Seldom is there such a renewed interest in the study of a compound isolated more than a half century ago as we see now with aldosterone. A new era has begun in the study of aldosterone in individuals free of myocardial infarction and of heart failure.

The mineralocorticoid hormone aldosterone was thought to be produced uniquely in the adrenal cortex and to act exclusively on epithelia to promote sodium retention and potassium excretion. However, it is now known that aldosterone also acts on nonepithelial tissues, such as brain, heart, and blood vessels. In addition, enzymes required for aldosterone biosynthesis are expressed in these same tissues, which may be consistent with local aldosterone production acting in a paracrine fashion.

With the introduction of angiotensin-converting enzyme (ACE) inhibitors and their presumptive elimination of angiotensin II, a major determinant of aldosterone production by the adrenal glands, the perception of the pathophysiologic importance of aldosterone in congestive heart failure has been minimized during the past 20 years. However, recent evidence has revived interest in aldosterone and its role in congestive heart failure.

The Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post–Acute Myocardial Infarction Infarction Heart Failure Efficacy and Survival Study (EPHESUS) clearly demonstrated that antagonizing aldosterone on top of inhibition of the ACE or on top of blocking of the angiotensin II receptor had a major beneficial effect in risk reduction of cardiovascular morbidity and mortality in severe heart failure and postmyocardial infarction.

Ventricular remodeling is the process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape, and function. Remodeling occurs in several clinical conditions, including myocardial infarction, cardiomyopathy, hypertension, and valvular heart disease. Hallmarks of remodeling include hypertrophy, loss of myocytes, and increased interstitial fibrosis, so that abnormalities of the cardiomyocytes and the extracellular matrix contribute to systolic and diastolic dysfunction. Left ventricular hypertrophy confers an excess risk of cardiovascular and cerebrovascular events in patients independently of the blood pressure level. Aldosterone can have an adverse effect on the heart, independent of arterial blood pressure and angiotensin II, including a vascular inflammatory response, myocyte necrosis, fibrosis, and hypertrophy.

Several studies in the past examining the association of serum aldosterone with left ventricular remodeling in individuals have reported inconsistent results. All these investigations were limited by small samples, selection bias, focus on hypertensive patients, and inconsistent adjustment for confounders. In this issue of Hypertension, Vasan et al. published their remarkable results from the Framingham Heart Study regarding the gender-specific relations of serum aldosterone to echocardiographic indices of cardiac structure and function in a large community-based sample of 2820 subjects (58% women, 42% men) free of myocardial infarction and heart failure.

Their important findings demonstrated that serum aldosterone was positively associated with a left ventricular geometric pattern suggestive for concentric remodeling in women but not in men. These findings are very intriguing and additional studies are warranted in the future to explore the possible mechanisms.

Gender differences have been reported in left ventricular remodeling responses to pressure overload. Women demonstrate a greater degree of increase in left ventricular wall thickness and concentric hypertrophy, partially explained by molecular differences in the remodeling process of the left ventricle. Because estrogen and aldosterone receptors are present in cardiac fibroblasts and myocytes, a study examining possible interactions between signaling effects of estrogen and aldosterone receptors that contribute to the gender-based differences in left ventricle remodeling is merited.

These recent findings regarding gender differences with aldosterone and left ventricular remodeling emerge once again, validating the exploration of gender-based differences in early cardiovascular disease as a basis for clinical strategies to improve outcomes for women in the future. Under-representation of women and lack of gender-specific reporting in most of the clinical trials continue to limit the available knowledge and evidence-based medicine needed to devise optimal managements for women with cardiovascular disease or, more importantly, in cardiovascular prevention. Because asymptomatic left ventricular dysfunction may exist long before the clinical syndrome of heart failure appears, therapy introduced during this phase may delay or prevent the occurrence of symptomatic heart failure with its poor prognosis.
It would be very interesting to examine the gender effect of selective aldosterone blockade in the approach of reversing the early process of cardiac remodeling and link this to final cardiovascular morbidity and mortality.

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