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COMMENTARY

Aldosterone and abnormal left ventricular geometry in chronic kidney disease

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In the previous issue of the Journal, Mulè *et al.*[1] report the results of a cross-sectional study aimed at assessing (1) plasma aldosterone concentrations and left ventricular mass (LVM) in essential hypertensive subjects with and without early chronic kidney disease (CKD) and (2) the association between plasma aldosterone, LVM and LV geometric patterns. The authors were able to demonstrate a gradual increase in plasma aldosterone levels, LVM index values and prevalence rates of concentric LVH from hypertensive patients with normal renal function to those with CKD stage I, II and III. Before addressing this issue in detail, some more general considerations on available evidence in this area might be useful.

Hypertensive patients with CKD face an increased risk of premature death, mainly from cardiovascular disease even in the early stages of renal disease. Subclinical structural and functional abnormalities of the cardiovascular system such as left ventricular hypertrophy (LVH), myocardial fibrosis, LV systolic/diastolic dysfunction, left atrial enlargement, carotid atherosclerosis, peripheral artery disease and vascular calcifications contribute to the risk of incident cardiovascular disease in CKD patients.

LVH, a cardinal manifestation of subclinical organ damage, has been consistently shown to predict all-cause and cardiovascular death, after adjustment for conventional and emerging risk factors in various clinical settings, including general population-based samples, hypertensive cohorts, patients with diabetes, coronary artery disease and CKD. Chronic elevation in blood pressure (BP), as typically occurs in untreated or uncontrolled hypertension, may lead to progressive alterations in cardiac structure and function. Both experimental and clinical studies have shown that, in addition to pressure elevation, volume overload as well as activation of growth factors implicated in essential hypertension contribute to LVH development. Although the pathogenesis of LVH in arterial hypertension remains to be fully elucidated, several lines of evidence indicate that hemodynamic stress combined with several factors, such as the activation of the sympathetic nervous system, the renin–angiotensin–aldosterone system (RAAS), insulin and several growth factors, substantially contribute to myocardial hypertrophic responses.[2]

In particular, RAAS activation is recognized to have a pivotal role in cardiac remodeling. This is because in addition to regulating BP, angiotensin II and aldosterone, the active components of RAAS, have been reported to increase myocardial mass and collagen content. Although RAAS was initially described as a circulating system of renal and adrenal origin, many of its components are also localized in the cardiac and vessel walls, where they directly affect the function of cardiomyocytes and non-cardiomyocyte cells, and endothelial and vascular smooth muscle cells. In the complex interplay of the hemodynamic, endocrine and genetic factors responsible for the development of cardiac remodeling, the role of aldosterone is of paramount relevance.

Several lines of evidence support the view that aldosterone increases myocardial mass in excess of that required to compensate for pressure overload and promotes fibroblast proliferation, the deposition of collagen, oxidative stress and inflammation. Consistent evidence of the influence of excess aldosterone on cardiac structure has been obtained in patients with primary aldosteronism. Compared with essential hypertensive patients, those with aldosteronism exhibit higher LV diameters, LVM indices, left atrial volumes and prevalence rates of LVH. Furthermore, LVH regression after surgical correction of primary aldosteronism strongly supports a direct, causal role of aldosterone in LVH development.[3]

The relationship between plasma aldosterone and LVM index has been documented in echocardiographic studies conducted in patients with essential hypertension across a wide range of ages as well as in population-based cohorts. In a pediatric population predominantly of African–American boys, Li *et al.*[4] showed a significant association between the aldosterone–renin ratio and the LVM index. This finding, which supports the hypothesis that aldosterone is an early marker of cardiac organ damage in children, has been confirmed in several reports.

Catena *et al.*[5] investigated the relationship between plasma aldosterone, hemostatic variables and cardiac morphology in 205 middle-aged patients with various grades of essential hypertension. They demonstrated that plasma aldosterone levels were associated with increased LVM index and that such association was partly related to the presence of high fibrinogen levels. Among the 2119 Framingham Offspring Study participants who underwent measurements of various biomarkers of inflammation, hemostasis, neurohormonal activation, RAAS and echocardiographic LVM index, only the aldosterone–renin ratio was significantly

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positively associated with abnormal LV geometric patterns (that is, eccentric and concentric LVH).[6]

In recent years, experimental and clinical investigations demonstrated a pathophysiological role for aldosterone and other RAAS components in renal damage and CKD progression.[7,8] The mechanisms for these adverse effects include mesangial cell proliferation, matrix expansion and tubulointerstitial inflammation, selective constriction of the efferent arteriole leading to glomerular hypertension. Studies in patients with primary aldosteronism reported a high prevalence of renal damage and higher rates of micro- or macro-proteinuria compared with age-matched essential hypertensive patients. Among available scarce data on the association between RAAS components and renal function in the general population, the findings provided by the sixth Framingham Offspring Study merit being mentioned. During a mean 9.5-year follow-up, 213 of 2345 participants developed CKD (that is, estimated glomerular filtration rate (eGFR) $<60\,ml\,min^{-1}$ per $1.73\,m^2$) and 186 developed microalbuminuria.[9] Both serum homocysteine and aldosterone were significantly associated with CKD incidence; moreover, aldosterone, homocysteine and B-type natriuretic peptide were significantly associated with incident microalbuminuria with a logarithmic relationship.

The report by Mulè *et al.*[1] provides a new piece of evidence on the association between plasma aldosterone and subclinical cardiac damage in the setting of CKD by showing that both plasma aldosterone concentrations and LVM index values were higher in hypertensives with impaired renal function as compared with their age-matched hypertensive counterparts with preserved renal function. In their analysis, the authors included 195 hypertensive patients (mean age 45 ± 12 years) with CKD and eGFR $\geqslant 30\,ml\,min^{-1}$ per $1.73\,m^2$, without macroproteinuria, diabetes mellitus and previous cardiovascular diseases, and 92 essential hypertensives (mean age 44 ± 13 years) with normal renal function according to the definition provided by the 2012 Clinical Practice Guidelines for the Evaluation and Management of CKD.

LVM indexed to body surface area and to a height to allometric power of 2.7 was ~11% and 14% higher, respectively, in the CKD group than in the control group. A total of 82 CKD patients (42%) and 21 patients with preserved renal function (26%) had echocardiographic LVH, as defined by LVM indexed to body surface area; the corresponding figures for LVM indexed to height$^{2.7}$ were 46% and 26%, respectively.

The more pronounced subclinical cardiac damage documented in the CKD patients was associated with 30% higher levels of plasma aldosterone (11.6 versus $8.1\,pg\,ml^{-1}$, $P<0.001$). Multivariable analyses showed that LVM indexed to body surface area or height$^{2.7}$ and relative wall thickness were independently correlated with plasma aldosterone, microalbuminuria and nighttime BP. These results are in line with the notion that alterations in cardiac structure induced by hypertension tend to be paralleled by alterations in different organs and that nocturnal BP is a stronger correlate of LVH and new-onset CKD than daytime or average 24-h BP. In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, nighttime systolic BP levels have been reported to be more strongly related to the progression of subclinical cardiac damage (that is, incident LVH) than the extent of day-to-night BP variations or daytime systolic BP levels.[10] A population-based study by Kanno *et al.*[11] demonstrated that nighttime BP was significantly related to the risk of CKD and all-cause mortality, but this was not the case for the 24-h, daytime, office BP and non-dipping pattern. Average nighttime BP was the only ambulatory component that was predictive of both renal outcomes (that is, development of proteinuria and glomerular filtration rate $<60\,ml\,min^{-1}$ per $1.73\,m^2$) and all-cause death in fully adjusted Cox's proportional hazard models.

A futher relevant aspect of the study by Mulè and coworkers addresses the differences in LV geometric patterns between CKD patients and those with preserved renal function. The authors used the traditional classification including three pathological LV geometric patterns: concentric hypertrophy; eccentric hypertrophy; and concentric remodeling. All these patterns are known to be associated with differences in hemodynamic profile, LV myocardial performance, plasma volume, clinic and ambulatory BP levels, and the extent of extra-cardiac organ damage. More importantly, pathological geometric patterns are associated with increased incidence of cardiovascular events, and, in particular, concentric hypertrophy is associated with the highest risk.[12] In the present study, eccentric LVH (that is, increased LVM and normal relative wall thickness) did not differ in patients with and without CKD. It is worth noting that the prevalence of this type of hypertrophy was similar across the various stages of CKD (stage I: 15%, stage II: 18% and stage III: 16%). By contrast, concentric LVH showed a significant, progressive increase from patients without renal impairment (10%) to those with stage I (23%), II (26%) and III (36%) CKD. Interestingly, the plasma aldosterone levels in patients with LV concentric geometry (that is, concentric LVH and concentric remodeling) were ~30% higher than in those with eccentric LVH.

Some limitations of the present study should also be acknowledged. First, the exclusion of patients with severe hypertension may have underestimated the strength of the association between LVM and plasma aldosterone. Second, no information was provided on the relationship between diastolic function and left atrial diameter or volume with plasma aldosterone.

In conclusion, the study by Mulè and coworkers supports the concept that even mild to moderate renal impairment in hypertensive patients is associated with elevated plasma aldosterone levels and portends a high risk of LV concentric geometry and concentric LVH. From a practical perspective, this observation suggests that effective BP lowering in the early stages of CKD by targeting the RAAS may prevent or reduce concentric LVH, a powerful predictor of incident cardiovascular disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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