Cardiac Structure and Function in Hyperaldosteronism

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Chronic activation of the renin–angiotensin–aldosterone system is known to be associated with cardiovascular injury. Primary aldosteronism (PA), either from bilateral adrenal hyperplasia or an aldosterone-secreting tumor, is one of the principal causes of secondary hypertension. The combined vascular resistance and sodium retention lead to increased afterload and result in increased left ventricular (LV) wall thickness, most often with minimal change in LV diameter. However, left ventricular hypertrophy (LVH) is more common and more pronounced in PA than in either essential hypertension or in other secondary forms of hypertension, such as pheochromocytoma or Cushing disease. Tissue Doppler studies have also demonstrated a higher prevalence of subclinical abnormalities of systolic and diastolic dysfunction in patients with this condition compared with age-matched patients with essential hypertension.

See Article by Cesari et al

The hormonal effects of aldosterone seem to amplify the hemodynamic effects of aldosterone-related hypertension by changing the composition of the cardiac extracellular matrix, a pathophysiology that has proven to be an important therapeutic target.

Secondary aldosteronism (SA), commonly associated with cirrhosis of the liver but also present in renal vascular disease, often results in higher circulating levels of aldosterone than is seen in PA but is not necessarily associated with hypertension. Specifically in cirrhosis, blood pressure and systemic vascular resistance are low because of obligatory splanchnic dilatation. The cardiac effects of SA in cirrhosis including LV remodeling, proarrhythmia, and reduced contractile reserve, are collectively referred to as cirrhotic cardiomyopathy. The principal hemodynamic finding is that of a high-output state, with higher systolic performance and lower peripheral vascular resistance than healthy controls, but the usual anatomic finding is a normal LV cavity diameter with increased LV wall thickness, similar to that seen in PA.

There is also echocardiographic evidence of diastolic dysfunction in patients with cirrhosis; most series report decreased early mitral inflow velocities and decreased left atrial contribution to ventricular filling. Animal models of PA and SA have demonstrated that myocardial fibrosis occurs in both forms of hyperaldosteronism, whether or not hypertension is present.

With this background, we will examine the interesting article by Cesari et al in this issue of Circulation: Cardiovascular Imaging. Their purpose was to investigate whether PA and SA, which both feature high aldosterone levels, but different hemodynamic loads and plasma renin levels, are associated with different echocardiographic phenotypes. Accordingly they studied a remarkably large number of patients with PA, collected over 23 years from 1992 to 2015, and contrasted their LV structure and function with a large group of patients with SA, primarily because of liver cirrhosis, during the same time period. By contrasting echo findings in PA and SA, the investigators hoped to tease out the effects of aldosterone (elevated in both PA and SA) from those of renin (elevated in SA but suppressed in PA). Furthermore, the investigators purposely excluded SA patients with arterial hypertension.

The authors found a large prevalence of LVH (using LV mass indexed to height based on allometric scaling work of de Simone and colleagues in both PA and SA, but the prevalence of LVH was an order of magnitude higher in PA. These data suggest the possibility that the higher prevalence of LVH was explained, not by pressure load per se, but by the combined effects of renin and of the added work that liver cirrhosis imposes on the LV. In fact the cardiac output and cardiac index in SA were subtly but significantly greater than that found in healthy controls.

Furthermore, the authors attempted to quantify the prevalence of inappropriate LV mass, following work from the Ganau group. Conceptually, inappropriate LV mass attempts to explain the excess LV mass observed when one accounts for variability because of sex, stroke work, and an index of body size. In other words, the higher-than-expected prevalence of LVH in SA cannot be attributed entirely to load or cardiac output, suggesting that activation of the renin–aldosterone–angiotensin system is partially responsible.

This higher prevalence of LVH is associated with a higher than expected prevalence of diastolic dysfunction, when tissue Doppler parameters and E/e' data are analyzed, suggesting that relaxation abnormalities lead to higher filling pressures. It should be noted that most of the diastolic dysfunction that is observed in both SA and PA is of the mild type, suggesting that it is subclinical. In PA, this higher prevalence of mild diastolic dysfunction may be partially related to elevated blood pressure. In SA, by contrast, it might conceivably relate to ultrastructural changes in the LV wall brought about by a profibrotic state. However, these data should be interpreted with some caveats borne in mind. Certainly, the addition of...
left atrial volume or linear dimension and inclusion of pulmonary artery systolic pressure would have provided support for significant diastolic dysfunction, as is suggested in recent guidelines for diastolic function analysis.\(^2\) It also is of concern that over the period of study, the methods used for assessment of diastolic function changed significantly—tissue Doppler, the principal method that we now use to define abnormalities in relaxation did not come into widespread use until the late 1990s. However, despite these limitations, the diastolic function data are plausible and supported by prior research in this area.

The authors also present data that suggest that subclinical systolic dysfunction is also present in PA but not in SA. They use the appropriate index for conditions where the relative wall thickness is higher than normal—fractional shortening at the midwall\(^18,19\)—as well as longitudinal strain and show that these indices are lower in PA than SA or normal controls. However, although it is true that midwall shortening and longitudinal strain are 8% to 13% lower, the systolic load is although it is true that midwall shortening and longitudinal strain also be appropriate for the level of load. Thus as is shown in the Figure, the reduced midwall shortening may be what is expected for the level of load, and not indicate contractile dysfunction.

To summarize, we interpret these data as strongly supporting the notion that in hyperaldosteronism, either primary or secondary, hypertrophic remodeling leads to diastolic dysfunction in the absence of contractile dysfunction. We look forward to further study of this issue with T1 mapping, which can assess collagen content and would assess such ultrastructural changes directly.\(^20\)

**Disclosures**

None.

**References**


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