Is salt-sensitivity of blood pressure a reproducible phenomenon–commentary

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Identification of intermediate phenotypes for variations in blood pressure responses has enhanced our range of therapeutic choices for hypertensive patients and has improved our ability to detect genetic factors responsible for blood pressure elevation. An example of therapeutic choice is the use of angiotensin-converting enzyme inhibitors and, now, angiotensin II receptor antagonists, in patients with elevated or normal renin levels. Sophisticated genotyping studies have identified a mutation producing a chimeric 11β-hydroxylase–aldosterone synthase gene as responsible for glucocorticoid-remediable aldosteronism [1]. Additional genetic alterations have been linked to other unusual forms of hypertension such as Liddle's syndrome [2]. It is likely that many more genetic abnormalities will be identified in hypertensive patients in the future. The success of these therapeutic and genetic approaches relies on the identification of intermediate phenotypes, which are unique characteristics that allow differentiation of individuals. The reproducibility of such characteristics is an important feature, lending confidence that they are meaningful observations and that they can be examined in different populations. One such characteristic that has been studied extensively by investigators all over the world is the response of blood pressure to alterations in sodium intake and extracellular fluid balance, commonly defined as the salt-sensitivity or resistance of blood pressure.

Although many different approaches have been used by various groups to define salt-sensitivity and resistance, the findings have been amazingly consistent [3]. In general, hypertensive individuals have been found more likely to exhibit salt-sensitive responses than are normotensives, although heterogeneity of response has consistently been demonstrated in both groups [4]. Several demographic characteristics have been reported to be associated with salt-sensitivity in different studies. The phenomenon appears to be more prevalent in African-Americans than in Caucasian-Americans and more common in older subjects than in younger ones [4]. Some studies have suggested that women are more likely than men to exhibit this response [5], but this finding has not been confirmed by other investigators. At least one study [6] has correlated salt-sensitivity with obesity but this also has not been a consistent observation. A host of physiologic differences between salt-sensitive and salt-resistant subjects have been described [3] and many more are likely.

One critical issue that has largely been neglected relates to the reproducibility of the response of blood pressure to variations in salt balance. Three studies, two with dietary manipulations in normotensive subjects [6,7] and one with a rapid intravenous saline loading–low-salt diet plus diuretic protocol both in normal and in hypertensive individuals [8], have reported that blood pressure responses were significantly reproducible in small groups of subjects. Zoccali *et al.* address this issue in their current report, concerning 14 mild hypertensives, in whom they assessed responses of blood pressure to changes in dietary sodium intake by means of 24 h ambulatory blood pressure measurements [9]. They conclude that the responses are not reproducible despite similar blood pressure changes being found within the groups when the study was repeated. The authors chose to use the 24 h measurements in an attempt to improve the precision of the blood pressure measurement. Two other groups have examined salt-sensitivity by using 24 h ambulatory blood pressure measurement in comparison with the casual or clinic-based measurements, with conflicting results [10,11]. Moreover, one of these studies observed that the salt-resistant patients were 'non-dippers' [11], thus altering the variability that might otherwise have been observed with the 24 h measurement. Thus, although the use of more frequent measurements may increase precision, it may obscure the phenomenon of salt-responsiveness which is defined by clinic blood pressure measurements.

Another concern with the study by Zoccali *et al.* is that only 14 subjects were studied, fewer than in any of the other studies. In addition, the ability to observe salt-sensitivity is also dependent on the inclusion of individuals likely to demonstrate the phenomenon as well as the use of a protocol adequate to demonstrate the response. The members of the population studied by Zoccali *et al.* were all aged less than 60 years, thus reducing the likelihood of salt-sensitive responses. The investigators chose levels

of dietary sodium intake of 170 and 40 mmol/day, a much more narrow range than that of any of the other published studies. Although the level of dietary compliance that the subjects achieved appeared, on the basis of urinary sodium excretion, to be excellent, a greater difference in dietary sodium intake may be required in order to demonstrate salt-sensitivity of blood pressure. Although such studies are hard to accomplish because of their arduous and lengthy nature, the limitations given above make it difficult to accept the null hypothesis and the conclusions of the authors. Future studies involving larger numbers of subjects, including some older individuals and a greater range of sodium intake will be required in order to determine that these responses are not reproducible.

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