Sodium Chloride and Aldosterone
Harbingers of Hypertension-Related Cardiovascular Disease
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Both dietary NaCl consumption and aldosterone have been implicated in the pathogenesis of hypertension-related cardiovascular disease. Animal, epidemiological, and clinical studies suggest that a high NaCl intake is associated with myocardial hypertrophy, independent of blood pressure. In vitro, NaCl directly induces hypertrophy in myocardial and vascular smooth muscle cells. Independent of the level of hypertension, NaCl induced cardiac hypertrophy may be mediated by nitric oxide synthase isoforms.1 In the rat, dietary NaCl restriction prevents oxidative stress and cardiac hypertrophy induced by angiotensin II infusion. Clinically, a high NaCl intake is associated with increased left ventricular mass in both normotensive and hypertensive individuals.2 In hypertensive patients, a high NaCl intake amplifies the effect of target organ damage, including increased left ventricular mass and microalbuminuria. Left ventricular mass decreases in response to dietary NaCl restriction,3 and in hypertensive patients the effect of NaCl on left ventricular structure may be modulated by variants in the angiotensin II type 2 receptor gene.2

Aldosterone is also associated with alterations of myocardial structure and function. Mineralocorticoid receptors are located in nonepithelial (heart, blood vessels, brain) as well as in epithelial tissues, and stimulation of these receptors may cause oxidative stress leading to vascular inflammation, fibrosis, and cardiac hypertrophy.4 Additionally, aldosterone may contribute to end organ damage by enhancing the proinflammatory effects of angiotensin II.5 In animal models, both cardiac load and high circulating aldosterone levels stimulate fibrosis within the myocardium, leading to left ventricular hypertrophy. Pathological patterns of left ventricular geometry have been associated with elevations of plasma or urine aldosterone in patients with essential hypertension, and the early onset of left ventricular hypertrophy has been described in patients with primary aldosteronism.

Studies with mineralocorticoid antagonists provide convincing evidence for the contribution of aldosterone to cardiac hypertrophy. Both animal and clinical studies have documented that spironolactone or eplerenone decrease cardiac hypertrophy and interstitial fibrosis, independent of an effect on blood pressure.6 In experimental models, aldosterone antagonists also protect against renal hypertrophy, tubulointerstitial fibrosis, glomerular injury, stiffening of the carotid artery, resistance artery remodeling, and endothelial dysfunction.7,8 Two clinical trials, the Randomized ALdactone Evaluation Study and the Eplerenone Postacute myocardial infarction Heart failure Efficacy Survival Study, demonstrated decreases in mortality in patients with heart failure treated with low doses of aldosterone antagonists compared to placebo-treated patients.8,9 The beneficial effects of mineralocorticoid receptor blockade have been attributed, at least in part, to attenuation of mineralocorticoid-induced myocardial oxidative stress and coronary vascular inflammation. Notably, the beneficial effects of mineralocorticoid antagonists on cardiac hypertrophy occur whether or not plasma concentrations or urine aldosterone excretion is elevated. An aldosterone synthase inhibitor (FAD286) has also been found to attenuate cardiac hypertrophy and interstitial fibrosis in uninephrectomized rats treated with angiotensin II and fed a high-salt diet.5

The proinflammatory effects of aldosterone are amplified by NaCl, possibly by increasing oxidative stress. In rats on a high NaCl intake, aldosterone stimulates fibrosis in the heart, great vessels, and kidney.5 NaCl restriction prevents both oxidative stress and cardiac hypertrophy in rats infused with angiotensin II. Similarly, in uninephrectomized rats chronic infusion of aldosterone has been shown to result in collagen accumulation in the myocardium and myocardial fibrosis in animals maintained on a high NaCl diet, but not in NaCl-deprived animals. Further, eplerenone attenuates vascular remodeling and cardiac fibrosis in stroke-prone SHR induced by high NaCl feeding.7

In this issue of Hypertension, Jin et al10 report on the “independent associations of left ventricular mass index with the urinary excretion of both sodium and aldosterone” in 250 normotensive and 67 untreated hypertensive white subjects. Subjects were grouped by quartiles of 24-hour urine sodium excretion. BMI and diastolic blood pressure, but not systolic blood pressure, were associated with higher sodium excretion rates. Somewhat surprisingly, there were no differences of plasma renin activity or aldosterone excretion among the 4 sodium excretion quartiles. Echocardiographic measures of left ventricular mass (LVM), left ventricular mass index (LVMI), and mean wall thickness (MWT) increased with higher sodium excretion; left ventricular mass index and left ventricular internal diameter (LVID) were positively associated with aldosterone excretion. Using stepwise multiple linear regression analyses, these associations were observed both before and after statistical adjustment for age, body

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weight, systolic blood pressure, and waist-to-hip ratio. In supplementary correspondence, an alternative regression model including diastolic rather than systolic blood pressure as a covariate did not alter these results. After additional statistical adjustment for aldosterone excretion, LVMI and MWT increased with sodium excretion; after adjustment for sodium excretion, LVMI and LVID increased with aldosterone excretion. In apparent contrast to several previous reports, MWT was not associated with aldosterone. These results were not altered by excluding the untreated hypertensive patients or subjects with BMI ≥30 kg/m² (Table S1, available online at http://hyper.ahajournals.org).

A strength of the study is its attempt to separate the effects of sodium and aldosterone on left ventricular structure. The authors conclude that alterations of cardiac structure are “independently” associated with both NaCl intake (as estimated by a single 24-hour urine sodium excretion) and aldosterone. However, based on statistical adjustment, the conclusion that NaCl and aldosterone are independently related to alterations of left ventricular structure may not be totally justified. To further evaluate the dependence or independence of NaCl intake, it would have been of interest to compare the contributions of aldosterone to alterations of cardiac structure at different levels of sodium intake. However, it may not be possible to exclude a contribution of NaCl to aldosterone-induced injury at usual ambient levels of NaCl consumption. Sodium intakes were relatively high even in the lowest quartile of sodium excretion (mean 97.1 mmol/24 hours ±29.4 SD), and theoretically to exclude a potential contribution of NaCl it might be necessary to evaluate subjects consuming a considerably lower NaCl intake.

Nevertheless, from a clinical perspective, this study provides additional support for the contributions of both NaCl and aldosterone to hypertension-related cardiovascular disease. Although correlates do not prove causality, studies such as that reported by Jin et al provide impetus for additional trials to further evaluate the cardiovascular protective effects of mineralocorticoid antagonists. Another objective of future clinical trials might be to identify those hypertensive patients most likely to benefit from mineralocorticoid antagonist therapy. Hypothetically, these might include blacks and obese hypertensives. Plasma aldosterone concentrations are correlated with blood pressure in blacks, and plasma aldosterone is higher in hypertensive than in normotensive blacks. Independent of blood pressure, plasma aldosterone is also associated with obesity, insulin resistance, and the metabolic syndrome in both blacks and whites. Consequently, there are groups of patients who predictably might be more responsive to the cardiovascular benefits of mineralocorticoid antagonists. Although the cardiovascular protective effects of aldosterone antagonists in humans are promising, identification of their full potential will require additional clinical trials.

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