Methodology of Sodium Sensitivity Assessment

The Example of Age and Sex

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This article addresses the methodology of sodium sensitivity assessment. There have been reports to suggest that a high sodium intake is a cause of elevated blood pressure and trials to indicate that a reduction in sodium intake may reduce blood pressure that is already high; the implications of these findings are discussed. Many studies on sodium sensitivity suffer from what could be called the "normal probability fallacy": without appropriate control conditions, an intervention such as sodium restriction may incorrectly be assigned to a more pronounced response in a subgroup of the study population. As an example, findings are reviewed of age and sex as determinants of a response of blood pressure to variations in sodium intake. The limited data available suggest that subjects that are older and have higher blood pressure levels seem to benefit more from a reduction in sodium intake. In addition, elderly subjects at a high dietary sodium intake may have a higher risk of developing hypertension. Findings in both nonexperimental and experimental studies tend to support this view. Findings on sex differences are less consistent. A systematic approach to the assessment of factors and mechanisms responsible for sodium sensitivity in some subjects is needed to determine who might benefit most. Until more data are available, there is little basis to discriminate sodium-sensitive from sodium-resistant hypertensive subjects.

The hypothesis that dietary sodium intake is related to blood pressure is not new. Yet, even though many studies over the past decades have addressed this issue, controversy remains about the importance of salt in the etiology and treatment of primary hypertension. One reason is that although some studies were able to demonstrate, for example, an effect of sodium restriction on blood pressure, the response is highly variable, with some subjects showing a fall in blood pressure and others apparently having a rise. This heterogeneity in blood pressure response to variations in sodium intake was noted as early as the first trial on salt intake and blood pressure and has led some to suggest that among normotensive and hypertensive subjects there are specific subgroups that are sodium sensitive and others that are not. In accordance with this view, several characteristics have been proposed to discriminate sodium-sensitive from non-sodium-sensitive subjects. Moreover, a number of pathophysiological disturbances in sodium and volume homeostasis and other changes in circulatory regulatory systems have been named responsible for the presence of sodium sensitivity in certain people.

Before sodium sensitivity is considered, there should be reasonable certainty about the association between sodium and blood pressure in a more general sense. Sodium sensitivity is modification of the effect of sodium by a third factor, conditional on the presence of an association between sodium and blood pressure. The search for parameters of sodium sensitivity is a search for detail, for quantification of an association that is established in qualitative terms. Unfortunately, there remains considerable debate on the very nature of the association between salt and hypertension. Even so, circumstantial evidence suggests that salt intake and blood pressure are related, although the practical significance of the association may be limited. Next, the question is whether the weak associations that are, in general, observed between sodium intake and blood pressure are reflections of a strong effect of sodium on blood pressure in some subjects and the absence of an influence or even the reverse effect in others. This article will discuss some methodological aspects of studying sodium sensitivity and the way the evidence for such a phenomenon might be balanced. Only the case for primary hypertension is addressed. It has not been the aim of this paper to provide an in-depth...
analysis of all data pertaining to sodium sensitivity from studies in humans and animals. Reviews may be found in other sections of this issue. To illustrate the various approaches that contribute to knowledge on sodium sensitivity, findings on sodium sensitivity in relation to age and gender will be reviewed.

**Sodium and Blood Pressure: Direction of the Association**

Many of the questions pertinent to the sodium-blood pressure association in general are similar to questions on sodium sensitivity. Moreover, the answers to those questions are more complicated for sodium sensitivity, and data are often insufficient or absent. A major distinction can be made between studies on the effect of a high sodium intake on the incidence of high blood pressure versus studies on the effect of a reduction in sodium intake on blood pressure level. The latter studies predominantly address the question of whether a moderate reduction of dietary sodium intake will bring a high blood pressure back to normal or assist in the pharmacological control of hypertension. Although they are potentially two sides of the same circulatory disturbance, the two do not necessarily go in combination. It may well be that a reduction in sodium intake is effective in lowering elevated blood pressure, although sodium has no role in the etiology of hypertension. By the same token, dietary manipulations are effective in the treatment of non-insulin-dependent diabetes mellitus, but so far no clear dietary determinants of the occurrence of the disease have been found other than caloric intake.

In the treatment of hypertension, many drugs are available that reduce blood pressure without the direct interference of a causal mechanism. The consequence of this notion is that evidence in favor or against a role of sodium in the treatment of hypertension does not dismiss either the possibility that sodium induces high blood pressure or the possibility that sodium plays no role in the etiology of hypertension. In general, study design and the interpretation of findings relate to one of these two possibilities. The apparent lack of distinction distorts the literature and therefore leaves the discussion on the importance of sodium in blood pressure control ambiguous.

**Nonexperimental and Experimental Studies**

Studies on sodium and blood pressure in humans can be categorized into two broad categories: nonexperimental and experimental (e.g., intervention studies). In nonexperimental studies, subjects are compared with respect to outcome (e.g., blood pressure level) and naturally occurring differences in exposure (e.g., sodium). The evidence is regarded stronger if the findings result from a prospective evaluation of the incidence of high blood pressure in a population with varying degrees of sodium intake. Due to obvious difficulties in conducting those studies, however, most of the present nonexperimental data on the association between sodium and blood pressure stems from cross-sectional studies, typically between rather than within populations. Although suggestive, this evidence is, in general, not taken as conclusive. The gold standard in assessing a causal association between a determinant and a certain outcome is the experimental study. This is not to say that without the availability of data from experimental studies practical measures cannot be justified. It may, for example, be difficult to perform the ultimate experiment that gives definite certainty on an association, or it may be ethically unjustified to conduct such a study due to compelling nonexperimental findings. A good example is the causal relation between smoking and lung cancer, on which consensus has grown without support from experiments in humans. For sodium restriction, along with other interventions aimed at blood pressure reduction, there is a clear need for data from randomized trials. Randomized intervention studies are probably the only way to remove the confounding effect of many factors potentially associated with both blood pressure and sodium intake. For example, social stress and sodium appetite have been associated, and either factor may or may not affect blood pressure. Much of the controversy on the part played by a high sodium intake in blood pressure elevation rests on the likelihood that confounding factors may explain the characteristically weak associations between sodium and blood pressure reported from nonexperimental studies. In recent years, a series of experimental studies has been reported, though not all comprised a control group and a minority had been placebo-controlled. A blinded experiment is important in any study of treatment efficacy, but it is particularly so in blood pressure research, because blood pressure is sensitive to many other factors apart from the one studied.

**A Priori and A Posteriori Hypotheses and the Normal Probability Fallacy**

Findings from studies are an important, but not the sole, element in the search for factors that may discriminate sodium-sensitive from non-sodium-sensitive individuals (Figure 1). In addition, findings in studies should be weighted according to their biolog-
ical plausibility. Ideally, at the start of a study, a firm view of the pathophysiology underlying sodium sensitivity is present. This is, however, in general not true. Rather, the findings in a study point to certain homeostatic mechanisms involved in sodium and blood pressure regulation and associated with the blood pressure response to variations in sodium intake. When these mechanisms are observed, replication of the study with a more selective focus on the presumed factors is necessary. For nonexperimental studies, replication of the findings in other studies will strengthen the hypothesis. For experimental studies, the next step is the selection of a study group that either has or doesn’t have the characteristic linked to sodium sensitivity and submission of this group to a second randomized trial. If the factor is indeed responsible for a high or low response, this will be shown in the study.

Many factors have been put forward that may characterize sodium sensitivity. Age, sex, race, the renin-angiotensin-aldosterone system, kallikrein, circulating catecholamines and urinary dopamine, response to stress, salt taste, forearm vascular resistance, baroreflex sensitivity, intracellular electrolytes, cellular transmembrane ion fluxes, haptoglobin phenotypes, concomitant intake of chloride, potassium, and calcium, oral contraceptive use, and a positive family history of hypertension are among the most frequently named. The importance of some of these factors, such as the renin-angiotensin-aldosterone system, was noted in both nonexperimental and experimental studies and enforced by an increasing understanding of the pathophysiology involved. Others merely emerged from single experimental studies. In these studies, characteristics were compared between subjects showing a fall or a rise in blood pressure when sodium intake was changed. Because no study has reported a clear bimodality in blood pressure response to either increases or decreases in sodium intake, the categories of responders and nonresponders depend on arbitrary cutoff points in an otherwise Gaussian distribution of responses. There is an obvious hazard in this approach. When blood pressure is measured twice in a group of subjects, even without any intervention, some will show higher and others lower blood pressure levels at the second measurement. These differences are the expression of the large intraindividual variability in blood pressure level. Some of this variability may result from measurement error, and some of it may reflect individual differences in, for example, sympathetic nervous system activity or other physiological phenomena. In the situation of a change in sodium intake between the two measurements, some of the variability may result from this intervention and, as such, relate to sodium sensitivity. Yet it is difficult, if not impossible, to assess the contribution of these components to the resulting change in blood pressure in an individual. There is a risk that physiological significance is assigned to random variation: the "normal probability fallacy" (Figure 2). This is not a unique characteristic of studies on sodium sensitivity. Rather, it reflects the general difficulty in interpreting findings when groups are dichotomized into responders and nonresponders. A cure would be to repeat the intervention in a subgroup that is selected on the basis of a previous response to the same maneuver. Unfortunately, this stage has not yet been reached for many of the proposed indicators of sodium sensitivity. Until data are available from randomized double-blind trials in groups of subjects sharing the characteristic linked to sodium sensitivity, there is insufficient basis for adequate conclusions. Moreover, these data are essential for the next step in the assessment of sodium sensitivity, that is, the individual predictive value of a certain characteristic for a beneficial response to changes in sodium intake.

Age and Sex

Nonexperimental Studies

Age and sex are candidates as markers of sodium sensitivity. These two factors are considered because of the differences in response between elderly and younger subjects and between men and women after exposure or treatment in other diseases. As expected, the first indications that sodium sensitivity increases with age came from early nonexperimental studies comparing different populations. The recently completed INTERSALT study is the largest and most carefully conducted interpopulation study on sodium and blood pressure. This study sets the norm for this kind of study and is likely to be the last effort to find evidence for an association between sodium and blood pressure using a geographic pathology approach. In the INTERSALT study, a weak relation between urinary sodium excretion and systolic blood pressure using a geographic pathology approach. In the INTERSALT study, a weak relation between urinary sodium excretion and systolic blood pressure is measured twice in a group of hypertensive subjects. Without appropriate control conditions, an intervention such as sodium restriction may be incorrectly assigned to a more pronounced response in a subgroup of the study population. In this case, physiological significance may be linked to a change in blood pressure that is larger than an arbitrary cutoff point (e.g., -4 mm Hg), whereas in reality all differences result from random variation.
pressure was observed, suggesting that a change in sodium intake of 100 mmol/day would be associated with a 2.2 mm Hg change in systolic blood pressure. In a subsequent analysis, the associations between sodium and blood pressure tended to be more marked in older compared with younger ages and in women compared with men.\textsuperscript{32} The size of the regression coefficients in women were twice the corresponding coefficients in men. Data were analyzed for sodium to potassium ratio (rather than for sodium only), the positive associations were consistently stronger in women and older age groups. A complete discussion of the interrelations of various electrolytes in blood pressure regulation goes beyond the scope of this paper, but it needs to be mentioned that the effects of sodium and potassium may be closely related and probably should be considered together.\textsuperscript{27} Therefore, findings supporting an association between sodium and blood pressure within single populations are not abundant, but some recent studies support a positive relation between sodium intake and blood pressure that becomes stronger with age.\textsuperscript{32,33} In a small but socioeconomically and ethnically homogeneous population in California, Khaw and Barrett-Connor\textsuperscript{33} reported significant positive correlations between sodium and blood pressure and inverse correlations with potassium in men and women aged 30–79 years. Correlations were better for the sodium to potassium ratio than for sodium or potassium alone. In these data, a clear age gradient was present, with the strongest association of sodium and blood pressure in those over 64 years. In contrast to the INTERSALT findings, the associations were more pronounced in men. In women, sodium intake was significantly only related to blood pressure in those using exogenous hormones. This agrees with findings in another intrapopulation study in which a positive association between sodium and blood pressure was observed only in women taking oral contraceptives.\textsuperscript{29} We\textsuperscript{34} recently studied the effect of differences in long-term sodium and potassium intake on change in blood pressure levels over time in a cohort of 233 children, combining data on sodium excretion and blood pressure obtained at a minimum of six subsequent annual exams. From this analysis, no relation between mean sodium intake and change in blood pressure could be detected. Yet, children with a high potassium intake showed lesser rises in blood pressure. Moreover, children in the upper third of the distribution of the sodium to potassium ratio had a mean blood pressure slope twice the population average. The latter association was stronger when children were older, but no differences were present between responses in boys and girls.

**Experimental Studies**

Experimental studies examining the incidence of hypertension in groups randomly assigned to different levels of sodium intake are virtually absent. Hofman et al\textsuperscript{35} studied a group of newborns randomly assigned to either a low or a normal sodium diet during the first 6 months of life. At the end of the intervention period, blood pressure was a significant 2.1 mm Hg lower in the low sodium group. When remeasured after 4 and 6 years, no differences in blood pressure persisted between the groups (D.E. Grobbee and A. Hofman, unpublished results). Although replication of this finding is awaited, it may indicate the presence of sodium sensitivity very early in life. More experimental data are available on the effect of reductions in sodium intake on actual level of blood pressure. It seems beyond doubt that diets with an extremely low salt content (e.g., the rice–fruit diet) lower blood pressure.\textsuperscript{36} Findings in trials of less stringent reductions in sodium intake have been less consistent, as is the quality of the studies. A major contribution to the methodology of sodium restriction trials came from the work by MacGregor et al,\textsuperscript{37} who were the first to report the findings from a randomized double-blind trial on moderate sodium restriction in hypertension. Over the past 2 decades, results from several trials have been published. In a pooled analysis of thirteen randomized trials, the average effect of moderate sodium restriction appeared limited.\textsuperscript{38} Systolic blood pressure fell, on average, by 3.6 mm Hg (range, 0.5–10.0 mm Hg), and diastolic blood pressure fell by 2.0 mm Hg (range, -3.2–7.0 mm Hg). Across these studies, a larger effect was found when participants in the trial were older or had a higher blood pressure level at the start of the study. No clear differences in response between men and women were observed, but the number of women included in study groups was small. Recently, the findings of a large, double-blind trial from Australia were reported.\textsuperscript{39} This study included 103 hypertensive patients randomly assigned to 8 weeks of sodium restriction or placebo intervention. The findings closely agree with the pooled results from previous trials, including the more pronounced effect in older ages and those with the highest baseline blood pressure levels. No studies have been undertaken in which subjects have been selected on the basis of age or sex before entry in a randomized trial of moderate sodium restriction. This “ultimate” experiment has yet to be conducted.

**Pathophysiology**

The pathophysiological correlates of sodium sensitivity in different age groups and sexes will be discussed in detail elsewhere in this issue.\textsuperscript{40} There are, however, several physiological arguments to support an increase in sodium sensitivity with increasing age. Older hypertensive and normotensive subjects tend to have lower renin values,\textsuperscript{41} although there is a marked heterogeneity in the renin-angiotensin-aldosterone profile. Alternatively, age-related changes in renal hemodynamics and sodium excretory capacity might contribute to sodium sensitivity in older age groups.\textsuperscript{42} In addition, a role for the adrenergic nervous system has been proposed.\textsuperscript{43}
but not all subjects.\textsuperscript{40} High sodium intakes between and within populations are weakly associated with a higher prevalence of hypertension.\textsuperscript{44,45} The extent to which the latter findings result from a residual confounding of factors that were not sufficiently controlled in the nonexperimental studies reporting the associations remains difficult to assess. In particular, there is concern that differences in other dietary factors, social stress, and physical activity may explain some of the findings. In contrast, it may be that the actual part played by sodium intake in the etiology of high blood pressure is greater than observed and that findings are attenuated by the error from both the estimates of sodium intake and the measurement of blood pressure.\textsuperscript{46} Whatever the explanation may be, it is clear from both experimental and nonexperimental studies that there is a marked heterogeneity in blood pressure response to variations in sodium intake between individuals. Not many of the range of potential indicators of sodium sensitivity have been sufficiently studied to permit solid conclusions, let alone guidelines for clinical practice. In particular, experimental studies in which subjects are selected on the basis of presumed sodium sensitivity before entering a double-blind randomized trial of sodium restriction versus placebo intervention are lacking. These studies are needed not only to conclusively assess the presence of sodium sensitivity but also to estimate the predictive value of the marker for adequate treatment of hypertensive subjects by changing their diets. The limited data available suggest that subjects that are older and have higher blood pressure levels seem to benefit more from a reduction in sodium intake. In addition, elderly subjects at a high dietary sodium intake may have a higher risk of developing hypertension. Findings in both nonexperimental and experimental studies tend to support this view. Findings on sex differences are less consistent, although there are some suggestions that oral contraceptive use in women may induce sodium sensitivity. This possibility is, however, barely supported by findings of a significant increase in prevalence of hypertension in oral contraceptive users. A systematic approach to the assessment of factors and mechanisms responsible for sodium sensitivity in some subjects is needed to determine who might benefit most. Until more data are available, there is little basis to discriminate sodium-sensitive from sodium-resistant hypertensive subjects. Tailoring of individual therapy and monitoring of the response remains a mainstay in the treatment of primary hypertension, especially when a nonpharmacological approach is pursued.

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