An Appraisal of Methods Recently Recommended for Testing Salt Sensitivity of Blood Pressure

Theodore W. Kurtz, MD; Stephen E. DiCarlo, PhD; Michal Pravenec, PhD; R. Curtis Morris, Jr, MD

According to a recent Scientific Statement of the American Heart Association (AHA), salt sensitivity of blood pressure (BP) is a trait in which BP "changes parallel to changes in salt intake."[1] It is said that salt sensitivity is "a risk factor for cardiovascular mortality and morbidity, independent of and as powerful as BP."[1] Although the criteria for identifying salt sensitivity are not standardized, it has been estimated that 30% to 50% of hypertensive humans are salt sensitive and ≈25% of normotensive humans are salt sensitive.[2,3] According to the AHA Scientific Statement, salt sensitivity of BP has become "an issue of clinical importance because the phenotype carries prognostic implications potentially as strong as those of traditional cardiovascular risk factors."[1] Various methods of testing for salt sensitivity have been applied in research settings; however, tests for salt sensitivity that are useful in routine clinical practice have yet to be identified.

Advances in understanding of the mechanisms and clinical significance of salt sensitivity have long been hampered by the lack of standardization in the methods used for assessing salt sensitivity.[4] In this analysis, we discuss the main research methods of testing for salt sensitivity and present current views on how best to assess this complex phenotype, including many views that were not addressed by the recent AHA Scientific Statement. To broaden the scientific consideration, we also present alternative perspectives on the

contention that salt sensitivity is a risk factor for cardiovascular mortality "independent of and as powerful as BP."[1]

Is There a Scientifically Superior Method of Testing for Salt Sensitivity? Consideration of the AHA View

The AHA provides some brief recommendations[1] on how to assess salt sensitivity with 2 different types of short-term protocols: (1) "outpatient dietary protocols" requiring a total time of ≈2 weeks to directly measure BP responses to changes in dietary intake of salt and (2) an "inpatient acute protocol," which might be viewed as an indirect test of salt sensitivity, requiring a total time of only ≈3 days to measure BP responses to furosemide and simultaneous dietary salt restriction in subjects who have been intravenously and orally administered salt beforehand.[5,6]

In published studies with either outpatient dietary protocols or the furosemide-based inpatient acute protocol, a subject is classified as salt sensitive if the protocol causes mean arterial pressure (MAP) to change by more than an arbitrary cutoff chosen by the investigators. The AHA Scientific Statement provides data that "exemplifies the need to choose arbitrary cutoffs for the magnitude of BP change used to classify subjects as salt sensitive."[1] Unfortunately, as noted by de Leeuw and Kroon, "the magnitude of the response above which pressure is considered to be salt-sensitive varies enormously among studies."[7] Although the limitations of using arbitrary and wide-ranging cutoffs for assessing continuous traits like salt sensitivity are well known,[4,7] investigators rely on such cutoffs when discussing the biological and demographic characteristics of salt-sensitive subjects.[1] The AHA Scientific Statement does not include recommendations on specific cutoffs and on which particular protocol provides the best current approach for identifying hypertensive or normotensive subjects with salt sensitivity.

According to the AHA Scientific Statement, "there is no evidence base to determine best research practices in terms of measurement of salt sensitivity of BP in humans."[1] Thus, the AHA does not provide guidance on whether a particular testing protocol for salt sensitivity is scientifically preferred and does not really distinguish between the recommended

From the Departments of Laboratory Medicine (T.W.K.) and Medicine (R.C.M.), University of California, San Francisco, San Francisco, CA; Department of Physiology, Wayne State University, Detroit, MI (S.E.D.); Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic (M.P.).

An accompanying Table S1 is available at http://jaha.ahajournals.org/content/6/4/e005653/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Theodore W. Kurtz, MD, Department of Laboratory Medicine, University of California, San Francisco, 185 Berry St, Suite 290, San Francisco, CA 94107. E-mail: ted.kurtz@ucsf.edu

outpatient dietary protocols and the furosemide-based inpatient acute protocol with respect to their accuracy and reproducibility in assessing BP salt sensitivity. Hence, the Scientific Statement does not propose or indicate that 1 of the methods discussed in the AHA recommendations, or any other method, be considered as the current reference method for assessing salt sensitivity.

Is There a Scientifically Superior Method of Testing for Salt Sensitivity? Consideration of an Alternative View

Per the view of many investigators, the evidence base demonstrates that a carefully performed dietary protocol is scientifically superior to other protocols, including the furosemide-based, inpatient acute protocol, for assessing salt sensitivity of BP. Specifically, the position of many investigators is that a carefully controlled dietary protocol (without any diuretic treatment) which includes a 1-week period of low salt intake, and a 1-week period of high salt intake, is the "gold-standard method" for assessing salt sensitivity.[8–12] Other investigators may not use the term gold-standard method, but they note that "the most reliable method to measure salt sensitivity is the blood pressure response to a change in dietary salt intake"[13] and refer to such dietary testing as "the standard reference procedure."[14] Here, we use the term "reference method" or "preferred method" rather than the term gold-standard method.

Table lists the main features of the dietary protocol that many investigators refer to as the preferred approach for assessing salt sensitivity. Considering the views and study results of a variety of investigators discussed below, we recommend that the current reference method of testing for salt sensitivity be based on a dietary protocol with these features. The dietary protocol can be performed on an inpatient or outpatient basis. We believe that a carefully performed inpatient dietary protocol (not furosemide-based) is likely to deliver highly reproducible results comparable to a carefully performed outpatient dietary protocol. However, we focus more on the outpatient-type dietary protocol because of its greater evidence base with respect to studies of reproducibility and prediction of cardiovascular risk.

Some of the features of the dietary test protocol described in Table, including the specified levels of salt intake, were mentioned in the AHA recommendations for outpatient dietary protocols.[1] However, in contrast to the AHA recommendations, the recommendations in Table: (1) designate a candidate reference method; (2) specify the BP cutoffs for use in identifying salt sensitivity; and (3) do not require that the period of high salt intake precede the period of low salt intake in the test protocol. We next discuss these issues in further detail and provide information demonstrating superior

Table. Candidate Reference Method of Testing for Salt Sensitivity

Dietary protocol with the following features:
1-week period of low salt intake of no more than 50 mmol NaCl/day
1-week period of high salt intake of ≈250 mmol NaCl/day*
Order of administration of different salt diets may vary per study objective
Prescription and monitoring of well-characterized diets throughout entire study†
Multiple measurements of 24-hour urine Na^+ excretion to confirm NaCl intake
BP measurements based on a highly reproducible salt sensitivity test protocol‡
Cutoff to classify normotensives as salt sensitive: MAP change ≥3 to 5 mm Hg§
Cutoff to classify hypertensives as salt sensitive: MAP change ≥8 to 10 mm Hg§

BP indicates blood pressure; MAP, mean arterial pressure.
*For double-blind, placebo-controlled testing of the BP effects of changes in salt intake, the high salt intake and the placebo can be administered in unmarked capsules.
†Because potassium,[15] nitrate,[16,17] and other dietary factors can affect BP, the contents of the diets should be carefully described for each study phase and contents should not be varied unless required as part of the study objective. Based on the diets that were used in studies of protocols with demonstrated high reproducibility for classifying subjects as salt sensitive,[18–20] a dietary potassium intake in the range of 60 to 80 mmol/day could be recommended.
‡Details of BP measurement techniques and the BP cutoffs used in test protocols reported to be highly reproducible can be found in the supplemental table (Table S1) and in publications by Sharma et al,[18] Overlack et al,[19] and Draaijer et al.[20]
§The specific cutoffs in these ranges should be prespecified. If the high salt intake amount happens to be somewhat lower than the target salt intake of 250 mmol/day, the cutoff may be based on the lower number in the recommended cut-off range. If the amount of salt administered is very close to, or somewhat above, the target salt intake of 250 mmol/day, the cutoff may be based on the higher number in the recommended cut-off range.

reproducibility of the preferred dietary protocol compared with other protocols for classifying subjects as salt sensitive. In addition, we discuss how the evidence base demonstrates that salt sensitivity diagnosed by the preferred dietary protocol, but not salt sensitivity diagnosed by the furosemide-based inpatient acute protocol, is an independent risk factor for time to a cardiovascular event.

Cutoffs for Classifying Subjects as Salt Sensitive in the Proposed Reference Method

When testing normotensive subjects with the proposed reference protocol and the physiological levels of salt intake described in Table, the cutoff for classifying someone with salt sensitivity is considered to be a change in MAP of at least 3 to 5 mm Hg in response to the change in salt intake[18,19,21]; when testing hypertensive subjects, the classification cutoff is generally considered to be a change in MAP of at least 8 to 10 mm Hg.[20,22,23] When ambulatory BP monitors have been

used in careful dietary studies of hypertensive subjects, the cutoff for diagnosis has been considered to be a change in the 24-hour measurement of MAP of ≈5 mm Hg.[11]
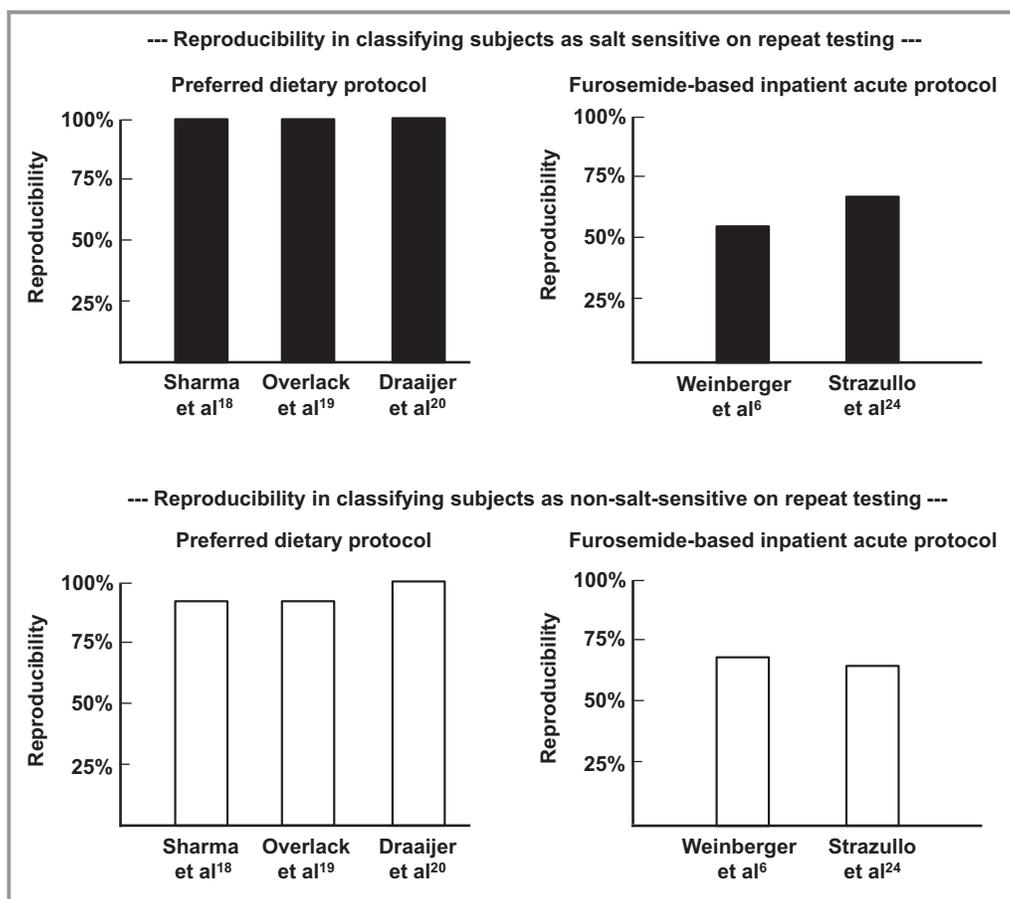
Reproducibility of Dietary Protocols to Test for Salt Sensitivity

When the preferred dietary protocol with the features described in Table is performed in either normotensive[18,19] or hypertensive subjects,[20] the reproducibility of the protocol for classifying subjects as salt sensitive or as non-salt-sensitive is very high (>90%; here we use the term reproducibility to mean test-retest repeatability; Figure). We believe that these studies are critical in that they provide strong evidence of excellent reproducibility of the preferred dietary protocol in classifying subjects for salt-sensitivity status. The reproducibility was high when the different salt diets were given in random order[19,20] and when the low-salt

diet was given before the high-salt diet.[18] This high level of reproducibility for identifying subjects with salt sensitivity has not been documented with any other test protocol.

It should be noted that dietary protocols appear to have poor reproducibility in classifying subjects for salt sensitivity when a standardized diet is not carefully prescribed throughout the entire study,[25,26] or when the amounts of salt administered in the low-salt phase and high-salt phase[27,28] do not approximate the amounts recommended in Table and in the AHA Scientific Statement.[1] Characteristics of dietary protocols showing excellent reproducibility in classifying subjects as salt sensitive, and those showing poor reproducibility, are shown in a detailed table in the supplement (Table S1).

According to the GenSalt investigators,[12] a testing method with features similar to the preferred dietary protocol showed evidence of reproducible results when subjects were given a repeat test even 4.5 years after the original test. However, the correlation coefficients of the BP changes between those

Figure. Reproducibility of different test protocols for classifying subjects as salt sensitive or non-salt-sensitive with repeat testing. Top panel, test-retest repeatability of different protocols for classifying subjects as salt sensitive (denoted by solid bars). Bottom panel, test-retest repeatability for classifying subjects as non-salt-sensitive (denoted by open bars). The features of the preferred dietary protocol are summarized in Table and detailed in the supplement (Table S1). The features of the furosemide-based inpatient acute protocol are described in references by Weinberger et al[5,6] and Strazullo et al.[24]

widely separated repeat tests were not high, and the investigators did not attempt to classify the subjects for salt sensitivity per specific cutoffs. It is possible that even if investigators use a test protocol with high reproducibility over a short period, an individual's BP response to a change in salt intake may vary over a period of years because of changes in age, environmental factors, or lifestyle or changes in the character of the disorder itself.

When Testing for Salt Sensitivity in Dietary Protocols, Should the Period of High Salt Intake Precede the Period of Low Salt Intake?

The recommendations of the AHA Scientific Statement suggest that in dietary protocols testing for salt sensitivity, the high-salt-intake period should precede the low-salt-intake period.[1] The AHA Scientific Statement suggests that dietary protocols start with a high-salt-intake period to uniformly suppress activity of the renin-angiotensin-aldosterone system (RAAS) and thereby minimize baseline variability in the hormonal system that regulates plasma sodium concentrations and arterial BP.[1] According to the AHA Statement, such suppression of RAAS activity by high salt intake "may confer more uniformity to the subsequent response to the low salt intake."[1] However, whereas baseline variability in activity of the RAAS may be decreased with high salt intake, variability in nitric oxide (NO) activity or sympathetic nerve activity may be increased (because salt-sensitive subjects can respond differently to a high salt intake than resistant subjects with respect to changes in activity of the NO system[29–31] and sympathetic nervous system[32,33]). The rationale for starting dietary protocols with a high–salt diet would seem to assume that when investigating biological responses to changes in salt intake, it is more important to suppress initial variability in the RAAS than it is to suppress initial variability in other systems that contribute to the regulation of BP.

We believe that investigators should make decisions about the sequential order of the low-salt-intake and high-salt-intake periods based on the study objectives. If the objective is to identify subjects who are salt sensitive, then randomized administration of the different salt diets is reasonable. When different salt diets have been administered in random order, the reproducibility of the preferred type of dietary protocol for classifying subjects as salt sensitive has been shown to be very high.[19,20] If the objective is to study the mechanisms whereby salt loading increases BP, then the period of low salt intake could precede the period of high salt intake, provided that a proper time control is included. To study the mechanisms whereby salt restriction lowers BP, then the period of high salt intake could precede the period of low salt intake. We caution against drawing conclusions about

disturbances that mediate salt-induced increases in BP, from studies of the BP-lowering effects of salt depletion.

Use of Short-Term Dietary Protocols to Estimate the Prevalence of Salt Sensitivity

Some investigators believe that short-term dietary protocols that test for salt sensitivity "may underestimate the phenomenon" because "they miss slow salt-sensitive responders" that would be detected in dietary protocols of longer duration.[34] For example, Hamlyn and Blaustein contend that "to properly capture the true BP response" in dietary intervention trials, each period of low salt intake and high salt intake should be of 3 months in duration.[34] However, this view appears to be at odds with the study results summarized by Aburto et al, suggesting that the reductions in BP that occur with reduced sodium intake in trials of less than 3 months in duration may actually be greater than those that occur in trials of more than 3 months in duration.[35] Moreover, even if short-term dietary protocols (<3 months) reveal fewer cases of BP salt sensitivity than long-term dietary protocols (>3 months), this does not address the utility of a diagnosis of BP salt sensitivity made with the short-term dietary protocol for: (1) predicting increased risk for adverse cardiovascular events or (2) investigating the mechanisms whereby increases in salt intake induce increases in BP.

Use of Unphysiological Amounts of Salt in Protocols to Test for Salt Sensitivity

Some investigators have studied or modeled the effects of extreme changes in salt intake on BP (>1000 mmol/day).[36,37] Extreme, unphysiological increases in salt intake appear to cause substantial increases in BP in nearly all normal individuals.[36] We recommend against the use of extreme, unphysiological changes in salt intake for assessing salt sensitivity because of the unclear relevance of such conditions to salt-induced changes in BP in real life. The levels of salt intake described in the proposed reference method in Table, and in the methodological recommendations of the AHA, are within the amounts consumed by humans in nonexperimental circumstances.[1]

Surrogate Methods of Testing for Salt Sensitivity as Alternatives to the Preferred Dietary Protocol

Although the proposed reference protocol provides a highly reproducible, direct method of testing for BP salt sensitivity, it also requires considerable time and resources to perform and

its use is generally limited to specialized research settings. Accordingly, there is major interest in identifying quick and relatively inexpensive surrogate (indirect) methods of testing for salt sensitivity.[13] A simple and reliable surrogate test would facilitate research on the mechanisms and consequences of salt sensitivity and could also be evaluated for use in routine clinical practice. To assess the performance of surrogate tests for identifying salt sensitivity, it is necessary to compare them against a reference method, or against a surrogate method that has been vetted by comparisons with the reference method, imperfect as it may be. Various investigators have developed surrogate tests of salt sensitivity. However, as discussed in the AHA Scientific Statement, most surrogate tests have considerable limitations or have not been extensively studied and require further validation.[1] Of the tests discussed, the furosemide-based "inpatient acute protocol"[5,6] is the most extensively studied surrogate method of assessing salt sensitivity. Although the furosemide-based inpatient acute protocol is too complicated for use in routine clinical practice, it has often been used in clinical research settings.

Is the Furosemide-Based "Inpatient Acute Protocol" Useful for Measurement of BP Salt Sensitivity?

The AHA Scientific Statement[1] provides specific recommendations on how to perform the furosemide-based "inpatient acute protocol" for assessing BP salt sensitivity, but does not provide recommendations for performing other surrogate methods of testing for salt sensitivity. This may suggest that the furosemide-based inpatient acute protocol, performed per the AHA recommendations, is a useful method for identifying subjects with salt sensitivity. To assist in understanding potential pitfalls of the furosemide-based inpatient acute protocol for identifying salt-sensitive subjects, we next discuss concerns about the accuracy and reproducibility of this method. We also discuss questions regarding the utility of this protocol for investigating mechanisms of salt sensitivity and for predicting cardiovascular outcomes.

The well-known inpatient acute protocol, derived from the work of Weinberger et al,[5,6] does not directly measure BP responsiveness to changes only in salt intake. Rather, it measures responsiveness to the BP-lowering effects of furosemide and simultaneous dietary salt restriction in subjects who have been intravenously and orally administered salt beforehand.[5,6] In this inpatient acute protocol, which could also be referred to as a furosemide-sensitivity test, individuals are classified as "salt sensitive" if their MAP decreases by 10 mm Hg or more in response to the combination of furosemide and dietary salt restriction.[5,6]

How Reproducible is the Furosemide-Based Inpatient Acute Protocol for Classifying Individuals as Salt Sensitive?

In referring to studies of the furosemide-based inpatient acute protocol by Weinberger and Fineberg,[6] the AHA Scientific Statement notes that the correlation between the changes in MAP occurring with repeat tests was 0.56, and that 4 of 28 subjects changed their status from salt sensitive to salt resistant or vice versa, suggesting "modest reproducibility" of the protocol.[1] However, this information does not provide a complete picture of the very limited reproducibility of the protocol with respect to classifying subjects as salt sensitive. In the study cited, it appears that only ≈55% of the subjects deemed to be salt sensitive in the first test were classified as salt sensitive on the repeat test (on the repeat test, ≈45% of the salt-sensitive subjects appear to have become classified as either "indeterminate" or "salt resistant").[6] This constitutes poor reproducibility of the inpatient acute protocol for classifying subjects as salt sensitive based on the 10-mm-Hg cutoff used by Weinberger et al.

Investigators using a classification scheme for salt sensitivity different from the one used by Weinberger et al have also reported results showing limited reproducibility of the furosemide-based inpatient acute protocol.[24] As shown in Figure, the reproducibility of a diagnosis of salt sensitivity made with the furosemide-based inpatient acute protocol, using the cutoffs of either Weinberger and Fineberg[6] or of other investigators,[24] appears substantially lower than the reproducibility of a diagnosis made with the preferred type of dietary protocol.[18–20]

How Accurate Is the Furosemide-Based Inpatient Acute Protocol for Classifying Subjects as Salt Sensitive?

Because the furosemide-based inpatient acute protocol has poor reproducibility in classifying subjects as salt sensitive, and does not measure the effects of only changes in salt intake on BP, we next address the question: How accurate is the furosemide-based inpatient acute protocol for determining whether an individual has BP salt sensitivity?

Multiple studies are available in which individuals tested with the furosemide-based inpatient acute protocol were also tested with a carefully performed, direct dietary protocol for salt sensitivity,[8,9,11,24,38] that is, the type of protocol that many investigators consider to be the preferred test for assessing salt sensitivity (Table).[8–12] The AHA Scientific Statement refers to several of these studies and notes that comparisons between results obtained using acute protocols and "slower dietary sodium intake" protocols "were

consistently significant."[1] However, the general comment that the comparisons between the 2 protocols "were consistently significant" does not address the accuracy of the furosemide-based inpatient acute protocol for identifying subjects with BP salt sensitivity as judged by the preferred dietary protocol.

Considering all of the comparative studies together,[8,9,11,24,38] the furosemide-based inpatient acute protocol appears to have an accuracy of only ≈65% to 75% for assessing salt sensitivity (where accuracy is defined as the number of true positives and true negatives divided by the total number of individuals tested). Thus, the furosemide-based inpatient acute protocol is characterized by limited accuracy and poor reproducibility with respect to determining whether a subject is, in fact, salt sensitive.

In the inpatient acute protocol,[5,6] it should be kept in mind that the effects of changes in oral salt intake on mechanisms regulating BP are susceptible to potential confounding by effects of furosemide and intravenous salt loading. For example, furosemide itself not only has effects on Na^+, K^+, $2Cl^-$ cotransporters in the renal tubule, but it also has effects on Na^+, K^+, $2Cl^-$ cotransporters in the vasculature.[39,40] In addition, administration of salt by the intravenous route may have different biological effects than administration of salt by the more physiological oral route.

Is Salt Sensitivity Diagnosed by the Furosemide-Based Inpatient Acute Protocol or by the Preferred Dietary Protocol an Independent Risk Factor for Cardiovascular Morbidity or Mortality?

Studies by Morimoto et al provide evidence that in hypertensive subjects, a diagnosis of salt sensitivity made with the preferred dietary protocol is an independent risk factor for time to a major cardiovascular event.[41] According to the AHA Scientific Statement, "more definitive proof of an independent role for salt sensitivity of BP as a cardiovascular risk factor was provided by Weinberger and colleagues"[42] who used the furosemide-based inpatient acute protocol for diagnosis of salt sensitivity. However, the retrospective cohort study of Weinberger et al[42] examined mortality risk (not cardiovascular risk) was exploratory in nature and yielded inconsistent results across different mortality analyses. In that study, in which the furosemide-based, inpatient acute protocol was used as the surrogate test for salt sensitivity, logistic regression analysis indicated that such "salt sensitivity" might be a risk factor for death.[42] However, because of the known limitations of logistic regression analysis, the investigators also performed a Cox proportional hazards analysis. In the Cox analysis, salt sensitivity assessed by the furosemide-based inpatient acute protocol was not an independent predictor of time to death.[42]

The AHA Statement notes that "the novel observation" in the study of Weinberger et al was that "the survival curves of salt resistant hypertensive subjects and salt sensitive normotensive subjects were not significantly different."[1] However, no information was provided in the study of Weinberger et al[42] on the power of the statistical analysis for detecting differences in survival curves between those 2 patient subgroups. Because the effects on mortality of salt sensitivity, as judged by the furosemide-based inpatient acute protocol, were inconsistent across the different analyses by Weinberger et al,[42] and because of the exploratory nature of retrospective cohort studies, the results of the Weinberger mortality studies with the inpatient acute protocol are not definitive.

We are unaware of any study demonstrating that a diagnosis of salt sensitivity with the furosemide-based inpatient acute protocol is an independent risk factor for time to cardiovascular death or to a cardiovascular event. The evidence to date indicates that salt sensitivity judged by a careful dietary protocol, but not salt sensitivity judged by the furosemide-based inpatient acute protocol, may well be an independent risk factor for time to a cardiovascular event. It remains to be established whether salt sensitivity judged by any type of protocol is an independent risk factor for time to death from cardiovascular causes (or from other causes).

The Impact of Protocol Selection on Understanding Mechanisms of Salt Sensitivity

The mechanisms of salt sensitivity are the subject of ongoing controversy and discussion.[1,29,43–52] Whereas a considerable degree of controversy stems from differing views on the interpretation of specific studies or theories, it can also be related to differences between the methods used to identify subjects with salt sensitivity. For example, studies with the furosemide-based protocol indicate that during the salt restriction phase, salt-sensitive hypertensive subjects undergo similar or greater increases in plasma catecholamines than do salt-resistant hypertensive subjects.[5,53–55] However, studies with the preferred type of dietary protocol indicate that during the salt restriction phase, salt-sensitive hypertensive subjects undergo smaller increases in plasma and urinary catecholamines than do salt-resistant hypertensive subjects.[32,33]

The method of testing for salt sensitivity may also influence understanding of the demographics of salt sensitivity. For example, studies with the furosemide-based protocol in normotensive subjects[5] indicated that "the frequency of salt sensitivity among blacks was similar to that seen among

whites."[2] However, studies with the preferred type of dietary protocol have indicated that salt sensitivity is more common in normotensive blacks than in normotensive whites.[56] This raises the question: In studies with a furosemide-based protocol, how should one interpret mechanistic and demographic findings pertaining to salt sensitivity if the observations have not been checked and confirmed in salt sensitivity studies with the preferred dietary protocol? Given the need for confirmatory testing, it is unclear how studies with the furosemide-based inpatient acute protocol advance understanding of the mechanisms and demographics of salt sensitivity beyond the knowledge gained from studies with the preferred dietary protocol.

Conclusions

According to the recent scientific statement from the AHA, salt sensitivity of BP is a common disorder that "carries prognostic implications potentially as strong as those of traditional cardiovascular risk factors."[1] Advances in understanding the mechanisms and consequences of salt sensitivity remain hampered by a lack of standardization of the protocols and criteria used to identify individuals with this disorder. Among the various methods of testing for salt sensitivity, the carefully controlled dietary protocol described herein provides the highest test-retest repeatability for identifying salt-sensitive subjects. Many investigators, ourselves included, consider such a dietary protocol to be the current reference method of testing for salt sensitivity. The reference dietary protocol requires considerable time and resources and is intended for use in research settings. Tests for salt sensitivity that are useful in routine clinical practice have yet to be identified. The most widely used surrogate test for salt sensitivity is a furosemide-based, inpatient acute protocol that includes potentially confounding features and demonstrates inferior test-retest repeatability and questionable accuracy for identifying subjects with salt sensitivity. Other surrogate tests for salt sensitivity have been described, but have undergone only limited tests of validation. Salt sensitivity, as judged by the preferred dietary test protocol, but not by the furosemide-based protocol or any other kind of protocol, has been demonstrated to be an independent risk factor for time to a cardiovascular event. It remains to be determined whether salt sensitivity judged by any type of testing protocol is an independent risk factor for time to death from cardiovascular causes or from other causes. Finally, even if a robust test for salt sensitivity is developed that can be easily performed and readily introduced into clinical practice, prospective studies will be required to determine whether the routine use of such a test would have beneficial effects on clinical outcomes.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Features of Dietary Protocols That Have Been Tested for Reproducibility in Classifying Subjects as SS or SR

Subject class	HTN	n	Low NaCl phase Dose/d, duration, MAP(mmHg)	High NaCl phase Dose/d, duration, MAP (mmHg)	Delta MAP mmHg	Diet control	Reproducibility in repeat tests
SS[1]	N	7	20 mmol/d, 7 days, 77.6 ± 2.8	220 mmol/d, 7 d, 83.2 ± 2.3	5.6[a]	Y[b]	100%
SR[1]	N	8	20 mmol/d, 7 days, 79.1 ± 2.6	220 mmol/d, 7 d, 79.0 ± 2.3	- 0.1	Y[b]	87.5%
SS[2]	N	30	20 mmol/d, 7 days, 83.1 ± 1.2	320 mmol/d, 7 days, 91.2 ± 1.3	8.1[c]	Y[d]	100%[e]
SR[2]	N	108	20 mmol/d, 7 days, 85.1 ± 0.6	320 mmol/d, 7 days, 84.6 ± 0.6	- 0.5	Y[d]	90%[e]
SS[3]	Y	4	20 mmol/d, 7 days, 105 ± 3.5	220 mmol/d, 7 days, 116 ± 4	11[f]	Y[g]	100%
SR[3]	Y	6	20 mmol/d, 7 days, 112 ± 5.3	220 mmol/d, 7 days, 108 ± 4.5	- 4	Y[g]	100%
SS[4]	Y	8	50 mmol/d, **6 days**, 105 ± 5.0	250 mmol/d, **6 days**, 122 ± 5.7	17[h]	**N**[i]	37.5% [j]
SR[4]	Y	22	50 mmol/d, **6 days**, 107 ± 2.6	250 mmol/d, **6 days**, 108 ± 2.6	1	**N**[i]	68%[j]
SS[5]	N	17 [k]	**56-82 mmol/d, 4 days** [l]	**312-380 mmol/d,** 7 days [l]	Not shown[m]	**N**[n]	66% overall [o]
SR[5]	N	13 [k]	**66-70 mmol/d**, **4 days** [l]	**488-500 mmol/d,** 7 days [l]	Not shown[m]	**N**[n]	for SS + SR
SS[6]	N	15 [p]	**62 mmol/d, 30 days** [q]	**140 mmol, 30 days** [q]	**Not shown**[r]	Y[s]	53% overall [t]
SR[6]	N	25 [p]	**62 mmol/d, 30 days** [q]	**140 mmol, 30 days** [q]	**Not shown**[r]	Y[s]	for SS + SR
SS[6]	Y	22 [u]	**62 mmol/d, 30 days** [q]	**140 mmol/d, 30 days** [q]	**Not shown**[r]	Y[s]	61% overall [v]
SR[6]	Y	11 [u]	**62 mmol/d, 30 days** [q]	**140 mmol/d, 30 days** [q]	**Not shown**[r]	Y[s]	for SS + SR
SS[7]	Y	4	40 mmol/d, 7 days	**170 mmol/d,** 7 days	Not shown[w]	Y[x]	25%[y]
SR[7]	Y	10	40 mmol/d, 7 days	**170 mmol/d,** 7 days	Not shown[w]	Y[x]	90%[y]

n indicates the sample size of subjects classified on the first test as SS or SR except in those studies[5,6] where the sample size indicates number of subjects consistently classified as SS or SR in both rounds of testing. HTN indicates whether the subjects studied had hypertension with Y indicating yes and N indicating no. MAP values indicate the absolute MAP levels in the first round of testing in each group (mean values ± S.E.M.). Delta MAP indicates the average magnitude of the salt-induced change in MAP in each group. Diet control indicates whether a standardized diet was carefully prescribed throughout the entire study. Reproducibility indicates the percentage of subjects that were classified the same way (SS or SR) in the repeat test as in the first test. **Results in bold:** Aspects of the protocols that differ substantially from those of the proposed reference dietary protocol, and the dietary protocol recommended by the AHA. SR indicates salt resistant; SS indicates salt sensitive.

Footnotes:

a. Blood pressure determined with an automated device from the average of 30 measurements obtained over a 1 hour period in supine subjects. Cutoff for
   classifying subjects as SS set as a change in MAP of ≥ 3 mmHg.

b. Standardized diet provided 60 mmol of potassium per day. See published study for additional diet details.

c. Blood pressure determined with an automated device from the average of 12 measurements obtained over a 1 hour period in sitting subjects. Cutoff for
   classifying subjects as SS set as a change in MAP of ≥ 5 mmHg.

d. Controlled diet provided 75 mmol of potassium per day. See published study for additional diet details.

e. Reproducibility of classifying subjects as salt sensitive or salt resistant on repeat testing was determined in a study that involved a subset of 31 subjects.

f. Blood pressure determined from the average of 6 measurements obtained over a 30 minute period in supine subjects. Cutoff for classifying subjects as SS set
   as a change in MAP of ≥ 8 mmHg.

g. Controlled diet provided 70 mmol of potassium per day. See published study for additional diet details.

h. Blood pressure determined with a 24 hour blood pressure monitoring device from the average of readings taken every 20 minutes during the day between 6 am
   and 9:59 pm, and every 30 min during the night. Cutoff for classifying subjects as SS set as a change in 24 hour average MAP of ≥ 10 mmHg.

i. Diet not controlled during the salt loading phase. Dietary instructions differed between salt restriction phase and salt loading phase. Potassium intake estimated
   to be approximately 90 mmol per day based on a single 24 hour urine collection study performed in each phase of the study.

j. Reproducibility of the testing protocol for classifying subjects as salt sensitive was determined from the results of 24 hour measurements of MAP. In an
   additional analysis, reproducibility was determined from the results of casual measurements of blood pressure. Based on the casual BP measurements,
   reproducibility of classifying the same subjects as SS on both tests was 23% and reproducibility of classifying the same subjects as SR on both tests was 76%.
   The casual blood pressure values were determined by averaging the results of 2 measurements taken 1 minute apart in sitting subjects.

k. In this study, the sample size represents the number of subjects consistently classified in both rounds of testing and does not represent the number of subjects
   that were in a particular category on initial testing. In addition to the 17 SS subjects and 13 SR subjects that were consistently classified, another 15 subjects
   gave inconsistent results on repeat testing. Of the subjects with inconsistent results on repeat testing, the numbers initially classified as SS versus SR were not
   reported.

l. Values for salt intake represent the ranges for mean salt intake estimated from measurements of 24 hour urine sodium excretion. Absolute values for MAP in SS
   and SR subgroups were not reported.

m. Blood pressure determined with a random-zero sphygmomanometer with measurements taken in sitting subjects at the end of each diet phase. Absolute values
   for salt-induced changes in MAP in the SS and SR subgroups were not reported. Cutoff for classifying subjects as SS set as a change in MAP of ≥ 5 mmHg.

n. Diet not controlled throughout entire study. Diet potassium content and urinary potassium excretion not reported.

o. Of the total number of subjects (45) entered into the study, 66% (30) were consistently classified in repeat tests. The
   number of subjects classified as SS on initial testing that failed to be classified as SS on repeat testing was not reported.

p. In this study, the sample size represents the number of subjects consistently classified in both rounds of testing and does not represent the number of subjects that were in a particular category on initial testing. In addition to the 15 SS subjects and 25 SR subjects that were consistently classified, another 35 subjects gave inconsistent results on repeat testing. Of the subjects with inconsistent results on repeat testing, the numbers initially classified as SS versus SR were not reported.

q. Values for salt intake represent the mean salt intake estimated from measurements of 24 hour urine sodium excretion. Target salt intake was approximately 50 mmol/day in the low salt phase and 150 mmol/day in the high salt phase. Absolute values for MAP in SS and SR subgroups were not reported.

r. Blood pressure determined with a random-zero sphygmomanometer in sitting subjects. The pressure measurements were not made on the last day of each diet phase as recommended in the preferred dietary protocol. Rather, blood pressure was determined from the mean of 5 pairs of measurements taken over the period between day 21 and day 30 of each dietary intervention period. Cutoff for classifying subjects as SS was set as a change in SBP greater than the median change in SBP of all subjects tested which was 6.4 mmHg. Absolute values for salt-induced changes in MAP in the SS and SR subgroups were not reported.

s. Controlled diet provided ~ 45 mmol potassium per day. See published study for additional diet details.

t. Of the total number of normotensive subjects (75) studied, 53% (40) were consistently classified in repeat tests. The number of subjects classified as SS on initial testing that failed to be classified as SS on repeat testing was not reported.

u. In this study, the sample size represents the number of subjects consistently classified in both rounds of testing and does not represent the number of subjects that were in a particular category on initial testing. In addition to the 22 SS subjects and 11 SR subjects that were consistently classified, another 21 subjects gave inconsistent results on repeat testing. Of the subjects with inconsistent results on repeat testing, the numbers initially classified as SS versus SR were not reported.

v. Of the total number of hypertensive subjects (54) studied, 61% (33) were consistently classified in repeat tests. The number of subjects classified as SS on initial testing that failed to be classified as SS on repeat testing was not reported

w. Blood pressure determined with a 24 hour blood pressure monitoring device from the average of readings taken at 15 minute intervals during the day between 7 am and 10:00 pm, and every 30 min during the night. Absolute values for salt-induced changes in MAP in the SS and SR subgroups were not reported. Cutoff for classifying subjects as SS set as a change in 24 hour average MAP of $\geq$ 10 mmHg.

x. Controlled diet provided 65 mmol of potassium per day. See published study for additional diet details.

y. Results reflect the analysis performed on 24 hour blood pressure recordings. When the analysis was performed on clinic blood pressure values determined from the average of 3 measurements obtained over 15 minutes in sitting subjects, the reproducibility of classifying subjects as SS in repeat testing was 50% and of classifying subjects as SR on repeat testing was 70%.

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An Appraisal of Methods Recently Recommended for Testing Salt Sensitivity of Blood Pressure
Theodore W. Kurtz, Stephen E. DiCarlo, Michal Pravenec and R. Curtis Morris, Jr

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