RESEARCH LETTER

Withdrawal of all medications is not necessary for accurate screening for primary aldosteronism: preliminary results

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Introduction Primary aldosteronism (PA) is considered the most common form of hormonal hypertension. It is often unrecognized and substantially contributes to the ongoing epidemics of poorly controlled blood pressure. Approximately 10% of unselected hypertensive patients show PA, with incidence ranging from 5.8% to 30%, depending on the population screened.[1,2] In PA, autonomous aldosterone secretion is associated with an escalating risk of cardiometabolic complications which by far exceeds the risk carried by matched patients with primary hypertension.[3]

According to the current guidelines, at least half of hypertensive patients should be screened for PA.[4] However, the rates of PA detection are very low.[5] The role of primary care, including general and internal medicine, is irreplaceable. Although an early diagnosis at a younger age is the most beneficial scenario, patients with PA are generally diagnosed several years after the onset of hypertensive disease.

Complicated and unrealistic diagnostic procedures are very important causes of this situation and withdrawal of antihypertensive drugs prior to screening is at the top of the list. Although the 2016 Endocrine Society (ES) guidelines allow the calculation of aldosterone-to-renin ratio (ARR) in patients during an ongoing therapy, interpretation of these ARRs requires some experience and knowledge about how particular medications influence the renin-angiotensin-aldosterone system. Simple, practical rules that could be widely applied by general practitioners are missing.[4] Therefore, this study aimed to evaluate the diagnostic accuracy of ARR and its components in an unprepared, heterogenic population at risk of PA and to elucidate if uniform cutoff values can be used with satisfactory outcomes.

Methods **Patients** This study was conducted at the Department of Endocrinology, Center of Postgraduate Medical Education in Warsaw, Poland, and approved by the local Ethics Committee. Participants were recruited from among those referred to the department for evaluation of a suspected adrenal pathology associated with hypertension and/or hypokalemia between April 2017 and January 2020. Informed consent was obtained from all participants prior to inclusion in the study.

Hormonal testing Serum aldosterone and direct renin concentrations (DRC) were measured by chemiluminescence immunoassay and ARRs (precisely, aldosterone-to–direct renin ratios [ADRRs]) were calculated. Basal biochemical parameters were also evaluated. Patients were allowed to take their usual medications, excluding only mineralocorticoid antagonists (MRAs), which were withdrawn at least 4 weeks prior to the first screening test. Patients were then further evaluated after drug withdrawal and/or modification, until the final diagnosis. Medical adjustments were followed by another ARR test(s). The seated saline infusion test was used as a confirmatory tool in patients with positive or inconclusive screening test results.

Statistical analysis The analyses were performed using Stata 13.1 software (StataCorp LLC, College Station, Texas, United States). The normality and Barlett's tests were used to determine the distribution of variables and the equality of variances. Non-normally distributed data were compared using the Mann–Whitney test and data following normal distribution were compared using the *t* test for equal variances. Pearson χ^2 or Fisher exact test was applied to compare the numbers and classes of antihypertensive drugs. Sensitivity and specificity for different cutoff values of ADRR, aldosterone, and renin were plotted as receiver operating characteristic (ROC) curves. Medcalc 19.7 (MedCalc Software Ltd, Ostend, Belgium) was used to determine the predicted

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optimal cutoff levels (defined as those with maximum Youden Index) and to compare the ROC curves according to DeLong's method (1988). For statistical analyses, DRC values below the analytical sensitivity limit of the assay were rounded up to 0.5 μIU/ml. A *P* value of less than 0.05 was considered significant.

Results A total of 100 adult patients were included in the study cohort: 20 in the PA group (5 with aldosteronoma and 15 with bilateral adrenal hyperplasia) and 80 in the control group. Hypertension was present in 95% of the study population. Almost 90% of hypertensive patients were treated with antihypertensive drugs (from all main drug classes, see Supplementary material, *Table S1*). The remaining patients were evaluated for unexplained refractory hypokalemia. Overall, 65 patients had adrenal lesions present in abdominal computed tomography (bilateral [17%] or unilateral [48%]). The groups were comparable in terms of age, sex, body mass index, duration and severity of hypertension, adrenal lesions found in computed tomography, and the number of drugs taken (TABLE 1).

Diagnostic performance of aldosterone-to–direct renin ratio and direct renin concentration The predicted optimal screening cutoff level of ADRR was greater than or equal to 2 ng/dl/μIU/ml and it was characterized by a sensitivity of 95% and a negative predictive value of 98.6% (area under the curve [AUC] = 0.938). After individualized preparation of each patient, the optimal cutoff value of ADRR did not change, but the performance improved (AUC = 0.966). Optimal screening cutoff level of DRC was below or equal to 10.47 μIU/ml and it had a sensitivity and a negative predictive value of 95% and 98.3%, respectively (AUC = 0.891) (Supplementary material, *Figure S1*). Serum aldosterone level was not accurate enough as a diagnostic tool (AUC = 0.757).

Discussion Screening for PA is rarely proposed to hypertensive patients. Clinicians are discouraged by the recommended preparations, mainly the need for drug wash-out or modifications prior to testing. It is not clear whether these adjustments should really be pursued and, if yes, to what extent. In our study, ADRR, both before and after individualized preparation of patients (AUC, 0.938 vs 0.966, respectively, *P* = 0.14), was almost as reliable as the "standard" test with most high-tech laboratory methods. For comparison, in a recent study by Guo et al,[6] the ADRR, ARR based on plasma renin activity (PRA), and the latest aldosterone-to–angiotensin II ratio had AUC values of 0.976, 0.958, and 0.963, respectively. The results of our study support the recently suggested, simplified approach to PA.[2] With the aim to "maximize the opportunity to test before it is lost," no preparations should be done before ARR evaluation. This approach, as well as the new definition of PA, are based on the conception that aldosterone excess is clinically insignificant if renin is not suppressed and can be easily increased by different stimuli (like drugs). The presence of renin suppression is also considered the most important indicator of cardiovascular risk in hypertensive patients as well as the predictor of the efficacy of MRA treatment in hypertension.[3] Therefore, if drugs such as angiotensin-converting enzyme inhibitors or thiazides can increase renin concentration, the diagnosis of PA is improbable. Conversely, β-blockers tend to suppress renin, but at the same time they usually lower aldosterone levels; therefore, in patients taking β-blockers PA can be easily excluded even if ADRR is slightly elevated. The most controversial issue in the early phase of the diagnostic procedure for PA is the continuation of treatment with MRAs (especially if they are used in high doses), as renin escape represents the basis of their therapeutic use. So, in our study we decided to withdraw MRAs in all participants prior to inclusion in the study. The questions of whether therapy including MRAs would influence the results of PA screening and which doses of MRA could be permitted require future studies.

Renin itself (as DRC or PRA) has just recently been proposed by Funder[7] as the determinative or even sole component of the screening procedure. He suggested the "traditionally accepted" PRA value of 1 ng/ml/h as the cutoff level; however, the threshold for DRC is not clear. The 2016 ES guidelines[4] list 2 conversion factors of PRC to DRC: 8.2 and 12 μIU/ml (for automated assays). In a recent review by Vaidya et al,[2] DRC values below 5 to 8.2 μIU/ml are considered "suppressed." In our study, the DRC cutoff level of 10.47 μIU/ml was optimal. Despite the long-standing use of ARR, the exact cutoff value of ADRR is similarly problematic. Previous studies on the interpretation of ADRRs during multidrug therapy have only suggested that cutoff values lower than the "standard" ones should be used.[8-10] However, the latest 2020 Consensus Statement[11] proposed lower cutoff values for general use. The range of ADRR values between 1.12 and 2.7 ng/dl/μIU/ml was suggested for chemiluminescent assay instead of the range between 2.4 and 4.9 ng/dl/μIU/ml, previously recommended in the 2016 ES guidelines.[4] This is consistent with the results of our study, since the ADRR cutoff value of 2 ng/dl/μIU/ml was found optimal for PA detection, independently of the "drug status."

In our study, hypokalemia was very indicative of PA (Supplementary material, *Table S2*). The measurement of not only serum electrolytes, but also their urinary excretion may be of value in patients suspected of PA. Recent studies on the use of spot urine samples instead of 24-hour urine collection fit in with the philosophy of simplifying the diagnostic procedures.[12]

Our study has several limitations. It was conducted in a single endocrinological center and the study cohort was relatively small. The prevalence of patients with adrenal lesions was high;

TABLE 1 Clinical and biochemical characteristics of the study cohort

Variable	All participants (n = 100)	PA (n = 20)	Control group (n = 80)	*P* value
Age, y	56 (40–63)	57.5 (46.5–61)	55.5 (40–63)	0.93
Female sex, n (%)	64 (64)	11 (55)	53 (66.2)	0.35
BMI, kg/m^2	28.42 (4.39)	28.42 (5.31)	28.42 (4.6)	0.997
History of hypokalemia, n (%)	40 (40)	15 (75)	25 (31.2)	<0.001
Spontaneous hypokalemia, n (%)	24 (24)	12 (60)	12 (15)	<0.001
Diuretic-induced hypokalemia, n (%)	16 (16)	3 (15)	13 (16.2)	0.24
Patients with adrenal lesions, n (%)	65 (65)	15 (75)	50 (67.5)	0.43
Serum Na^+, mmol/l	141.43 (2.02)	142.24 (1.86)	141.22 (2.02)	0.04
Serum K^+, mmol/l	4.2 (0.43)	3.84 (0.09)	4.29 (0.04)	<0.001
DRC, μIU/ml	16.13 (3.89–50.98)	2.87 (0.66–5.76)	20.85 (8.97–61.63)	<0.001
Aldosterone, ng/dl	12.2 (8.67–18.75)	18.75 (13.25–24.3)	11.3 (7.27–16)	<0.001
ADRR, ng/dl/μIU/ml	0.64 (0.22–2.62)	5.08 (3.33–20.74)	0.45 (0.2–1.12)	<0.001
ADRR after patient's preparation, ng/dl/μIU/ml	0.69 (0.22–2.57)	6.03 (3.98–19)	0.48 (0.19–0.98)	<0.001
SST[a], n (%)	27 (27)	20 (100)	7 (8.7)	-
Aldosterone after SST[a], ng/dl	11.6 (5.9–14.8)	14.35 (9.38–17.7)	4.19 (3.4–5.61)	<0.001
	Hypertensives (n = 95)	PA (n = 19)	Control group (n = 76)	*P* value
Duration of hypertension, y	7 (2–14)	10 (4.5–17.5)	6.5 (1.2–12)	0.99
Age of hypertension onset, y	43 (35–55)	42 (38–48)	44.5 (33–55)	0.46
Uncontrolled BP, n (%)	66 (69.5)	17 (89.5)	49 (64.5)	0.049
Mean systolic BP on admission, mm Hg	145.89 (21.15)	148.95 (17.2)	145.13 (22.06)	0.48
Number of antihypertensive drugs at the time of screening	2 (1–3)	2 (1–3)	2 (1–3)	0.83
MRA withdrawal, n (%)	17 (17.9)	5 (26.3)	12 (15.8)	0.32

Data are presented as mean (SD) or median (interquartile range) unless otherwise indicated.

a Seated saline infusion test was used for a confirmation of the primary aldosteronism diagnosis, with aldosterone level >6 ng/dl after SST regarded as a positive result

Abbreviations: ADRR, aldosterone-to–direct renin ratio; BMI, body mass index; BP, blood pressure; DRC, direct renin concentration; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism; SST, seated saline infusion test

however, patients with hypertension and adrenal pathology were not at increased risk of PA diagnosis, provided they were not hypokalemic (Supplementary material, *Table S2*). After the first ADRR evaluation, the diagnostic protocol was not uniform for all patients. Patients with very low aldosterone levels (<6 ng/dl in recumbent position), DRC exceeding 15 μIU/ml and "standard" ADRR lower than 1 ng/dl/μIU/ml did not undergo confirmatory testing, because PA was improbable in such circumstances anyway. The strength of our study is the thorough radiological and hormonal evaluation of the patients, including all hormonal axes. This may partly explain the high detection rate of inactive adrenal abnormalities in the cohort. All patients underwent follow-up, including subtype diagnosis and adrenalectomy, if indicated.

In conclusion, ADRR greater than or equal to 2 ng/dl/μIU/ml and/or DRC not exceeding 10.47 μIU/ml showed a high sensitivity and ADRR lower than 2 ng/dl/μIU/ml and/or DRC greater than 10.47 μIU/ml showed a high negative predictive value in the first-step testing for PA, regardless of the ongoing treatment. Such screening protocol is particularly advantageous, because it is simple and can be performed immediately. In our study, 70% of patients without PA could have been spared from further evaluation on the basis of each of the suggested screening tests. Both tests can be used as primary/ambulatory care screening tools to select patients who are at the greatest risk of PA confirmation and could benefit from further diagnostic work-up in specialized centers.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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