not differ between SS and SR.

Both Na<sup>+</sup>-salts induced significant increases in serum levels of Na<sup>+</sup> in SS and SR. In both groups, the increase was slightly larger with NaCl than with NaHCO<sub>3</sub>, the difference being significant in SS (Table 3). As expected, NaHCO<sub>3</sub>-loading induced a small but significant decrease in serum K<sup>+</sup> in both SS and SR (Table 3). Serum K<sup>+</sup> levels remained within the normal range in all but one SR subject who developed mild hypochloremic alkalosis with NaHCO<sub>3</sub>-loading. The NaHCO<sub>3</sub>-induced decrease was slightly but significantly larger in SS than in SR. NaCl-loading induced a significant increase and NaHCO<sub>3</sub>-loading a significant decrease in serum Cl<sup>-</sup> in both SS and SR (Table 3).

In SS, but not in SR, BP varied directly and highly significantly with the serum concentration of Na<sup>+</sup> (R=0.541, P<0.0001). When sNaS only were included in the analysis the relationship was stronger than in all SS combined (Figure 5).

For SS and SR combined the responses to NaHCO<sub>3</sub> of serum Na<sup>+</sup>, aldosterone and PRA but not those of hematocrit or K<sup>+</sup> were strongly predicted by the responses to NaCl.

## Discussion

In the currently studied blacks, half were judged to be salt-sensitive (SS), half salt-resistant (SR). In at least two thirds of the SS, selective dietary Na<sup>+</sup>-loading with NaHCO<sub>3</sub> induced a pressor effect of at least 5 mmHg, despite a sustained restriction of dietary NaCl. Thus, salt-sensitivity occurs not only frequently in blacks, but in many it is “sodium-selective” (sNaS) in that Na<sup>+</sup>-loading is pressor without concomitant Cl<sup>-</sup>-loading. In sNaS, the mean NaHCO<sub>3</sub>-induced increase in MAP was fully two thirds that induced by equimolar NaCl-loading. To our knowledge, these observations provide the first demonstrations both that a non-Cl<sup>-</sup> salt of Na<sup>+</sup> can induce a pressor effect; and that any salt other than NaCl can induce a pressor effect in humans.

In one third of the currently studied SS, selective Na<sup>+</sup>-loading induced little or no pressor effect. For such salt-sensitivity that is induced only by Na<sup>+</sup>- and Cl<sup>-</sup>-loading combined<sup>6, 10–12</sup> we assign the modifier, “classic” (cSS). In sNaS, NaHCO<sub>3</sub> induced a pressor effect similar to that induced by NaCl in cSS. For all subjects combined the pressor response to NaHCO<sub>3</sub>-loading varied directly and highly significantly with the pressor response to NaCl-loading. The pressor effect of NaHCO<sub>3</sub>-loading amounted to half that of NaCl-loading. These observations would suggest that in many salt-sensitive blacks, a selective pressor effect of dietary Na<sup>+</sup> is a major component of the pressor effect of dietary NaCl, and the magnitude of the selective pressor effect of Na<sup>+</sup> a major determinant of the severity of NaCl-sensitivity.

In previous studies of mainly white hypertensive subjects,<sup>6, 11</sup> and of animal models of salt-sensitive hypertension<sup>13–15</sup> in which selective dietary loading of Na<sup>+</sup> failed to elicit a pressor effect, the failure might be inferred to reflect a failure to expand PV to some critical extent.<sup>5, 7</sup> As judged by the currently observed changes in hematocrit, it appears that both NaHCO<sub>3</sub> and NaCl induced expansion of PV. In accord with previous observations,<sup>6</sup> the current observations would indicate that PV expansion with NaHCO<sub>3</sub> was about half that with NaCl, not only in SS but also in SR.

NaCl-induced PV expansion is formulated to be a critical event in the pathogenesis of salt-sensitive blood pressure by entraining a transient increase in cardiac output (CO) that elicits a pressor effect in two phases and ways: 1) an immediate direct pressor effect; and several days later, 2) an indirect, sustained pressor effect that is mediated by an increase in systemic vascular resistance (SVR) occurring only in autoregulatory response to the increase in CO.<sup>2, 3</sup> However, in NaCl-loaded salt-sensitive subjects,<sup>16–19</sup> the apparent extent of neither PV expansion<sup>16–19</sup> nor increase in CO<sup>20</sup> induced by NaCl has predicted the extent of salt-sensitivity. In a recent study comparing normotensive salt-sensitive and salt-resistant blacks with respect to the time courses of their hemodynamic and metabolic responses to NaCl-loading, we observed similar increases in Na<sup>+</sup> balance, PV and CO. By contrast, in the 2 groups, the divergent pressor responses induced by dietary NaCl-loading were attended from their outset by divergent vascular responses, SVR decreasing sharply and immediately in the salt-resistant, but changing little in the salt-sensitive subjects.<sup>20</sup> In all subjects combined, the changes in SVR induced by NaCl on the 2<sup>nd</sup> day of its loading were strongly predictive of the changes induced by NaCl on MAP on the 7<sup>th</sup> day of its loading; NaCl-induced changes in PV and CO were not predictive. These observations indicate that in the SS subjects studied, an impaired systemic vasodilatory response to NaCl-loading, but not an abnormally increased PV or CO, is critical to the pathogenesis of salt's pressor effect.

In keeping with these observations, in the current study, the extent to which loading with either NaCl or NaHCO<sub>3</sub> induced PV expansion does not account for the extent of either salt's pressor effect. As judged by the decrease in hematocrit, the increase in PV induced by NaCl-loading in the SS is indistinguishable from that induced in SR. Indeed, while inducing a pressor effect

only slightly less than that induced by NaCl, NaHCO<sub>3</sub> induced in the sNaS a decrease in hematocrit only one-third that induced by NaCl in the SR. In all SS combined, as well as in sNaS and cSS subgroups, the Na<sup>+</sup>-induced mean changes in MAP adjusted for changes in hematocrit were not different from unadjusted mean changes in MAP. These observations and considerations suggest that in most salt-sensitive blacks, the pressor effect of dietary NaCl involves something more than its capacity to mediate osmotic expansion of PV, the only capacity of NaCl called for in the traditionally formulated mechanism of NaCl's pressor effect.<sup>2, 3, 5</sup>

In the SS, and particularly in the sNaS subgroup, BP varied directly and highly significantly with the plasma concentration of Na<sup>+</sup>, with and without Na<sup>+</sup>-loading, but not with changes induced in BW or hematocrit. This observation suggests that in some salt-sensitive humans, the plasma concentration of Na<sup>+</sup> attained with Na<sup>+</sup>-loading may critically determine the extent of the pressor effect of dietary NaCl. The observation accords with observations Qi et al. reported in the NaCl-loaded Dahl SS/Jr rat, in which BP varied directly and highly significantly with plasma Na<sup>+</sup> concentration, irrespective of the hydration state orally imposed.<sup>21</sup> Qi et al. proposed, as have others,<sup>4, 22, 23</sup> that "directly mediated increases in plasma Na<sup>+</sup> can increase arterial BP in rats by mechanisms that are apparently not related to fluid volume changes." An increase in plasma Na<sup>+</sup> concentration may elicit a pressor effect by increasing CSF Na<sup>+</sup> concentration<sup>24</sup> and by thereby activating central sympatho-excitatory mechanisms that give rise to increased sympathetic outflow.<sup>21, 25-27</sup>

In SS but not in SR, NaHCO<sub>3</sub><sup>-</sup>, as well as NaCl-loading, induced a clear-cut reduction in RBF and hence, a robust increase in renal vascular resistance, a phenomenon previously described only with NaCl-loading in salt-sensitive humans<sup>28, 29</sup> including normotensive blacks.<sup>19</sup> Clearly, the Cl<sup>-</sup>-component of NaCl is not required to elicit this dysfunctional renal hemodynamic response to Na<sup>+</sup>-loading. It has been proposed that a similar renal hemodynamic response is critically involved in the salt-sensitivity of patients with "non-modulating" essential hypertension.<sup>30</sup> The extent of Na<sup>+</sup>-induced renal vasoconstrictive changes in those with salt-sensitivity has been related to the extent of their pressor response.<sup>19, 31</sup>

## Perspectives

In establishing the fact of "sodium-selective" salt-sensitivity, and its occurrence in many blacks who are salt-sensitive, the current observations extend to human relevance the consideration of ion-selective pressor phenomena, previously observed only as Cl<sup>-</sup>-sensitive hypertension in the spontaneously hypertensive rat,<sup>32</sup> and in the stroke-prone spontaneously hypertensive rat.<sup>33, 34</sup> In some instances of salt-sensitivity, initiation of the pressor effect of dietary NaCl would appear to require something beyond, or other than, an abnormally enhanced renal retention of its ionic components and their complimentary osmotic capacities to expand PV,<sup>20, 33, 34</sup> possibly an increase in plasma Na<sup>+</sup> that elicits an increased CNS sympathetic outflow.<sup>4, 21-23, 25</sup> Accordingly, the current observations expand the scope of possible pathogenic mechanisms of human hypertension and hence the scope of its potential treatment and prevention.

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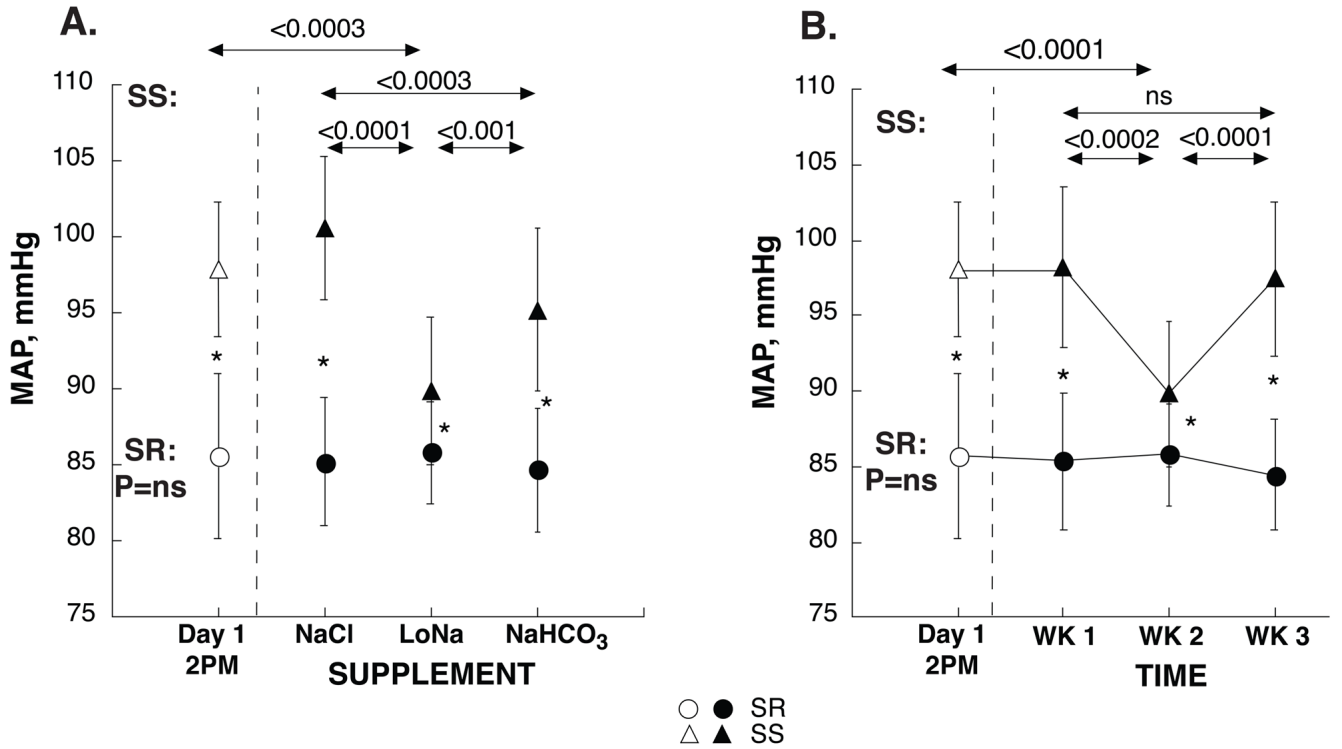
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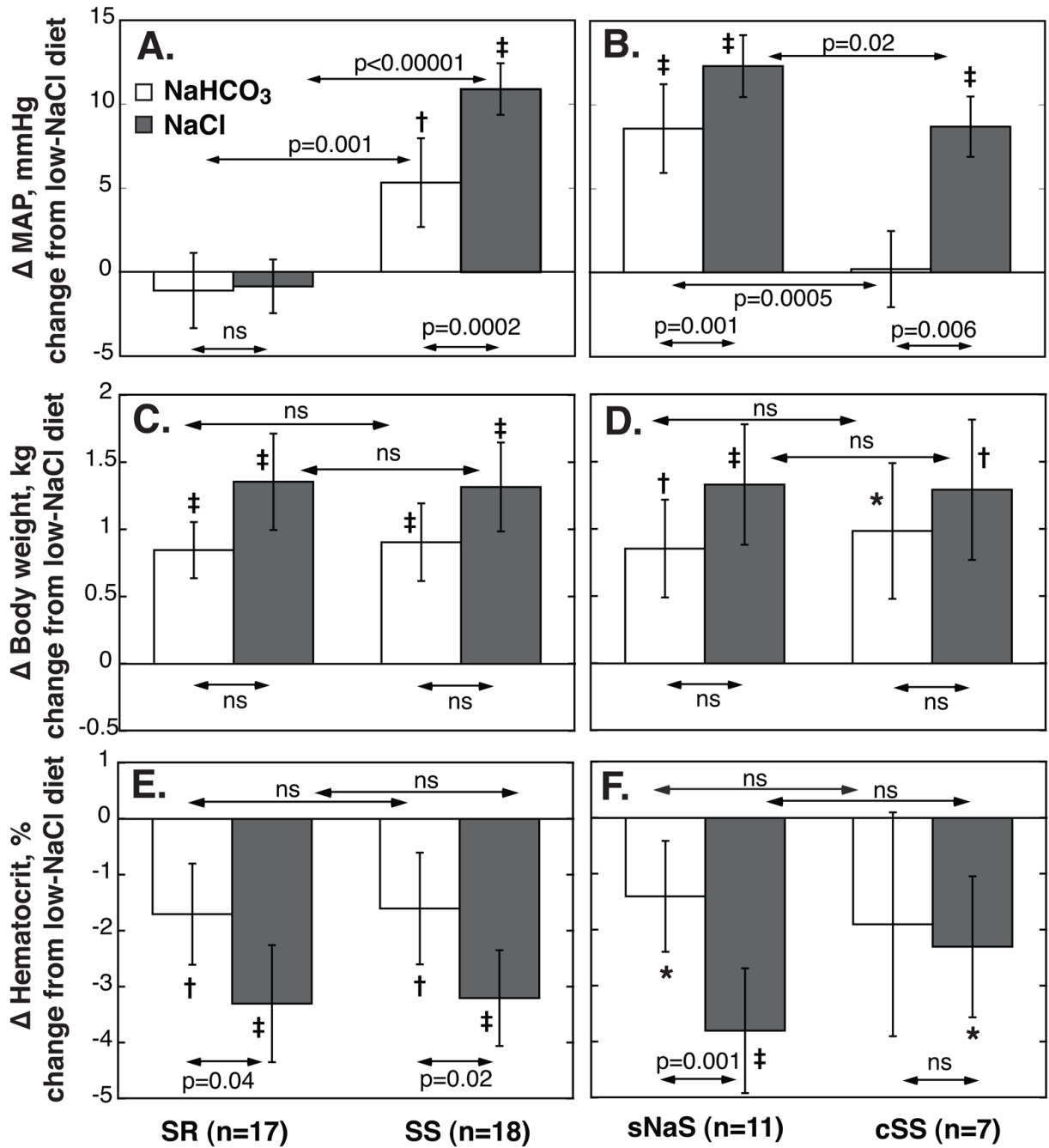
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**Figure 1. Initial MAP and MAP during oral loading of NaCl, low-Na<sup>+</sup> and NaHCO<sub>3</sub> in SS (▲) and SR (●) subjects, respectively**

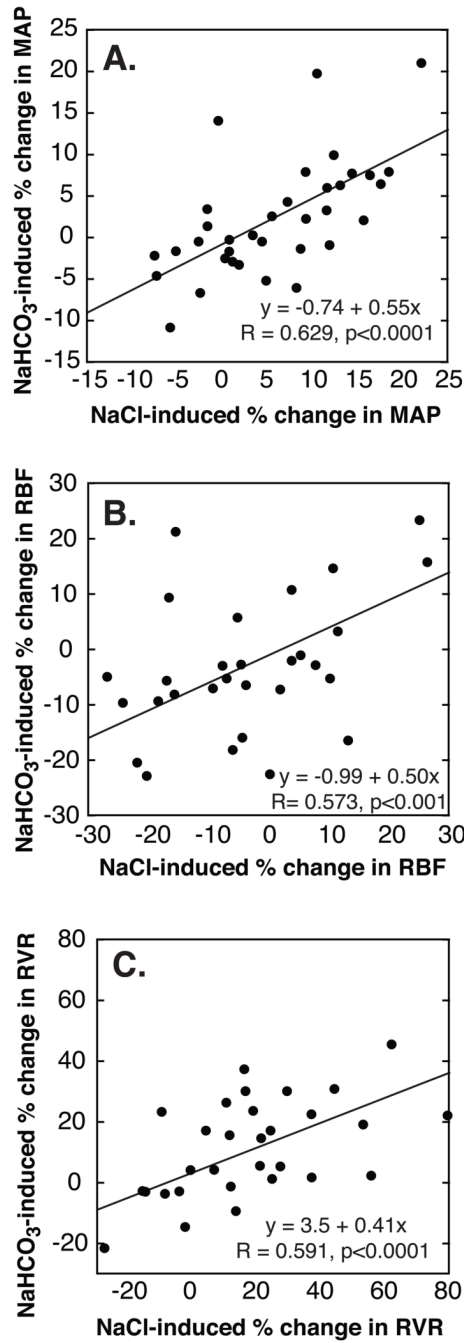
Na<sup>+</sup> was supplemented as NaCl during the 1<sup>st</sup> week and as Na-HCO<sub>3</sub> during the 3<sup>rd</sup> week, or vice versa. About half of the subjects received NaCl first. For all participants, week 2 was the low-Na<sup>+</sup> period. Panel A shows MAP values grouped by supplement; panel B shows the 3-week time course of MAP in the same subjects. “Initial” BP was obtained at 2PM on the 1<sup>st</sup> day of study, shortly after subjects were admitted, using the same standardized procedure as throughout the study. Other BP values are daily averages of days 5 and 6 of each of the 3 study periods. ★ SR subjects had significantly lower BP than SS,  $P < 0.0001$ . In SR subjects MAP did not change with changing levels of dietary Na<sup>+</sup>. In SS subjects, MAP was significantly lower with low Na<sup>+</sup> intake compared to values both on admission and during Na<sup>+</sup>-loading with either NaCl or NaHCO<sub>3</sub>. The sequence in which Na<sup>+</sup>-salts were loaded did not affect their pressor effects (panel B).



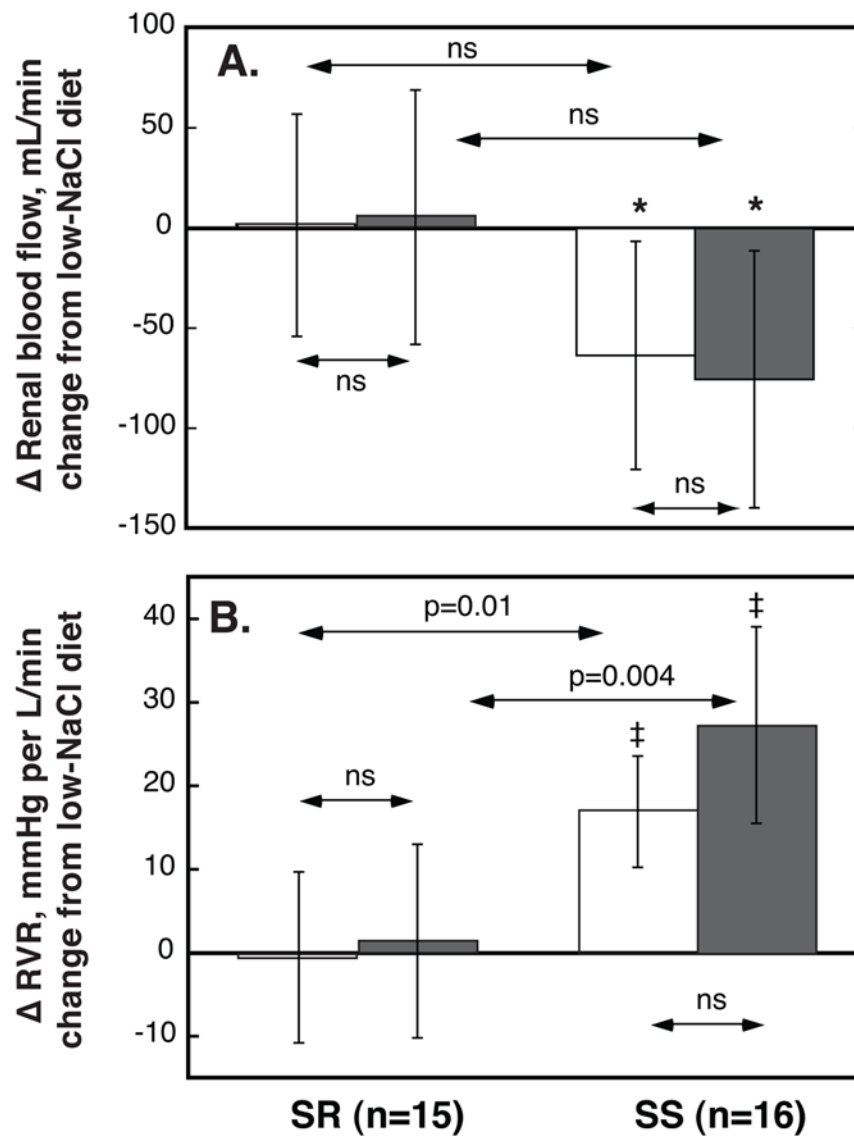
**Figure 2. NaHCO<sub>3</sub>- (□) and NaCl-induced (■) changes in MAP, body weight (BW) and hematocrit in salt-resistant (SR) and salt-sensitive (SS) subjects, left panels, and in selective sodium-sensitive (sNaS) and classic salt-sensitive (cSS) subgroups, right panels**

Values are average changes from baseline (average of days 5 and 6 of low-NaCl) on days 5 and 6 of Na<sup>+</sup>-loading periods. Values are means, error bars are 95% C.I. P values for within-group comparisons of Na<sup>+</sup>-loading vs low-NaCl period: ★P<0.05; †, P<0.01; and ‡ P<0.001; respectively. NaHCO<sub>3</sub>-loading induced a significant pressor response in SS but not in SR, panel A. In 11 of 18 SS the NaHCO<sub>3</sub>-induced pressor effects was ≥5 mmHg (sNaS), in 7 SS it was <5 mmHg (cSS), panel B. Responses of BW (panels C and D) and hematocrit (panels E and F) are shown in the right panels.

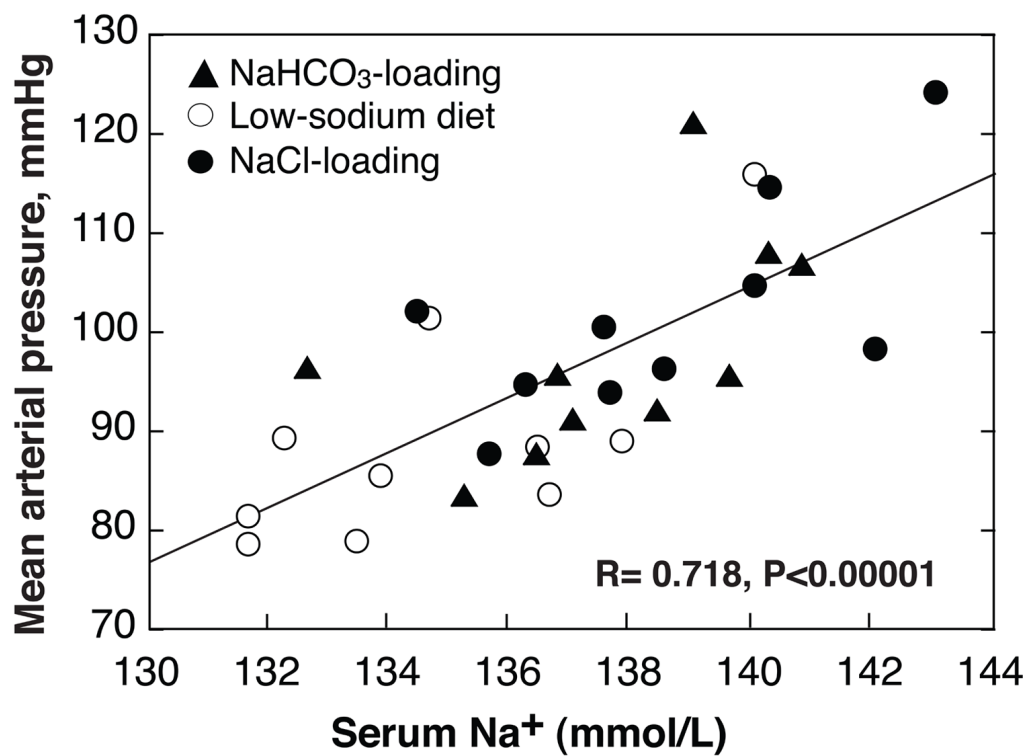
E and F) to Na<sup>+</sup>-loading did not differ between SR and SS and between sNaS and cSS, respectively.



**Figure 3. Relationship between NaCl- and NaHCO<sub>3</sub>-induced changes in MAP, renal blood flow (RBF) and renal vascular resistance (RVR) in all subjects combined**  
 NaCl-induced changes in MAP (A), RBF (B) and RVR (C) are highly predictive of NaHCO<sub>3</sub>-induced changes. For all subjects combined, the magnitude of the NaHCO<sub>3</sub>-induced changes amounts to about half that induced by NaCl. NaCl- and NaHCO<sub>3</sub>-induced effects are presented as % change from low-NaCl baseline.



**Figure 4.** NaHCO<sub>3</sub>- (□) and NaCl-induced (■) changes in renal blood flow, panel A, and renal vascular resistance (RVR), panel B, in salt-resistant (SR) and salt-sensitive (SS) subjects. Values are average changes from day 7 of low-NaCl to day 7 of Na<sup>+</sup>-loading periods. Values are means, error bars are 95% C.I. P values for within-group comparisons of Na<sup>+</sup>-loading vs low-NaCl period: ★P<0.05; †, P<0.01; and ‡ P<0.001; respectively. In SS but not in SR NaHCO<sub>3</sub> and NaCl induced decreases in RBF and increases in RVR. The changes in both variables were similar with the two salts.



**Figure 5. Relationship between serum Na<sup>+</sup>-concentration and mean arterial pressure in sodium-selective salt-sensitive (sNaS) subjects at the ends of low-NaCl diet (○) and Na<sup>+</sup>-loading with either NaCl (●) or NaHCO<sub>3</sub> (▲)**  
In sNaS plasma Na<sup>+</sup> with and without Na<sup>+</sup>-loading is highly predictive of BP.

**Table 1**  
Demographic characteristics of salt-resistant (SR) and salt-sensitive (SS) subjects

Variable	SR	All SS	sNaS	SS Subgroups	cSS
n (%)	17 (49%)*	18 (51%)*	11 (61%) <sup>†</sup>		7 (39%) <sup>‡</sup>
Age, yrs	45.2±2.7	49.6±1.8 §	49.0±2.5		50.7±2.3
BW, kg	82.5±4.4	79.7±5.9	77.3±8.6		83.5±6.7
BMI, kg/m <sup>2</sup>	27.2±1.4	24.8±1.3 <sup>‡</sup>	24.5±2.7		25.3±2.1
Initial SBP, mmHg	120±8	133±6 <sup>‡</sup>	133±7		134±11
Initial DBP, mmHg	68±4	80±4 <sup>‡</sup>	82±4		77±6
SBP≥140 or DBP≥90 mmHg, n (%)	2 (12%)	5 (28%)	3 (27%)		2 (29%)
Serum Creatinine, mg/100mL	1.0±0.1	0.9±0.1	0.9±0.2		0.9±0.1
Serum Na <sup>+</sup> , mmol/L	137.9±0.9	139.6±1.1 <sup>‡</sup>	139.5±2.1		139.6±2.8
Serum K <sup>+</sup> , mmol/L	4.2±0.1	4.2±0.1	4.3±0.3		4.2±0.2
Serum Cl <sup>-</sup> , mmol/L	103.1±1.3	103.2±1.4	102.9±1.8		103.6±2.0
Total CO <sub>2</sub> , mmol/L	26±2	28±1	28±2		29±3.5

Values are mean and 95% CI; sNaS: "sodium-selective" salt-sensitive; cSS "classic" salt-sensitive;

\* Percent of total number of subjects enrolled;

<sup>†</sup> Percent of all salt-sensitive subjects;

<sup>‡</sup> t-test: p<0.05. "Initial" SBP and DBP was obtained at 2PM on the 1<sup>st</sup> day of study, shortly after subjects were admitted, using the same standardized procedure as throughout the study.

Blood pressure, pulse pressure (PP), body weight (BW), hematocrit, aldosterone and PRA during low NaCl intake (lowNa) and during oral Na<sup>+</sup>-loading with NaCl and NaHCO<sub>3</sub>, respectively, in salt-resistant (SR) and salt-sensitive (SS) subjects and in SS sub-groups (sodium-selective salt-sensitive, sNaS, and classic salt-sensitive, cSS)

Table 2

Variable	Diet	SR (n=17)			All SS (n=18)			SS Subgroups			cSS (n=7)		
		mean	95% CI	p*	mean	95% CI	p*	mean	sNaS (n=11) 95% CI	p*	mean	95% CI	p*
MAP, mmHg	NaHCO <sub>3</sub>	84.7	4.1	ns	95.2	5.4	<0.001	99.9	7.4	<0.001	87.7	3.1	ns
	Low Na	85.8	3.4	ns	89.9	4.8	<0.001	91.4	7.5	<0.001	87.4	3.8	<0.001
	NaCl	84.9	4.2	ns	100.7	4.7	<0.001	103.7	6.9	<0.001	96.1	3.3	<0.001
SBP, mmHg	NaHCO <sub>3</sub>	117.5	5.2	ns	128.9	6.8	<0.001	135.4	8.5	<0.001	118.7	6.3	ns
	Low Na	117.1	3.7	ns	120.2	5.6	<0.001	122.3	8.7	<0.001	117.0	4.5	<0.001
	NaCl	118.5	4.5	ns	137.4	6.0	<0.001	141.3	8.4	<0.001	131.3	6.2	<0.001
DBP, mmHg	NaHCO <sub>3</sub>	68.3	3.7	ns	78.4	4.9	<0.01	82.3	7.0	<0.001	72.2	2.6	ns
	Low Na	70.1	3.4	ns	74.7	4.5	<0.001	76.0	7.1	<0.001	72.7	3.7	<0.001
	NaCl	68.2	4.1	<0.05	82.4	4.3	<0.001	84.9	6.4	<0.001	78.5	3.0	<0.001
PP, mmHg	NaHCO <sub>3</sub>	49.2	2.8	<0.01	50.5	3.4	<0.001	53.1	3.3	<0.001	46.5	6.1	ns
	Low Na	47.0	1.9	<0.001	45.5	2.1	<0.001	46.3	3.0	<0.001	44.3	2.4	<0.01
	NaCl	50.3	1.8	<0.001	55.0	3.2	<0.001	56.5	3.6	<0.001	52.7	5.9	<0.05
BW, kg	NaHCO <sub>3</sub>	83.1	4.5	<0.001	79.4	6.1	<0.001	77.5	9.0	<0.01	82.5	6.7	<0.05
	Low Na	82.3	4.5	<0.001	78.6	6.0	<0.001	76.7	9.0	<0.001	81.5	6.4	<0.01
	NaCl	83.7	4.6	<0.001	79.9	6.1	<0.001	78.0	9.1	<0.001	82.8	6.7	<0.01
Hct, %	NaHCO <sub>3</sub>	41.5	2.2	<0.01	42.6	1.4	<0.01	42.9	2.0	<0.05	42.1	1.7	ns
	Low Na	43.2	2.2	<0.001	44.2	1.7	<0.001	44.4	2.3	<0.001	44.0	2.6	<0.01
	NaCl	39.8	1.7	<0.001	41.0	1.6	<0.001	40.5	1.6	<0.001	41.7	3.1	<0.05
Aldo, % ng/100mL	NaHCO <sub>3</sub>	4.0	2.0/7.0	<0.01	3.0	2.0/4.0	<0.001	3.0	2.0/4.0	<0.05	3.0	2.0/4.0	<0.05
	Low Na	18.0	13.0/31	<0.001	9.0	6.0/11.0	<0.001	9.0	7.0/10.5	<0.05	11.0	6.0/23.0	<0.05
	NaCl	4.0	2.0/6.0	<0.05	3.0	2.0/5.0	<0.01	3.0	2.0/5.0	<0.05	3.5	3.0/5	<0.05
PRA, % ng/mL/hr	NaHCO <sub>3</sub>	1.1	0.5/1.9	<0.001	0.4	0.2/0.7	<0.001	0.3	0.3/0.7	<0.01	0.6	0.1/2.1	<0.05
	Low Na	3.0	2.6/7.9	<0.001	2.3	0.8/4.9	<0.001	2.2	1.3/3.9	<0.05	2.4	0.7/11.0	<0.05
	NaCl	0.4	0.2/0.3	<0.001	0.3	0.1/0.5	<0.001	0.3	0.2/0.4	<0.05	0.3	0.1/0.9	<0.05

\* compared to low Na<sup>+</sup> diet;

% values are median and 25<sup>th</sup>/75<sup>th</sup> percentile



Serum electrolyte and creatinine concentrations during oral Na<sup>+</sup>-loading with NaCl and NaHCO<sub>3</sub>, respectively, in salt-resistant (SR) and salt-sensitive (SS) subjects and in SS subgroups (sodium-selective salt-sensitive, sNaS, and classic salt-sensitive, cSS)

Table 3

Variable	Diet	SR (n=17)			All SS (n=18)			SS Subgroups			* p		
		mean	95% CI	p	mean	95% CI	p	mean	95% CI	p			
Na <sup>+</sup> , mmol/L	NaHCO <sub>3</sub>	136.3	1.43	<0.001	137.8	1.14	<0.001	137.6	1.56	0.0015	138.1	1.77	<0.01
	Low Na	133.0	1.42		135.1	1.20		134.8	1.75		135.6	1.58	
	NaCl	137.4	1.33	<0.001	138.6	1.14	<0.001	138.5	1.73	<0.001	138.6	1.40	<0.01
K <sup>+</sup> , mmol/L	NaHCO <sub>3</sub>	3.8	0.15	<0.01	3.6	0.11	<0.001	3.7	0.16	<0.001	3.6	0.14	<0.05
	Low Na	4.1	0.15		4.1	0.12		4.2	0.12		4.0	0.23	
	NaCl	4.0	0.09	<0.05	3.9	0.14	<0.001	3.9	0.20	<0.01	3.8	0.17	ns
Cl <sup>-</sup> , mmol/L	NaHCO <sub>3</sub>	97.6	1.71	<0.01	97.8	0.91	<0.001	97.9	1.26	<0.001	97.6	1.40	<0.01
	Low Na	99.5	1.15		100.9	0.81		101.1	1.10		100.6	1.23	
	NaCl	105.4	1.20	<0.001	105.3	0.77	<0.001	105.6	0.96	<0.001	104.8	1.26	<0.01
HCO <sub>3</sub> <sup>-</sup> , mmol/L	NaHCO <sub>3</sub>	30.8	1.31	<0.001	33.0	0.77	<0.001	33.2	1.24	<0.001	32.7	0.83	<0.001
	Low Na	25.9	1.18		27.0	0.73		26.8	1.00		27.3	1.10	
	NaCl	25.9	1.33	ns	26.7	0.90	ns	26.5	1.36	ns	26.9	1.10	ns
Creatinine, mg/100mL	NaHCO <sub>3</sub>	1.03	0.08	ns	0.99	0.10	ns	1.00	0.15	ns	0.96	0.12	ns
	Low Na	1.00	0.07		0.97	0.09		1.00	0.14		0.93	0.08	
	NaCl	0.95	0.09	<0.05	0.93	0.10	ns	0.98	0.16	ns	0.87	0.05	<0.05

\* compared to low Na diet