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COMMENTARY

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Bypass of confirmatory tests for case detection of primary aldosteronism in leaner patients?

Konstantinos Stavropoulos MD[1] | Konstantinos P. Imprialos MD[1] | Michael Doumas MD, PhD[2]

[1]Second Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2]VAMC and George Washington University, Washington, DC, USA

Correspondence
Konstantinos Stavropoulos, MD, Second Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece.
Email: konvstavropoulos@hotmail.com

1 | INTRODUCTION

Primary aldosteronism (PA) is the most common cause of secondary hypertension.[1] It is well established that patients with this clinical syndrome have greater target organ damage and cardiovascular morbidity and mortality compared with patients with essential hypertension with equal blood pressure levels.[2] The US Endocrinology Society guidelines suggest that PA affects 6.1% of the hypertensive population and acknowledge that the prevalence is even higher in specific subgroups.[3] Particularly, PA becomes more prevalent in the settings of severe and drug-resistant hypertension (approximately 12% and 11.5%, respectively).[4,5] However, the exact prevalence of this clinical syndrome is still debatable with contradictory findings deriving from several epidemiological studies.[6] A recently published meta-regression analysis of 39 studies that evaluated the prevalence of PA among patients with hypertension[7] revealed high heterogeneity between the included studies. In 36 614 patients from referral centers and 5896 participants from primary care, the prevalence of PA varied from 1% to 29.8% and 3.2% to 12.7%, respectively. Of great importance, it was noted that the outcomes were independently affected by both the method of patient selection (P<.001) and the type of screening (P=.02).

The diagnostic algorithm follows the typical detection of metabolic disorders: screening, confirmation, and localization.[1] Patients with severe hypertension, hypokalemia (spontaneous or drug-induced), drug-resistant hypertension, presence of hypertension before 40 years of age, adrenal incidentaloma, and/or obstructive sleep apnea raise the clinical suspicion for PA and should undergo a screening procedure.[3] The calculation of plasma aldosterone to plasma renin activity ratio (ARR) is the preferable screening method for PA. An ARR >30 (or >20 in some centers) along with increased aldosterone levels (>15 mg/dL) could be indicative of PA but not confirmatory. Subsequently, a confirmatory test (intravenous saline infusion, fludrocortisone test, oral sodium load, or captopril test) needs to be conducted for the confirmation of PA.[1] In brief, failure of suppression in aldosterone levels confirms the autonomous production of this steroid hormone and suggests the presence of PA. The localization of the disease (via adrenal venous sampling, adrenal imaging, or nuclear imaging) is of paramount importance, since it defines the proper therapeutic decision. Adrenal venous sampling is the gold standard method for the accurate localization of PA. In the case of a unilateral adenoma, surgical excision of the affected adrenal gland should be considered, whereas in bilateral adrenal hyperplasia, a mineralocorticoid receptor antagonist should be administered.[3]

The introduction of the ARR as a screening test for PA significantly improved the detection of the disease.[8] However, the ARR carries inherent limitations that need to be considered. First, the ARR can be found in values >30 in patients without PA as in the case of patients with low plasma renin activity, which is found in approximately 30% of patients with essential hypertension, and becomes more common in older hypertensive individuals and in the setting of drug-resistant hypertension.[5,9] Second, the majority of antihypertensive drugs affect the ARR.[10] In brief, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and mineralocorticoid receptor antagonists decrease the ARR by elevating renin levels and can lead to false-negative results. On the other hand, β-blockers and centrally acting agents suppress renin synthesis, thus increasing the ARR and result in false-positive results. Only α-blockers and nondihydropyridine calcium antagonists have a neutral or minimal effect on the ARR and the replacement of prior antihypertensive treatment with these agents is indicated 2 weeks (6 weeks for mineralocorticoid receptor antagonists) before screening; however, this is not always feasible in everyday clinical practice. Third, it is well established that both plasma

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aldosterone and renin levels are influenced by the posture of the individual, exhibiting higher values in patients in the upright position and lower values in patients in the supine position.[11] Last, time of sampling, potassium levels, and salt intake exert significant effects on the ARR. Low sodium intake could upregulate renin excretion, decreasing the ARR, which, in turn, leads to a false exclusion of PA. Therefore, a liberal sodium diet should be encouraged by the physician prior to the screening test.

Given that the abovementioned conditions could lead to a false-positive result in up to half of screened patients,[1] the confirmation of the disease is of paramount importance. Fludrocortisone seems to be the gold standard test for the confirmation of PA and includes 4-day administration of 0.1 mg fludrocortisone every 6 hours, along with sodium and potassium supplementation.[1] However, the use of this mineralocorticoid-mimetic agent increases the risk of hypokalemia and requires close monitoring and hospitalization. The intravenous infusion of 2 L of 0.9% NaCl is the most widely used confirmatory test. However, caution needs to be taken with the presence of chronic kidney and cardiovascular disease because of the elevated risk for cardiorespiratory complications. Similar risks are presented with the captopril test. Oral sodium load includes the risk of inappropriate 24-hour urine collection and overlook of diagnosis in the setting of chronic kidney disease. Collectively, despite research efforts to simplify the diagnostic algorithm of PA and to reduce unnecessary tests,[12] detection of the disease remains tricky, time consuming, and expensive, and needs to be performed by experienced physicians in specialized centers.

In the current issue of the *Journal*, Tirosh and colleagues[13] conducted a prospective observational study of 59 patients with highly suspected PA to assess the impact of body mass index (BMI) on the diagnostic accuracy of the disease. Participants were classified into five subgroups according to BMI: (1) <25 kg/m^2, (2) 25–29.9 kg/m^2, (3) 30–34.9 kg/m^2, (4) 35–39.9 kg/m^2, and (5) >40 kg/m^2. Forty-six individuals underwent a saline suppression test, oral salt loading test, or both, and PA was identified in 29 of them (63%). Positive confirmatory test results were found in 22 of 28 patients with an ARR ≥20, whereas only 7 of 31 patients had a positive test result with an ARR <20. Patients with an ARR ≥20 had a significantly higher systolic blood pressure compared with patients with lower ARR levels (142±16 vs 131±18; *P*=.02), but no difference was observed in diastolic blood pressure and BMI. Also, BMI was found to have a significant U-shaped correlation with plasma aldosterone concentration (*r*=.5, *P*=.003), plasma renin activity (*r*=.6 [*P*=.01] for an ARR ≥20 and *r*=.2 [*P*=.02] for an ARR <20), suppressed urinary aldosterone, and suppressed plasma aldosterone concentration (*r*=.11 and *r*=.25, respectively). More importantly, in participants with PA, BMI was also found to have a U-shaped correlation with plasma aldosterone concentration when measured in patients either in the supine position or after suppression test (*r*=.6 [*P*=.004] and *r*=.6 [*P*=.05], respectively). No correlation between BMI and plasma renin activity was observed, probably because of the commonly undetectable plasma renin activity levels that were found in 79% of participants with PA. Finally, the receiver operating characteristic curve for participants with BMI <30 kg/m^2 suggested excellent accuracy of the ARR for case detection of PA (area under the receiver operating characteristic curve, 0.970), whereas lower accuracy was presented in obese individuals (area under the receiver operating characteristic curve, 0.621). Specifically, in 17 patients with BMI <30 kg/m^2, the ARR had a 100% positive predictive value in both the 20 and 30 cutoff values. The use of an ARR <20 cutoff in this BMI subgroup was associated with a greater negative predictive value compared with ARR <30 (75% and 60%, respectively). Also, the use of an ARR <20 compared with an ARR <30 had superior negative and positive predictive value in obese participants (58.3% and 76.5%, respectively), as well as in the total cohort (65% and 84.6%, respectively).

Tirosh and colleagues conducted a clinically meaningful study that provides significant data for the diagnostic approach of PA. From a clinical point of view, the most important finding is the 100% accuracy of the ARR in the case detection of PA in patients with BMI <30 kg/m^2. A finding that (if confirmed by larger studies from other groups) could potentially lead to the bypass of confirmatory testing in nonobese patients. Furthermore, an ARR cutoff point of 20 could be preferable for the exclusion of PA, as it was observed to have a better negative predictive value, in all BMI subgroups. The confirmation and adoption of the abovementioned finding could provide significant benefits in the diagnosis of PA by reducing time and cost and simplifying the diagnostic approach. Moreover, the pathophysiological explanation of the U-shaped correlation between BMI and plasma aldosterone concentration seems interesting.

The most important strengths of the study by Tirosh and coworkers are the prospective design, the appropriate selection and diagnostic approach of the participants, and the conduction of the study by a National Institutes of Health group that is highly specialized in PA and is of the highest scientific standards. The most important limitations of the study are the small sample of participants and the absence of a control group of patients with essential hypertension with equal values of BMI. Moreover, the measurement of 24-hour urinary sodium excretion only in patients who underwent oral sodium load but not saline intravenous infusion seems to be another limitation of the study. Even if a high-sodium diet that is required for the proper evaluation of ARR was encouraged by the researchers, this has to be proved by 24-hour urinary measurements.

2 | CONCLUSIONS

Tirosh and colleagues conducted a clinically meaningful study. Future randomized clinical studies need to investigate whether the calculation of ARR could confirm the diagnosis of PA in leaner patients. The design and conduction of relevant randomized clinical studies could unveil novel perspectives in the debatable field of who and how to screen for PA.

CONFLICTS OF INTEREST

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