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Hypertension

EDITORIAL

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Most physicians tend to think of hyperaldosteronism only in connection with attempting to find patients with primary aldosteronism due to an adrenocortical adenoma, with a view to curing hypertension by adrenalectomy. It is becoming increasingly clear that most primary aldosteronism is due to bilateral adrenocortical hyperplasia, so most cases should be treated medically. Primary aldosteronism due to bilateral hyperplasia is driven by germline variants in at least six genes.[1] It seems likely that true curable unilateral adenomas may be due to somatic mutations. Usually, primary aldosteronism is identified by a high ratio of serum aldosterone to renin (ARR). However, in 2020, Brown et al[2] refined the diagnosis of primary aldosteronism by defining it as excess production of aldosterone, assessed as a 24-hour urinary aldosterone >12 µg. They found that primary aldosteronism was present in 22% of patients with resistant hypertension and was not reliably detected by an ARR.[2]

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In this issue of *Hypertension*, another landmark paper from some of the same authors addresses the issue of excess aldosterone secretion in patients with masked uncontrolled hypertension (MUCH), and its association with excess sympathetic activity.[3] MUCH was defined as controlled office blood pressure (BP <130/80 mm Hg) but uncontrolled out-of-clinic BP by 24-hour ambulatory BP monitoring (awake daytime ambulatory BP ≥130/80 mm Hg). Patients with MUCH and nocturnal hypertension have increased cardiovascular risk. The authors and others had previously reported that patients with MUCH had increased sympathetic activity, assessed by microneurography and laser Doppler flowmetry, compared to those with controlled primary hypertension (CHTN). Increased activity in the sympathetic nerves of the renal artery increases renal production of renin, which in turn results in secondary hyperaldosteronism. This probably underlies the mechanism of action of renal artery denervation. In this study, patients with MUCH had increased sympathetic activity out-of-clinic compared with CHTN.

The authors compared activation of the renin/angiotensin/aldosterone axis in patients with CHTN versus patients identified as having MUCH by ambulatory BP recordings. In clinic, plasma levels of serum aldosterone, plasma renin, and ARR did not differ between MUCH and CHTN. However, outside of clinic 24-hour urinary aldosterone was significantly higher in patients with MUCH and was correlated with higher 24-hour urinary catecholamines and metanephrines. Hyperaldosteronism, defined by a 24-hour urine >12 µg, was found in 34.9% of MUCH versus 16.7% of CHTN (P=0.026), but those patients did not have a high ARR in clinic.

Strengths of this study included a novel hypothesis, careful and appropriate inclusion and exclusion criteria, and assessment of serum creatinine and urea, plasma renin and aldosterone, as well as 24-hour urine collections to assess out-of-clinic urinary sodium, aldosterone secretion, plasma catecholamines, and metanephrines. A weakness, perhaps, was that patients with white-coat hypertension (WCH) and nocturnal nondipping hypertension were not studied.

This paper raises interesting questions about WCH. Although WCH is commonly regarded as benign, it

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is associated with increased sympathetic activity and increased responses to mental stress, progression to sustained hypertension, and increased intima-media thickness.[4] Patients with a greater BP response to mental stress have faster thickening of the myocardium,[5] faster progression of carotid atherosclerosis,[6] and higher plasma catecholamines during the stress task.[7] As reviewed in 2015, WCH is not benign.[4]

Why does this study matter? MUCH is common, particularly in Blacks, older patients, diabetics, and those with chronic kidney disease. With new lower BP targets, MUCH may be as prevalent as 66% of patients with hypertension.[3] A meta-analysis reported that MUCH is associated with increased cardiovascular risk.[8] The findings in this article suggest that aldosterone antagonists, and perhaps β-blockers, which reduce renin release due to sympathetic activity, may be therapies that should be considered to control MUCH.

This article expands our understanding of hyperaldosteronism. High levels of aldosterone are important not only with regard to control of hypertension, but because independent of BP, aldosterone has direct adverse effects on the myocardium and the arteries.[9,10] It is, therefore, important to be more aware of hyperaldosteronism and to consider more use of aldosterone antagonists.

This study also confirms that the important reason to assess ambulatory BP is not for the purpose of identifying WCH so that patients can be spared antihypertensive drugs; it is to identify patients with MUCH and nocturnal nondipping, who are at increased cardiovascular risk, and are missed by office BP readings.[4]

With regard to future directions for research in this field, it would be very interesting to evaluate sympathetic activity and its relationship to excess aldosterone secretion in patients with WCH and nocturnal nondipping hypertension. It would also be interesting to investigate the role of renal denervation, carotid baroreceptor stimulation, and α-adrenergic blockers in MUCH, WCH, and nocturnal nondipping hypertension.

ARTICLE INFORMATION

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