New Insight Into the Role of Aldosterone/Renin Ratio in Elevated Peripheral and Central Blood Pressure*

Emmanuel L. Bravo, MD, Mohammed A. Rafey, MD, MS
Cleveland, Ohio

The role of plasma aldosterone concentration (PAC) in the pathogenesis of hypertension took an interesting turn a few years ago when several clinical trials claimed a higher prevalence of primary hyperaldosteronism in patients thought to have primary or essential hypertension, particularly those with resistant hypertension (1). A few clinical trials demonstrated that, on the basis of these data, the addition of an aldosterone antagonist to the milieu of antihypertensive medications led to significant reduction in blood pressure (BP) in patients with resistant hypertension (2). The debate has continued among experts in hypertension on the significance of PAC and the aldosterone/renin ratio (ARR) in the control and management of hypertension (3).

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Activation of the renin-angiotensin-aldosterone system is pivotal in regulating and in maintaining arterial BP within the normal range. Plasma renin and aldosterone levels are an example of a tightly coupled enzyme–hormone pair, the individual components of which do not provide sufficient information but when evaluated in combination as a ratio provide additional clues that guide further diagnostic work-up. Renin secretion is regulated by several factors, including renal baroreceptors and the macula densa, activation of which causes release of renin in response to a reduction in renal perfusion pressure and decreased sodium chloride delivery, respectively. Renin catalyzes the rate-limiting step in the production of angiotensin II, an important regulator of aldosterone synthesis by the zona glomerulosa of the adrenal glands. Aldosterone release results in increased sodium re-absorption at the tubular level of the distal nephron and results in BP elevation. By contrast, in primary hyperaldosterone state there is unregulated release of excess aldosterone from adrenal cortex resulting in excessive retention of salt and therefore hypervolemia, which suppresses renin production (4,5).

Although initial research focused more on PAC excess and the primary hyperaldosterone state, 2 recent studies in the past few months have contributed enormous information on this topic and the effect on BP. Alvarez-Madrazo et al. (6) recently demonstrated that ARR is continuously distributed and is affected by several factors, including age, gender, plasma potassium levels, and body mass index and is strongly heritable. Their study also clarified that arbitrary cutoff points for elevated ARR do not identify patients with primary hyperaldosteronism, because normotensive individuals (although in a much lower proportion compared with hypertensive individuals) might have similar elevation in ARR.

A study by Doi et al. (7) in an animal model has provided strong evidence that, in addition to the aldosterone synthase enzyme—universally accepted as a crucial molecule for aldosterone synthesis—2 other enzymes, namely hydroxyl-Delta5-steroid dehydrogenase, 3-beta- and steroid delta-isomerase-6 (HSD3b6) play a significant role in aldosterone synthesis. Disruption of cryptochrome genes that are responsible for HSD3b6 leads to excess aldosterone production and the development of salt-sensitive hypertension in mice. In this study, subsequent treatment with eplerenone, an aldosterone antagonist, resulted in lowering of BP to normotensive levels.

Although the true prevalence of the primary aldosterone state continues to be debated, Tomaschitz et al. (8), in this issue of the Journal, take a step closer in further clarifying the role of PAC excess as well as ARR levels in predicting peripheral and central BP. Measurement of central aortic BP and evaluation of the role of the ARR on this measurement add a unique value to this study.

Tomaschitz et al. (8) performed this study as part of the Ludwigshafen Risk and Cardiovascular Health Study and show a steady and significant relationship between the ARR and increasing peripheral and central BP. Individuals (n =
3,056) with a mean age of 62.5 years, 31.9% of which were women, participated in this study; in addition to measurement of their peripheral BP, their central aortic systolic BP was measured as well, because they were undergoing cardiac catheterization as part of the protocol for the primary study. The PAC and plasma renin concentration were measured in a standardized fashion. A very high proportion of participants (32.8%) were found to have resistant hypertension on the basis of criteria defined by international guidelines. In the highest quartile of ARR, 12.8% of the participants had a ratio of more than 50 pg/ml/pg/ml, an arbitrary threshold considered by some hypertension experts as an indication for further evaluation for primary hyperaldosteronism. Increasingly higher ARR deciles were associated with a steady rise in peripheral and central systolic and diastolic BP and systolic aortic BP. This relationship persisted irrespective of renal and cardiac function (on the basis of cystatin C and N-terminal pro-brain natriuretic peptide levels). In those who were normotensive, this ARR/BP relationship persisted with respect to diastolic BP when the levels were below 80 mm Hg. An interesting finding was that the elevated levels of plasma renin concentration at lower deciles of ARR (10-fold higher in ARR decile 1 compared with ARR decile 10), although associated with high angiotensin II levels, did not translate to high aldosterone levels, even when adjusted for antihypertensive medications and cardiac and renal dysfunction.

The authors deserve to be commended on moving beyond discussion on the relevance of the level of ARR in diagnosis of primary hyperaldosteronism to evaluating the relationship of ARR with BP levels. This study clearly identifies the role of increasing ARR in the pathogenesis of uncontrolled hypertension. It is also the first study that addresses the relationship of ARR with central BP, a parameter that is being increasingly accepted as the true BP experienced by target organs including the heart, brain, and kidney. Evidence from recent clinical trials is accumulating that demonstrates that not only is central BP a better predictor of cardiovascular outcomes but that, with treatment, a lower central BP independent of peripheral BP is likely associated with better outcomes (9,10).

Furthermore, data from this study seem to justify a wider and more routine use of aldosterone antagonists in patients with elevated BP, to not only improve BP control but also negate the deleterious effects of excess aldosterone on the vasculature in general and target organs in particular.

One important limitation of the study is its reliance on BPs (peripheral and central) measured in the acute setting when the patients were undergoing cardiac catheterization. Clear evidence exists that BP is a dynamic entity and that BP measurements performed in less than ideal settings as outlined by national guidelines might not represent true BP. As the authors have emphasized, the cross-sectional design of this observational study precludes conclusions with regard to causality. However, intervention studies with a specific aldosterone antagonist might provide some indication of causality.

Elevated ARR and PAC are associated with elevated peripheral and central BPs. It is important for clinicians—rather than dwelling on the controversy of whether a high ARR signifies the primary hyperaldosterone state—to recognize that an elevated ARR probably signifies an excess in PAC and that addition of an aldosterone antagonist could both improve BP control and optimize measures of arterial stiffness as well.

Reprint requests and correspondence: Dr. Emmanuel L. Bravo, Department of Nephrology and Hypertension, Glickman Urology and Kidney Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue Q-07, Cleveland, Ohio 44195. E-mail: bravoe@ccf.org.

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