Sodium, Left Ventricular Mass, and Arterial Hypertension

Is It Time to Look for a New Paradigm?

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Western dietary habits, based on processed foods high in sodium (Na^+) and low in potassium (K^+), has been linked to the increasing prevalence and incidence of arterial hypertension.[1,2] Accordingly, both the 24-hour urinary Na^+ and Na^+/K^+ excretion, which reflect the dietary amount of these 2 electrolytes, have been shown to have significant direct relations with blood pressure (BP).[1,2] Thus, high salt intake harms the cardiovascular system by raising BP and might be directly responsible for increasing left ventricular (LV) mass, as suggested in clinical and experimental studies.[3,4] Low K^+ intake is thought to amplify the harmful effects of Na^+ intake.[5] Consistent with this scenario, there is also evidence that high salt intake aggravates and, conversely, dietary salt restriction prevents (or at least mitigates) LV hypertrophy in patients with essential hypertension. There are open and still controversial questions on this issue concerning the real impact on public health and the physiological and temporal relationships among dietary Na^+/K^+ balance, amount and quality of increase in LV mass, and development of arterial hypertension that still need to be clarified.

In this issue of *Hypertension*, Rodriguez et al[6] documented a significant association between 24-hour urinary Na^+/K^+ excretion and LV mass in a large subpopulation of the Coronary Artery Risk Development in Young Adults cohort, formed predominantly by normotensive young adults. This relation was substantially less evident for the 24-hour urinary Na^+ excretion alone. In simple words, the authors found that LV mass index increases by <1 g/m$^{2.7}$ for each 131 mmol of 24-hour urinary Na^+ excretion and by a little more than 1 g/m$^{2.7}$ for each increase of 1.14 of the 24-hour urinary Na^+/K^+ ratio. Statistically there is no doubt that these relations are significant,[6] but doubts might raise about their impact on biology. However, despite the tiny amount of LV mass modification for the remarkable changes in electrolyte excretion, the statistical evidence that dietary electrolyte intake is a pressure-independent correlate of LV mass might have important pathophysiological and clinical relevance, because LV mass might mediate, at least in part, the increased pressure-independent cardiovascular risk related to excessive Na^+/low K^+ intake. It is also interesting that body mass index variance blunts the association of LV mass with 24-hour urinary Na^+ excretion alone, which raises the question of how much the described associations are related to overweight-obesity, a condition that has greater prevalence than diabetes mellitus or hypertension in this Coronary Artery Risk Development in Young Adults subpopulation. In contrast, combination of Na^+ excretion with K^+ excretion maintains statistical independence, supporting the role of low K^+ as a booster of high Na^+ intake effects.

Another argument supporting the importance of the reported relation between 24-hour urinary Na^+ excretion and LV mass is the relative normality of this Coronary Artery Risk Development in Young Adults subpopulation (very low prevalence of hypertension and diabetes mellitus). This relative normality is likely to keep the variability of LV mass index confined within limits (the coefficient of variation was 26%), more than other parameters, more directly sensitive to environmental factors (eg, urinary electrolyte excretion, exhibiting a much higher coefficient of variability), and reduces the chance of detecting significant correlations. Thus, documentation of a significant relation in this context is very important.

The above considerations suggest prudence in the evaluation of a possible dose-response in the reported relationship because, in the studied context, a dose-response can be only considered in the setting of a young and relatively healthy population with the above reported levels of variability. Actually, the possible effect of high Na^+ and low K^+ intake might be substantially greater in different contexts, when other stimuli have impact on the magnitude of LV response.

The impact of 24-hour urinary Na^+/K^+ excretion on LV mass is, therefore, not surprisingly stronger than the 24-hour urinary Na^+ or K^+ excretion alone, also because the ratio reduces the variability and the very likely right skewed distribution of the single components. In fact, the variability of the Na^+/K^+ ratio was substantially lower (40%) than that of the single components (75% and 82%, respectively).

This is also consistent with the previous evidence that 24-hour urinary Na^+/K^+ excretion also predicts the risk of hypertension better than the individual electrolyte components.[2,7] Because K^+ intake has been shown to exert a powerful, dose-dependent inhibitory effect on sodium sensitivity, it is reasonable that the simultaneously reduction of K^+ amplifies the unfavorable influence of the excessive Na^+ intake on cardiovascular phenotype.[5]

Overall, the general notion that the association of excessive Na^+/reduced K^+ intake with LV mass is at least as close as, and perhaps closer than, BP is confirmed. One possible

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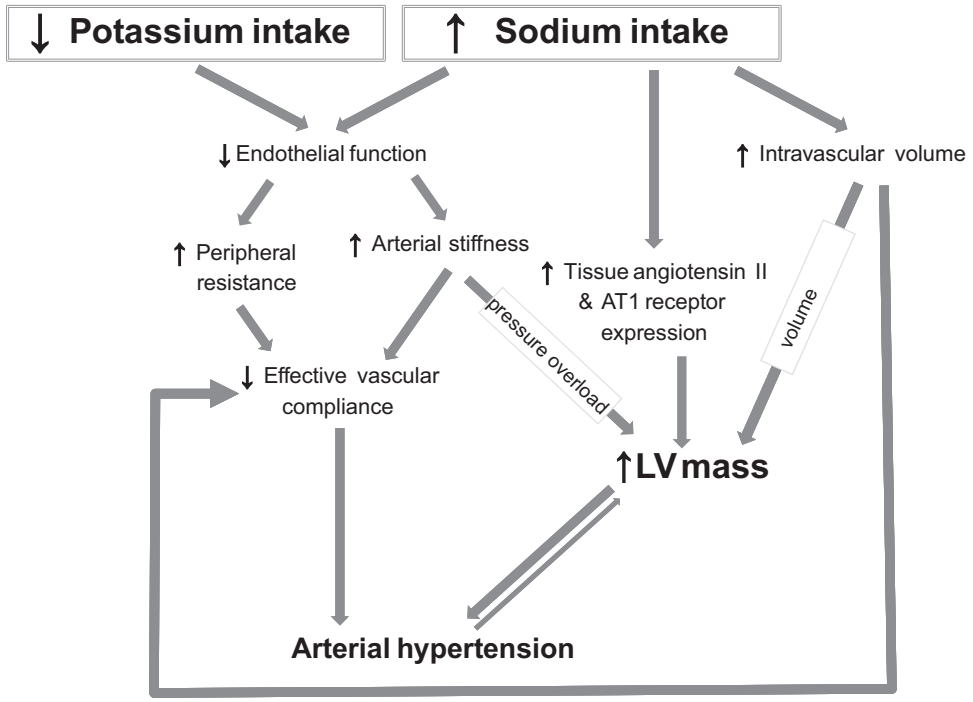

Figure. Possible interrelations among unbalanced electrolyte intake, high LV mass, and arterial hypertension.

explanation is that, compared with the high fluctuations of spot BP measurements, the magnitude of LV mass more accurately reflects the average steady-state increase in cardiac workload to which heart is exposed over time than the occasional cuff BP recording. Accordingly, it is not possible to exclude the possibility that the described association of 24-hour urinary Na^+/K^+ excretion with LV mass simply reflects the relation between 24-hour urinary Na^+/K^+ excretion and LV loading conditions that are not necessarily always reflected by occasional peripheral BP values.

An attractive hypothesis is that high Na^+/low K^+ intake tracks volume expansion and increases volume output, a hemodynamic effect that is combined with the impairment of endothelial function and increase in arterial stiffness related to excessive Na^+ intake[8] and potentiated by low K^+ intake.[9] The other component that might facilitate the effect of Na^+/K^+ balance on development of LV hypertrophy is the stimulating effect of high Na^+ intake to increase angiotensin II type 1 receptor protein expression,[10] which can also at least in part explain the antihypertrophic effect of angiotensin II type 1 receptor blockade, even in rat models on high salt diet and normal or low circulating plasma renin.[11]

Because high values of LV mass can precede the appearance of high cuff BP values,[2,12] alternative to a traditional view, the study by Rodriguez et al[6] also suggests different pathways, including potential reverse causation of the association between high BP and LV mass (Figure). As shown in the Figure, the intake of a high Na^+/K^+ ratio takes part in the relationship between high LV mass and high BP through 3 distinct mechanisms: (1) causing endothelial dysfunction and promoting arterial stiffness and inadequate compensatory decrease in peripheral resistance when output volume increases; (2) increasing intravascular volume and LV performance through Starling mechanism; and (3) enhancing intramyocardial expression of angiotensin II type 1 receptor protein. The first 2 mechanisms are coresponsible for the increase in cardiac workload and development of LV hypertrophy. The third one, in addition to the prohypertrophic effect, also contributes to altering LV myocardial structure, promoting fibrosis and alteration of the extracellular matrix.

In a reverse causation scenario, increased LV mass provides more strength to push blood into a less compliant arterial system because of increased stiffness of conduit arteries or/and increased vascular resistance. The alteration of these 3 components (ie, strength, stiffness, and resistance) and their balance yields peripheral evidence of high BP. Biological changes caused by inappropriate balance of Na^+ and K^+ intake might well take a key role in precipitating events.

Disclosures

None.

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