Will the Lessons From Primary Aldosteronism Change the Treatment of Hypertension and Left Ventricular Hypertrophy?

Richard J. Auchus, Mark H. Drazner

The renin-angiotensin-aldosterone system effectively defends against volume depletion, but in most developed nations, dietary sodium is high, and aldosterone production should be suppressed. The syndrome of primary aldosteronism demonstrates the consequences of autonomous aldosterone production in a sodium-replete society. For many years, primary aldosteronism was thought to be an esoteric disorder only diagnosed by academicians at a handful of institutions worldwide. Conn, Biglieri, Bravo, and others characterized the syndrome and developed diagnostic strategies circa 1960–1980. Most clinicians, however, could not execute these algorithms, and management was unsatisfactory because of poor methods for localizing aldosterone production and limited options for medical management. Interest shifted to other mechanisms of hypertension, but during the last 20 years, the advent of commercial assays for renin and aldosterone, the broader use of adrenal vein sampling, and the development of selective aldosterone antagonists have rejuvenated interest in primary aldosteronism. Furthermore, end-organ damage is more severe in primary aldosteronism than in essential hypertension, and considerable evidence implicates the activation of mineralocorticoid receptors in these tissues as the mechanism.

Implicit in this aldosterone renaissance is the importance of making the diagnosis of primary aldosteronism to allow implementation of tailored therapy. Proteinuria is more prevalent in patients with primary aldosteronism than in those with essential hypertension, and the excess proteinuria largely reverses after treatment with surgery or spironolactone. Thus, the benefits reaped from the detection of primary aldosteronism and the implementation of targeted therapy extend beyond optimal control of blood pressure.

Another malady associated with primary aldosteronism is left ventricular (LV) hypertrophy (LVH). LVH is associated with adverse cardiovascular events and all-cause mortality. Therapy, which leads to regression of LVH in hypertensive subjects, reduces these risks. Despite the importance of LVH as a risk factor and the high prevalence of LVH in primary aldosteronism, the influence of targeted therapy on LVH in this disorder was unknown until now.

In this issue of Hypertension, the group in Udine presents the results of their long-term follow-up of a cohort of hypertensive subjects, including groups with aldosterone-producing adenomas treated with adrenalectomy, idiopathic hyperaldosteronism treated with spironolactone, and essential hypertension treated with drugs other than spironolactone. With a mean follow-up of 6.4 years, systolic blood pressure declined 30 mm Hg in spironolactone-treated patients and 33 mm Hg in adrenalectomized patients. In concert with this reduction in blood pressure, the prevalence of LVH decreased from 38% to 8% among those adrenalectomized and from 30% to 7% among those treated with spironolactone (P < 0.05 for both). In these groups, LV mass indexed to height fell 15% to 20%, from 52.8 to 42.8 g/m² in adrenalectomized patients, and from 51.6 to 43.9 g/m² in spironolactone-treated patients.

The data presented by Catena et al raise several important questions regarding the treatment of primary aldosteronism, as well as the management of hypertension in general. First, in primary aldosteronism, is adrenalectomy equivalent to aldosterone antagonist therapy? In the present study, mean blood pressure declined comparably in the 2 groups at the end of follow-up, within 2 mm Hg. A significant reduction in LV mass was seen with adrenalectomy but not spironolactone after 1 year, but the indexed LV mass at the end of follow-up was only slightly higher in the spironolactone arm, and we are not told whether this difference was statistically significant. Furthermore, it is not known whether these slight differences in blood pressure and LV mass reduction translate into improved clinical outcomes. It is also important to recognize that direct comparison of the adrenalectomized and pharmacologically treated patients may not be justified, because individuals with aldosterone-producing adenomas chosen for adrenalectomy appeared to show greater aldosterone excess than those with idiopathic hyperaldosteronism, as typically observed. Spironolactone effectively treats the hypertension and hypokalemia of aldosterone-producing adenomas, but whether spironolactone would have been equally efficacious in reducing LVH among those with a demonstrated adenoma is uncertain.

The second question concerns the criteria used to diagnose primary aldosteronism. Catena et al relied on a single serum aldosterone measurement after saline infu-
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20 mm Hg. The prevalence of primary aldosteronism in provides impressive systolic blood pressure reductions of serum aldosterone after saline infusion (eg, 20 to 40 pg/mL).

Further complicating this issue is that, in the subjects with primary aldosteronism, the reduction in LV mass was significantly related to the reduction in blood pressure in multivariable analysis. Was the LV mass regression of 32 g (spironolactone) and 44 g (adrenalectomy) observed after a mean of 6.4 years by Cateno et al greater than would be expected for the 30- to 33-mm Hg reduction in blood pressure achieved in this study? In comparison, the Losartan Intervention for Endpoint Reduction Study achieved a 28-mm Hg reduction in systolic blood pressure over 5 years with losartan and other drugs, and this therapy led to a 47-g reduction in LV mass. Overall, it is difficult if not impossible to cleanly dissociate the relative contributions of blood pressure lowering and direct effects of cardiac mineralocorticoid receptor blockade on LV mass regression in the study by Cateno et al.

The fourth important question raised by Catena et al is what role aldosterone antagonism should play in the treatment of hypertension among the broad population of patients with essential hypertension who would have lower values of serum aldosterone after saline infusion (eg, 20 to 40 pg/mL). In resistant hypertension, spironolactone therapy often provides impressive systolic blood pressure reductions of >20 mm Hg. The prevalence of primary aldosteronism in patients with resistant hypertension is ~20%. Yet spironolactone nicely lowers blood pressure in this subgroup, whether individual patients meet the strict criteria for primary aldosteronism or not. Perhaps this distinction also matters little in promoting the regression of LV mass. Therapy with eplerenone has been shown to regress LVH beyond that achieved with converting-enzyme inhibitor therapy alone in patients with essential hypertension.

There is little argument that surgical management of an aldosterone-producing adenoma is a beneficial and gratifying treatment approach, particularly for young patients with severe disease in whom the adverse effects of spironolactone are most bothersome. The debates concerning primary aldosteronism center on the populations who should be screened, the pathogenesis and optimal management of idiopathic hyperaldosteronism, and the distinction of low-renin hypertension from aldosterone excess. Do all patients with hypertension and evidence of end-organ damage benefit from aldosterone antagonist therapy? If so, why do they benefit if aldosterone is low? What would be the result of a study that randomly assigned patients with aldosterone-producing adenomas, idiopathic hyperaldosteronism, and essential hypertension to spironolactone versus other antihypertensives? How will these treatments influence clinical outcomes, including myocardial infarction, stroke, and overall survival in patients with various forms of hypertension?

Already, aldosterone antagonism is an accepted therapy for patients with heart failure and LV systolic dysfunction. The data from Cateno et al strongly support the continued use of therapy targeted against aldosterone excess among those with primary aldosteronism. Their data also highlight the need for additional investigation into whether aldosterone antagonism should be more broadly adopted in essential hypertension, particularly in those patients with LVH. We suspect that aldosterone antagonists will benefit others with hypertensive cardiac hypertrophy given their efficacy in resistant hypertension, even if direct effects from antagonism of mineralocorticoid receptors in the heart are not a major mechanism. Furthermore, until these data are available, it is prudent to normalize the blood pressure in patients with hypertension and LVH by any means possible.

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References


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