Untangling Essential Hypertension: The Potential Roles of Aldosterone and Atrial Natriuretic Peptide

The prevention and treatment of hypertension is critically important, as high blood pressure is the most common chronic disorder (~1 billion affected individuals) and a leading contributor to death worldwide. In 90% of cases, the underlying cause is unknown; that is, these individuals exhibit “essential” hypertension. It is generally accepted that essential hypertension is a complex polygenic disorder with multiple environmental precipitants.1

That said, significant insight into potential contributors to essential hypertension has been gained from studies of uncommon forms of hypertension. In the 1950s, Conn described patients with adrenal adenomas and excess aldosterone secretion who had elevated blood pressure and hypokalemia.2,3 A growing body of evidence suggests that excess aldosterone secretion, even in the absence of clinically evident adenomas or adrenal hyperplasia, may contribute to hypertension. For instance, it has been shown that plasma aldosterone levels, even within the normal range, are associated with hypertension, metabolic syndrome, and chronic kidney disease.4,5

In this issue of Mayo Clinic Proceedings, the study by Cannone et al6 provides further support to the hypothesis that relative hyperaldosteronemia may contribute to elevated blood pressure in some individuals with essential hypertension. The authors examined 1550 participants from the Rochester Epidemiology Project in whom extensive phenotyping, including measurement of circulating aldosterone concentrations, was performed. The investigators confirmed that individuals with hypertension had higher circulating aldosterone concentrations than did those without hypertension. Furthermore, aldosterone levels increased with the number of antihypertensive medications taken.

The association between aldosterone levels and antihypertensive medication use may reflect worse disease severity in those requiring multiple antihypertensive medications. Individuals taking 3 or more antihypertensive medications had the highest aldosterone levels, although they had similar blood pressures as individuals with untreated hypertension, suggesting more difficult-to-control blood pressure. It is also conceivable that some antihypertensive medications directly promote aldosterone secretion. For instance, the authors noted that individuals taking diuretics had higher aldosterone levels than did those receiving drug regimens that did not include diuretics.

An intriguing additional observation was the finding that circulating aldosterone levels were inversely correlated with atrial natriuretic peptide (ANP) levels in individuals with hypertension. Atrial natriuretic peptide is a cardiac-derived hormone with natriuretic, diuretic, and vasodilatory properties.7 Atrial natriuretic peptide is also an endogenous inhibitor of the renin-angiotensin-aldosterone system, due in part to suppression of aldosterone secretion from the adrenal glands.8,9 The finding that individuals with hypertension with higher aldosterone levels had relatively low ANP levels is unexpected, as the conditions associated with hyperaldosteronemia (high blood pressure and salt retention) are typical triggers for ANP release.
These data raise the possibility that one cause of excess aldosterone is insufficient secretion of natriuretic peptide. In other words, primary deficiencies in ANP production could lead to inadequate suppression of aldosterone secretion. For instance, many previous studies have shown low natriuretic peptide levels in obese and black individuals, two groups with a high prevalence of hypertension. One model of the interaction between ANP and aldosterone in some individuals with hypertension is shown in the Figure.

Cross-sectional comparisons of ANP concentrations in individuals with and without hypertension can be challenging, given the confounding effects of cardiac afterload (a stimulus for ANP release) and medications. Nonetheless, it may be informative to examine ANP levels in individuals with hypertension but not taking any antihypertensive medications. From the data provided, individuals with untreated hypertension appeared to have similar ANP levels (median, 11.8 pg/mL; 33rd-66th percentile, 7.3-15.6 pg/mL) as normotensive individuals (median, 11.1 pg/mL; 33rd-66th percentile, 7.4-15.7 pg/mL), despite substantially higher blood pressure (mean, 152/81 mm Hg vs 129/72 mm Hg). This pattern may be further evidence of a relative natriuretic peptide deficiency.

Overall, the work by Cannone et al. advances our understanding of the interaction between the neurohormonal system and blood pressure. First, it supports that we should consider neurohormonal activity on a continuum rather than in a binary fashion (e.g., normal vs abnormal). Second, it raises the possibility that, in the future, therapies for hypertension could be selected on the basis of the underlying pathophysiology for a given patient. Relatively high aldosterone levels in a patient with hypertension, particularly someone with uncontrolled blood pressure despite several medications, may motivate the earlier use of mineralocorticoid receptor antagonists. The findings of the present study also suggest that natriuretic peptide-directed therapies could be considered in certain settings. Such therapies may be particularly useful for groups previously shown to have a relative natriuretic peptide deficiency, such as obese or black individuals. For example, sacubitril-valsartan augments bioavailable natriuretic peptide by inhibiting the enzymatic breakdown of ANP and B-type natriuretic peptide. This medication is an effective blood pressure-lowering agent, but its current approval is limited to symptomatic heart failure with reduced ejection fraction. Another approach developed by Burnett and colleagues is the use of synthetic natriuretic peptide analogues, which has yielded promising initial results. Such strategies may ultimately improve our ability to treat common forms of hypertension and to prevent its complications.

Giovanni Davogusto, MD
Thomas J. Wang, MD
Deepak K. Gupta, MD
Division of Cardiovascular Medicine
Department of Medicine
Vanderbilt University Medical Center
Nashville, TN

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Correspondence: Address to Thomas J. Wang, MD, Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University Medical Center, 2220 Pierce Avenue, PRB 383, Nashville, TN 37232 (Thomas.j.wang@vanderbilt.edu).

REFERENCES