A Perspective on the Salt–Blood Pressure Relation

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Current recommendations for a population-wide decrease in dietary salt consumption come from a conclusion that a substantial portion of the population with essential hypertension is salt-sensitive. It is difficult to determine the appropriateness of these recommendations because of critical gaps in knowledge of the salt–blood pressure relation. There is no agreement on a definition of salt-sensitive blood pressure changes. There is no consensus about mechanisms of changes; several have been suggested but none seems universal. In fact, differing results suggest marked heterogeneity in the mechanisms of salt-sensitive hypertension, and some evidence points to the possibility that arterial pressure of hypertensive subjects is controlled differently than that of normotensive subjects during manipulation of salt intake. Because salt-sensitive blood pressure changes are not always related to the magnitude of the positive sodium balance, it seems possible that for some people the current recommendations for modest dietary sodium restriction may be inadequate to influence blood pressure control for the prevention of hypertension. (*Hypertension* 1991;17[suppl I]:I-166-I-169)

This is a confusing time in the evolution of knowledge relating salt intake to hypertension. This workshop has clearly shown some of the problems that have developed along with that knowledge. First, there is the problem of arriving at a definition of what constitutes salt-sensitive blood pressure changes. Second, there is the problem of mechanisms of changes, about which there is no clear view. Finally, there is the public health issue that concerns the advisability of recommending a decrease in salt consumption by all people for the purpose of preventing hypertension or lessening cardiovascular morbidity and mortality in some.

Definition

The definition of salt sensitivity is an important problem because a consensus would facilitate study design and data analysis. Several definitions have been proposed, but with the exception of that of Falkner et al, they rely on the difference in arterial pressure during a period of a low salt intake versus a normal or high salt diet. A description of three definitions will suffice to illustrate the different approaches that have been taken. The most widely applied one comes from use of the National Institutes of Health protocol and is a 10% or greater rise in mean arterial pressure (MAP) from the seventh day of a 10 mM sodium intake to the seventh day of a 240 mM sodium intake. A similar definition was used by Campese et al, who studied three levels of sodium intake in a randomized fashion (10 mM, 100 mM, and 200 mM). The second definition comes from the Indianapolis studies, which used 1 day of salt loading with 2 l isotonic NaCl solution given intravenously followed by 1 day of salt depletion with a 10 mM dietary sodium intake and three 40 mg doses of furosemide. Sodium sensitivity was defined as a 10 mm Hg or greater fall in MAP between that after the salt load to the morning after salt depletion. The third definition was used by Falkner et al, who added 10 g NaCl by tablet to the usual diet of adolescents over a 2-week period. Salt-sensitive blood pressure changes were defined as a 5 mm Hg or greater rise in MAP after 2 weeks of extra salt feeding.

Definitions that concern differences in blood pressure between low sodium and high sodium intakes raise the question of relevance for free-living people who, in industrialized societies, are unlikely ever to have sodium intakes as low as 10 mM/day. Although such studies are useful for investigating mechanisms of blood pressure changes from a low to a high sodium intake or vice versa, they may have little significance for the population as a whole.

Giving salt to hypertensive patients already eating a usual sodium diet has not been a popular approach to the study of salt-sensitive blood pressure changes, but there is some information about the effects of high salt intake in normotensive subjects. Kirkendall et al showed that normotensive subjects could toler-
ate a 410 mM sodium intake/day for 1 month without a change in arterial pressure. Luft and coworkers studied 14 normotensive young men (seven white, seven black) with progressively rising sodium intakes from 10 mM/day to either 800 or 1,500 mM/day; each sodium intake was given for 3 days only. Very small increases in blood pressure were found. Before the Kirkendall study, there had been a few relevant investigations. McQuarrie et al reported in 1936 that when salt was fed to four diabetic children, marked increases in arterial pressure were found and that a normal child had a similar blood pressure response to salt feeding. They also found slight but lesser increases in arterial pressure when sodium salts other than that of chloride were used. McDonough and Wilhelmj fed 25–60 g/day NaCl to a young normotensive man over a 23-day period and noted a gradual, progressive increase in systolic and diastolic pressures. A case report published by Lower and Brown described a 52-year-old man with a long history of hypertension that was shown to result from chronic ingestion of large amounts of baking soda.

The INTERSALT report suggested that a decrease in sodium intake of 100 mM/day (from 170 to 70) would substantially lessen the age-related rise in arterial pressure in industrialized societies. Although the recommendation is for a life-long dietary change, there is no information available to indicate how such a change might affect salt sensitivity. A worthwhile clinical study would be one that investigated whether giving a normal salt intake (e.g., 170 mM/day) to normotensive subjects accustomed to a 70 mM/day intake would raise pressure over a 2–3-month period. This would be a test of salt sensitivity with relevance for public recommendations.

**Mechanisms**

The problem of understanding mechanisms of salt-sensitive blood pressure changes suggests that they are complex, multifactorial, and probably interrelated. Mark, in his presentation at this conference, presented evidence for neurogenic mechanisms in a salt-sensitive animal model. Ferrario et al has implicated vasopressin as influencing the pressor effect of salt, whereas Bohr cited evidence for increased membrane permeability to sodium. Earlier studies in hypertensive humans had noted the now-familiar sluggish response of plasma renin activity to salt depletion and suggested it as a mechanism for the fall in arterial pressure. 1,2 Campese et al found that in some, but not all, patients with salt-sensitive blood pressure, a high salt intake for 1 week failed to suppress plasma norepinephrine levels and concluded that a neurogenic mechanism was responsible for the rise in pressure with salt loading. A recent study, which used multiple regression to analyze mechanisms of salt sensitivity in humans, did not find this relation but, in contrast, suggested that intracellular sodium accumulation and inadequate suppression of the renin-angiotensin system were involved in the elevation of pressure produced by salt loading.

Yet another report indicates the complexity of the mechanisms responsible for changes in blood pressure in response to changes in salt intake. Multidimensional response surface modeling was used for determining the influence of a number of variables in the rises in pressure occasioned by giving 3.88 mM sodium/kg/day intravenously for 3 days either after 4 days of salt depletion or after a 3-day control period during which sodium intake was 150 mM/day. The variables measured were plasma concentrations of aldosterone, norepinephrine and epinephrine, plasma renin activity, plasma volume, and sodium balance. Blood pressure responses of hypertensive subjects were highly predictable (R²=0.86–0.90) with eight to nine variables involved. The variables most frequently encountered were the plasma concentrations of aldosterone, norepinephrine, and epinephrine; the other variables did not appear to be so important. Blood pressure changes in the normotensive group were not nearly as predictable as in the hypertensive group, suggesting that blood pressure of the normotensive group during changed sodium intake is controlled differently than it is in the hypertensive group.

The reports cited suggest that mechanisms of blood pressure responses to changes in sodium intake are varied and probably highly individualized. This seems the reasonable explanation for the lack of consensus about reasons for salt-sensitive blood pressure changes. Another possibility for the lack of consensus is random variation in responses of arterial pressure control systems when salt intake is markedly changed.

**The Public Health Issue**

The recommendation for a general reduction in dietary salt intake is based on the assumption that salt raises arterial pressure in people who cannot excrete sodium normally. This was first proposed by Ambard and Beaujard in 1905, was made a contemporary concept by Borst and Borst-De Geus in 1963, and has been greatly expanded by Guyton and coworkers.

Several studies in the last almost 40 years have examined the hypothesis that sodium retention is quantitatively related to salt-induced increases in arterial pressure. The results of these studies are summarized in the table. In 1951, Corcoran et al reported no relation between sodium balance and blood pressure changes produced by salt restriction and subsequent salt loading. Later, another report from the Cleveland Clinic showed that hypertensive patients who became normotensive with salt depletion retained more sodium when subsequently salt loaded than did patients whose blood pressures were unaffected by the changed sodium intake. A similar difference between salt-sensitive and salt-resistant hypertensive subjects was reported by the same group several years later. Two reports from the National Institutes of Health had similar findings.
and, in addition, showed a markedly positive correlation between the amount of sodium retained during salt loading and the rise in blood pressure. However, Campese et al, who used the same protocol, failed to find greater sodium retention during salt loading in salt-sensitive hypertensive subjects in comparison with salt-resistant subjects. Finally, Dustan and Kirk, using a protocol almost identical to that of the two earlier Cleveland Clinic studies, found that Spearman correlations between sodium balance and blood pressure changes showed no quantitative relation between the two. It therefore seems reasonable to conclude that there is as much heterogeneity in the quantitative relation between sodium balance and blood pressure as has been found for other mechanisms as mentioned above. This raises the question whether a simple reduction of sodium intake by 100 mM/day could influence the arterial pressure of the individuals with truly salt-sensitive hypertension. It would be instructive to know the responses of a sizable group of hypertensive patients to stepwise reduction in sodium intake. This would extend a recent study of MacGregor et al that examined arterial pressure responses of 20 mildly hypertensive subjects (supine blood pressure, 163/100±4/2 mm Hg) who were randomly assigned to 4-week periods of 50, 100, and 200 mmol sodium intake. They found that a stepwise reduction of arterial pressure was produced by the two lower sodium intakes and concluded that there is no threshold effect. In contrast, the study conducted by Weinberger et al indicated that sodium intake must be reduced at least to 80 mM/day before an effect on blood pressure is seen. It seems likely, however, that there is as much heterogeneity in pressure responses to reduced sodium intake as there is for the other variables, and it may be that some individuals will achieve a fall in arterial pressure with modest sodium intake whereas others require rigid restriction.

The foregoing discussion has not provided a satisfactory definition of salt-sensitive hypertension. All studies that included a normotensive control group have reported that some fraction had blood pressure responses characteristic of salt-sensitive hypertension. From the public health aspect, we would be in a much better position than is now the case if we knew that such responses predict subsequent development of hypertension.

### References


**KEY WORDS** • sodium • blood pressure • sodium-dependent hypertension
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