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ORIGINAL ARTICLE

Effect of acute salt ingestion upon core temperature in healthy men

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Salt intake may cause conflict for the cardiovascular system as it attempts to simultaneously maintain blood pressure (BP) and temperature homeostasis. Our objective was to determine the effect of a salt and water load *vs.* a water load upon rectal temperature (Tre) in healthy volunteers. Twenty-two healthy, non-hypertensive Caucasian men enrolled in two trials in which they ingested either salt and body temperature water (SALT), or body temperature water (WATER). BP, Tre, cardiac index, peripheral resistance and urine output were monitored one, 2 and 3 h post-baseline. Changes in the dependent variables were compared between those subjects who were salt sensitive (SS) and those who were salt resistant (SR) at the same time intervals. The percentage change reduction in Tre was greater following SALT compared with WATER at +120 min (-1.1 ± 0.7 *vs.* $-0.6 \pm 0.5\%$, $P=0.009$) and at +180 min (-1.3 ± 0.8 *vs.* $-0.7 \pm 0.6\%$, $P=0.003$). The percentage change reduction in Tre was greater in the SR group compared with the SS group at +180 min (-1.6 ± 0.9 *vs.* $-0.9 \pm 0.5\%$, $P=0.043$). SALT decreased Tre more than WATER. SS individuals maintained temperature homeostasis more effectively than SR individuals following SALT. These results may explain why some individuals are SS while others are SR. If these results are generalizable, it would be possible to account for the role of sodium chloride in the development of SS hypertension.
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INTRODUCTION

The hemodynamic consequences of salt and water intake are understood.[1–4] An increase in cardiac output is the first hemodynamic change following salt and water intake. Any immediate increase in blood pressure (BP) is due to the increased cardiac output. Within a matter of hours following salt and water loading, peripheral resistance increases and cardiac output decreases. As peripheral resistance increases, BP increases, thereby increasing salt and water excretion. BP equilibrates when the renal output of salt and water equals the net intake of salt and water. The term pressure-natriuresis describes the phenomenon whereby salt and water intake raises BP, which, in turn, increases renal excretion of salt and water.[1,4,5]

'Autoregulation' has been proposed as an explanation for the vasoconstriction that follows salt and water loading: in response to the increased blood flow to the kidneys and end organs that occurs when cardiac output increases following salt and water loading, vasoconstriction ensues in order to downregulate blood flow.[1,2,4]

There are several limitations with autoregulation in terms of its ability to explain the hemodynamic changes that follow salt and water intake. Autoregulation cannot explain the decrease in peripheral resistance that immediately follows salt and water intake.[2,6–8] Furthermore, autoregulation cannot explain why, in some normal subjects and salt-resistant (SR) subjects, BP decreases within the first several hours to days following salt and water intake.[7,8] Most importantly, autoregulation cannot explain why some individuals are salt sensitive (SS) and some are SR.

Given the limitations of autoregulation as an explanation for the hemodynamic changes that follow salt and water intake, it has been proposed that salt and water intake makes it difficult for the body to simultaneously maintain both BP and temperature homeostasis.[9] The cardiovascular system is not only responsible for regulating BP, it is also involved in temperature regulation as it transports heat from the internal organs and muscles to the cutaneous circulation.[10] Conflict between the simultaneous goals of BP homeostasis and temperature homeostasis might explain the hemodynamic consequences of salt and water intake.

The initial decrease in peripheral resistance that accompanies salt and water intake is due to vasodilatation. This presumably occurs in an attempt to maintain BP homeostasis by increasing intravascular volume in the face of increased extracellular fluid. If vasodilatation includes the cutaneous circulation, and/or if increased cardiac output increases cutaneous blood flow, heat loss will accelerate, and the result

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will be a drop in core body temperature. In order to maintain body temperature, vasoconstriction might occur in order to diminish cutaneous blood flow and thereby limit heat loss. In the process, BP will increase. Thus, pressure-natriuresis may reflect the body's attempt to minimize heat loss and defend core body temperature. Although there is little experimental evidence to support this theory, there is some indirect evidence based upon studies in rats that have shown that hypertonic saline infusion decreases core temperature compared with isotonic saline.[11–13]

That some individuals are SS while others are SR may be due to differences in defending core body temperature. Given the same intake of salt and water, individuals who are SS might maintain temperature homeostasis while tolerating a higher BP, whereas individuals who are SR might tolerate a lower core temperature while maintaining BP homeostasis.

Since rectal temperature (Tre) approximates core body temperature, we designed an experiment to determine the effect of salt and water intake upon Tre. We hypothesized that salt and water ingestion would lower Tre more than would water alone. We designed a simultaneous experiment to test the hypothesis that SR individuals would experience a lower Tre than SS individuals following a prescribed intake of salt and water.

METHODS

Subjects

Twenty-two healthy men were recruited via flyers and word of mouth to participate in the present study. Participants were all non-hypertensive (systolic BP <140 and diastolic BP <90 mm Hg), disease-free Caucasians who were not utilizing medications or dietary supplements that influence BP. Informed consent was obtained from each subject before participation, and the study protocol was approved by the Kent State University Institutional Review Board for The Protection of Human Subjects.

Screening visit and instrumentation

Before reporting to the Exercise and Environmental Physiology Laboratory, subjects were asked to avoid caffeine, strenuous exercise and/or high-calorie or high-salt meals. Upon arrival, body weight was obtained with a balance beam scale (Homs, Western Germany) to the nearest ounce, and then converted to metric. Next, volunteers sat quietly for 5 min before BP assessment. BP was screened by auscultation of the brachial artery using a stethoscope and an aneroid manometer.[14] For the remainder of testing, impedance cardiography (Bio-Z, Cardiodynamics, San Diego, CA, USA) was used to monitor mean arterial pressure (MAP), cardiac index (CI) and systemic vascular resistance index. All measurements were made in duplicate (two 5-s strips) and the resulting average was reported. Systemic vascular resistance index was monitored throughout the trials but was deemed inappropriate to use for data analysis. The impedance cardiography calculates systemic vascular resistance index utilizing an estimated central venous pressure of 6 mm Hg, but similar protocols have shown that central venous pressure increases nearly twofold with salt loading.[15]

Experimental testing

The current study employed a within-subjects design. Subjects participated in two experimental trials separated by a 1 week washout period. One trial consisted of the ingestion of sodium chloride tablets with water (SALT), and the other trial consisted of the ingestion of water only (WATER). The order in which subjects completed the trials was counterbalanced. Subjects were requested to refrain from eating for at least 8 h before each trial. To minimize circadian influence on thermoregulation, all trials were done in the morning hours (0600–1000) in a temperature-controlled testing chamber (25 °C air) (Western Environmental Chamber; 718 Soscol Ave, Napa, CA, USA). During the trials, subjects remained shirtless and wore only underwear, shorts and socks, and remained semirecumbent[16] in a nylon-mesh chair.

Upon arrival on testing days, subjects emptied their bladders and were asked to insert a rectal probe 13 cm beyond the anal sphincter (ER400-12, Respiratory Diagnostic Products, Irvine, CA, USA). Subjects were then fitted with four electrodes (two on the neck and two on the ribs) as previously described.[17]

The experimental trials consisted of a 1-h baseline period (BASE), a 1-h ingestion period (ING) and 2 h of recovery period (REC). To ensure participant safety, data were monitored continuously and logged every 10 min. Herein, data are presented as follows: BASE (end of 60-min rest), +60 min (end of ING), +120 min (end of 1-h REC), +180 min (end of 2-h REC). During SALT, buffered salt tablets (Lannett Pharmaceuticals, Philadelphia, PA, USA) were administered along with 1.0 liters of commercially available water (Crystal Geyser, San Francisco, CA, USA) warmed to 37 °C. The tablets consisted of 287 mg of chloride, 180 mg of sodium and 15 mg of potassium, and subjects consumed one pill every 2–3 min so as to achieve a total dosage of NaCl of $\sim$11 g. The amount of NaCl needed to elicit a significant change in BP was determined in previous pilot studies in our lab, and researchers sought to deliver a body weight-dependent dose. During WATER, 1.0 l of commercially available water that was warmed to 37 °C was consumed. Subjects were allowed to urinate ad libitum during the study protocol, and subjects emptied their bladders at the completion of the protocol. All urine output from the beginning to the end of the protocol was collected in sterile beakers, and the volume of urine output for each subject was quantified.

After the completion of data collection, subjects were divided into two groups based upon their degree of salt sensitivity. As previously described in a detailed review,[18] precise definition of salt sensitivity is elusive. After consulting similar protocols,[8,16] subjects were labeled as SS if, during the course of the protocol, there was an increase in MAP >10 mm Hg. Conversely, subjects were labeled as SR if, during the course of the protocol, the change in MAP was $\leqslant 10$ mm Hg.

Statistical analysis

Repeated measures (+60, +120 and +180) analyses of variance (ANOVAs) were performed to compare the percentage change from baseline for MAP, Tre and CI responses between treatments (SALT, WATER). Salt sensitivity was entered as a between-subjects factor in the ANOVA, and independent *t*-tests were used to elucidate differences in SS ($n=10$) *vs.* SR individuals ($n=12$). The Kolmorgorov–Smirnov test was used on all data to ensure normality. In the event that the assumption of sphericity was violated, the Greenhouse-Geisser correction was interpreted. *Post hoc* analysis of significant interaction effects was performed via Bonferroni-corrected paired samples tests. Statistical significance was set *a priori* at alpha >0.05. A modern statistics software package was used for all data analysis (SPSS version 17.0 for Macintosh, Chicago, IL, USA). All data are presented as mean ± s.d.

RESULTS

All of the subjects ($n=22$) exhibited normal resting MAP (82 ± 6 mm Hg) as measured via impedance cardiography, and all of the data passed the test of normality. Most of the subjects were young men (mean age 23 ± 6 years) and all were within the normal range for body weight (94.2 ± 12.8 kg). The mean NaCl ingestion per subject was 11.5 ± 1.3 g. Table 1 contains the data from all 22 subjects and addresses the first hypothesis, while Table 2 and Figure 1 have the subjects divided into SS *vs.* SR and address the second hypothesis.

Analysis for the dependent variable MAP via repeated measures ANOVA revealed significant main effects for treatment ($F(1,14)=4.870$, $P=0.045$, $\eta_p^2=0.258$), time ($F(2,28)=23.318$, $P\leqslant 0.001$, $\eta_p^2=0.625$) and a between subjects main effect for sensitivity ($F(1,14)=8.661$, $P=0.011$, $\eta_p^2=0.382$). A significant interaction effect was also revealed for time by sensitivity ($F(2,28)=13.855$, $P\leqslant 0.001$, $\eta_p^2=0.497$). A significant treatment by time interaction was also found; however, the analysis was in violation of the assumption of sphericity. Thus, the Greenhouse-Geisser correction was interpreted ($F(1.372,19.207)=3.891$, $P=0.032$, $\eta_p^2=0.218$). Bonferroni-corrected *post hoc* analysis revealed that results between treatments were signi-

Table 1 Hemodynamics and rectal temperature response to salt or water ingestion (*n*=22)

	SALT	*% change from BASE*	*WATER*	*% change from BASE*	*Between treatments*
MAP					
BASE	82 ± 6		83 ± 6		
+60	91 ± 7	14 ± 10	86 ± 5	4 ± 6	0.017
+120	86 ± 5	5 ± 6	86 ± 7	4 ± 6	0.475
+180	84 ± 7	3 ± 6	84 ± 5	2 ± 5	0.606
CI					
BASE	2.89 ± 0.56		2.95 ± 0.51		
+60	2.99 ± 0.56	5 ± 17	2.75 ± 0.48	−7 ± 7	0.072
+120	2.69 ± 0.62	−4 ± 3	2.56 ± 0.54	−13 ± 12	0.408
+180	2.58 ± 0.55	−7 ± 3	2.53 ± 0.44	−14 ± 9	0.885
Tre					
BASE	37.20 ± 0.33		37.01 ± 0.27		
+60	36.91 ± 0.31	−0.8 ± 0.4	36.76 ± 0.29	−0.6 ± 0.4	0.294
+120	36.82 ± 0.27	−1.1 ± 0.7	36.77 ± 0.27	−0.6 ± 0.5	0.009
+180	36.76 ± 0.26	−1.3 ± 0.8	36.74 ± 0.31	−0.7 ± 0.6	0.003

Abbreviations: BASE, baseline period; CI, cardiac index; MAP, mean arterial pressure; Tre, rectal temperature.
Data are presented as a percentage change from baseline (mean ± s.d.).
Significance between treatments was obtained with a Bonferroni-corrected paired samples *t*-test and all data were normally distributed, *n*=22.

Table 2 Demographic characteristics of salt sensitive and salt resistant subjects

Variable	*Units*	*SS (n=10)*	*SR (n=12)*	*Significance*
Age	Years	25 ± 10	23 ± 3	0.442
Weight	kg	89 ± 10	98 ± 14	0.115
Urine output SALT	ml	464 ± 310	361 ± 250	0.409
Urine output WATER	ml	839 ± 360	633 ± 473	0.271
Seated resting MAP	mm Hg	81 ± 5	83 ± 6	0.125

Abbreviations: MAP, mean arterial pressure; SR, salt resistant; SS, salt sensitive.
Data are presented as mean ± s.d. Seated-resting MAP was obtained during screening visit.
Significance between groups was obtained with an independent sample's *t*-test.

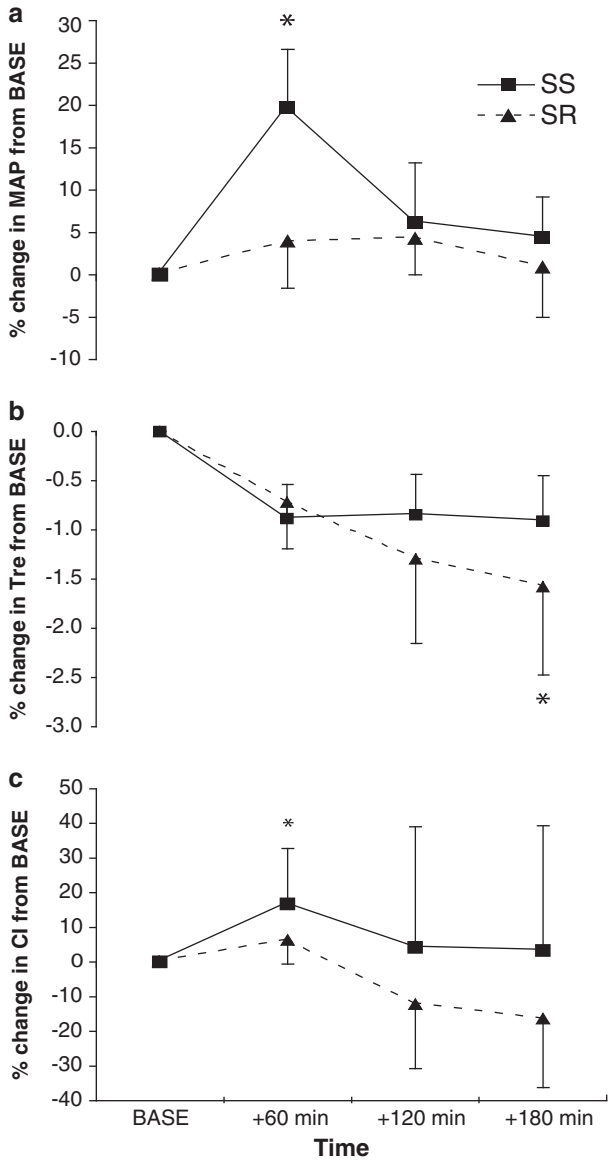

Figure 1 Percent change in MAP, Tre and CI for SS (□) and SR (△) subjects during SALT. Data are displayed as mean ± s.d. Standard deviations are split for clarity. *$P<0.001$ between groups (independent *t*-test).

ficantly different at +60 min (P=0.017, ES=0.657). Thus, SALT significantly raised MAP compared with WATER at the end of ING, irrespective of salt sensitivity (Table 1). As shown in Figure 1a, SS subjects experienced a much larger increase in MAP than SR subjects following ING ($P<0.001$). As this is how we classified the two groups, it follows that MAP was different at this time point.

Analysis for the dependent variable Tre via repeated measures ANOVA revealed a main effect for treatment ($F(1,14)=18.931$, P=0.001, η_p^2=0.575). Significant interaction effects were found for time by sensitivity ($F(2,28)=12.296$, P=0.001, η_p^2=0.468), treatment by time ($F(2,128)=7.252$, P=0.003, η_p^2=0.341) and a three-way interaction between treatment, time and sensitivity ($F(2,28)=3.687$, P=0.038, η_p^2=0.208). Thus, over the course of the trial, sensitivity and treatment both affected Tre independent of each other. To explain the three-way interaction, subsequent Bonferroni-corrected *post hoc* analysis revealed that at +120 min (P=0.009, ES=0.725) and +180 min (P=0.003, ES=0.820) the percentage change reduction in Tre was significantly greater following SALT compared with WATER, when looking at all 22 subjects together. Further, as shown in Figure 1b, at +180 min, the percentage change reduction in Tre was greater in the SR group compared with the SS group (P=0.043).

Repeated measures ANOVA revealed a main effect for salt sensitivity ($F(1,14)=6.749$, P=0.021, η_p^2=0.325), as well as a significant treatment by sensitivity interaction effect for the dependent variable CI ($F(1,14)=5.892$, P=0.029, η_p^2=0.296). Thus, when all values were pooled across time, CI was significantly higher following SALT. Further, as shown in Figure 1c, SS individuals had larger increases in CI at +60 min (P=0.001).

Urine output was significantly higher following WATER compared with SALT ($P<0.001$); however, there were no between-group differences (Table 2).

DISCUSSION

This study found that SALT ingestion lowers Tre more than WATER ingestion. In addition, Tre decreases more in SR individuals than in SS

individuals following SALT. The explanation for these findings may be that maintenance of core body temperature is vital enough that it influences hemodynamics following an acute stressor. The explanation for the SS *vs.* SR results may be that SR individuals maintain BP equilibrium more effectively than SS individuals following salt and water intake, but tolerate a greater alteration of temperature homeostasis in the process. Conversely, it may be the case that SS individuals maintain core temperature equilibrium more effectively than SR individuals, but tolerate a greater alteration in BP homeostasis in the process. Perhaps differences in tolerance to a reduction in core body temperature following salt and water intake determine whether individuals are SR or SS.

Our data are consistent with the premise that vasodilatation occurred among the subjects in this study following SALT, and the vasodilatation likely involved the cutaneous circulation. With regard to sympathetic control of the circulation, it is apparent that cutaneous and visceral blood flow are operated independent of each other.[19] The cutaneous circulation serves a vital role in thermoregulation whereas visceral blood flow is acutely regulated via the baroreflex to sustain basal BP. Several integrative physiology studies have shown that some vascular beds vasoconstrict and some vasodilate in responses to different stressors.[20–22] Following salt loading, if vasodilatation in visceral vasculature is sufficient to maintain BP homeostasis, cutaneous vasodilatation should be unnecessary and any decrease in Tre would be minimal. However, our results suggest that vasodilation did occur in the cutaneous vasculature. Although not directly measured in the current study, it is possible that renal and skin blood flow were different between SS and SR individuals. The capacity for vasodilation in either the visceral and/or cutaneous vasculature may help explain salt sensitivity.

Much of what is understood about the hemodynamic consequences of salt and water loading is based upon experiments with subjects that are SS or have abnormal kidney function.[1–4,23] With few exceptions, when salt and water loading occur in normal humans, or humans who are SR, BP does not rise.[6–8] Unfortunately, there is currently no explanation as to why some individuals are SS and others are SR. This situation has hampered understanding the etiology of essential hypertension.

Our study offers an explanation as to why some individuals are SS and others are SR. If our results are generalizable to different age groups, women and non-Caucasians, it would be possible to account for the role of sodium chloride in the development of SS hypertension: salt and water loading raises BP in SS individuals, and the elevated BP persists for a finite period of time during and after the salt and water intake. These transient BP elevations, whether brief or prolonged, might initiate the complex changes within the walls of the arteries and arterioles, termed vascular remodeling, that characterize individuals with essential hypertension.[10] As a result of vascular remodeling, the lumens of the arteries and arterioles decrease in caliber as the walls of these blood vessels irreversibly thicken. The physiological manifestation of vascular remodeling is increased peripheral resistance and elevated baseline BP.

If our study results are generalizable, it is conceivable that there is no congenital, physical abnormality, renal or otherwise, that characterizes individuals who are SS. Rather, as a consequence of an intolerance to a reduction in core temperature that manifests as temporary elevations in BP after ingesting sodium chloride, perhaps vasculopathy in the kidneys develops gradually in individuals who are SS, as a direct result of innumerable transient elevations in BP that subtly and cumulatively cause vascular remodeling. If so, then salt sensitivity is a functional condition with pathological consequences, whereas the vasculopathy that characterizes essential hypertension is an acquired condition. The results of our study suggest a theoretical model for understanding the etiology of SS hypertension which is capable of explaining the multitude of phenomena associated with essential hypertension and salt sensitivity that have been identified by hypertension and kidney researchers over a period of decades.

In healthy young men, isotonic saline has been shown to elicit an acute increase in CI as assessed by echocardiography.[6] Similarly, MAP and CI both increased following a 60-min infusion of 3% saline in a mixed gender sample.[16] The results of the current investigation are in general agreement with both these studies, although methodological issues must be considered. The percentage change from BASE of MAP and CI tends to support the animal literature as well.[1–3]

In this preliminary study, we sought to control for any factors that might affect hemodynamics and/or thermoregulation. All trials occurred in the morning and subjects reported after an overnight fast. These precautions minimized variability of Tre at BASE by controlling for the circadian rhythm and the thermic effect of food. We expected that sitting in 25 °C for 4 h would lower Tre, irrespective of treatment, because the basal metabolic rate would be at a minimum. To ensure that the temperature of water itself did not affect Tre, we heated it to 37 °C. Although 37 °C saline has been used in some cardiovascular protocols,[15,24] two salt loading protocols administered water that was 20–22 °C.[25,26] Water drinking has been shown to induce thermogenesis.[27,28] In this protocol, thermogenesis was likely the same between treatments because the volume and temperature of the water was the same. It has previously been shown that gastric emptying is complete in less than 1 h,[29] so the effects of gastric distension on hemodynamics[30] were likely minimal by the end of the trial.

A long REC is also a strength of the current investigation. Guyton[1] and others[23,31–33] have presented the hemodynamic responses to SALT loading, which involves a time delay as the kidneys filter the excess sodium from the blood.[34] It follows that the effects of SALT *vs.* WATER on Tre were more pronounced during REC, compared with ING, because salt promotes acute vasodilatation[33] that facilitates heat loss through the complex cutaneous circulation over time.[9] Ingestion of water alone resulted in greater urine output (that is, less fluid retention and less vasodilatation during the experiment), which is likely due to the acute inhibition of antidiuretic hormone (ADH), whereas the combined salt and water load was excreted less quickly (that is, greater fluid retention and greater vasodilatation during the experiment).

More than 90% of all renal oxygen consumption is a result of the active transport of sodium via Na+, K+-ATPase.[35,36] By definition, this process produces heat. A recent study showed that a 1-week low salt diet in normotensive men reduced medullary oxygen consumption.[37] Although not directly measured, it is likely that a high-salt load would cause increased oxygen consumption by the kidneys, thereby increasing heat production. Whether this process might increase urine temperature is yet to be determined. Nevertheless, in the current investigation, Tre and urine output both decreased with SALT, suggesting that urine temperature has only a minor role in this process.

A few limitations must be acknowledged in the present investigation. First, our sample contained young and healthy Caucasian men. Accordingly, generalization to other ages, women, different ethnicities or individuals with medical illnesses, must be made with caution. Second, plasma blood samples were not obtained so the role of hormones, ions or endothelial factors under these conditions is yet to be determined. Third, the oral route of salt and water administration, as opposed to intravenous saline[7] may be criticized. As this protocol was conducted in a non-hospital setting, the Institutional Review Board would not approve intravenous saline loading. On the

other hand, oral ingestion is what occurs in the real, non-experimental world. Compared with intravenous saline administration, oral ingestion of salt and water is more physiological.

Another potential limitation is that we used a non-conventional method for distinguishing salt sensitivity from salt resistance, and we did not attempt to validate our method by comparing the results of our methodology with other more established methods of distinguishing salt sensitivity from salt resistance. As reviewed by Weinberger,[18] the criteria for determining salt sensitivity are inconsistent. In the literature, different quantities of salt, different lengths of loading time (acute *vs.* dietary) and the threshold change in BP for distinguishing salt sensitivity are not uniform. From a pragmatic perspective, our method has the advantage of being shorter in duration than other methods, and our method does not require that investigators control the quantity of dietary salt for days at a time. Future studies could clarify the interaction between thermoregulation and cardiovascular function following an acute sodium load.

CONCLUSION

We found that salt and water intake lowered Tre more than water by itself in healthy and young Caucasian men. We also found that SR individuals tolerate a greater reduction in Tre than SS individuals following salt and water loading. Our findings are consistent with the hypothesis that salt intake causes conflict for the cardiovascular system in terms of simultaneously maintaining BP and temperature homeostasis. An understanding of the etiology of essential hypertension has proven elusive, in part because it has not been possible to explain what distinguishes SS from SR individuals. If our results are generalizable, it would be possible to account for the role of sodium chloride in the development of SS hypertension. Thus, the results of our study suggest a theoretical model for understanding the etiology of essential hypertension.

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