Tijana Lalić

INFLUENCE OF ANTIHYPERTENSIVE THERAPY, SODIUM INTAKE AND THE CONCENTRATION OF POTASSIUM IN PLASMA ON CONCENTRATION OF ALDOSTERONE AND PLASMA RENIN ACTIVITY

ABSTRACT: Introduction: Primary aldosteronism (PA) is a group of disorders which are characterized by inadequate and non-suppressible production of aldosterone. The prevalence of PA is increasing in hypertensive population. The golden standard of screening for primary aldosteronism, determination of aldosterone/plasma renin activity (ARR), is influenced by numerous exogenous and endogenous factors. Testing cannot always be conducted under optimal conditions.

Objective: To determine influence of antihypertensive drugs and concentrations of potassium and sodium in blood and urine on values of aldosterone and plasma renin activity.

Methods: In this retrospective study, we analyzed medical reports of patients admitted to Department of thyroid gland disease in the period from 2009 to 2011, with increased risk for primary aldosteronism. Body weight and height, sodium and potassium in serum and urine, plasma aldosterone concentrations and plasma renin activity, data on medicines and comorbidity were analyzed in all patients. In processing data, statistical methods descriptive analysis, Student T test and univariate linear regression were applied.

Result: Of 137 patients, there were more patients with resistant hypertension (53,28%) than with adrenal tumors (46,72%). Most patients used calcium channel blockers. Treatment with alpha blockers and calcium channel blockers does not influence ARR. Beta blockers and ACE inhibitors can influence ARR and diuretics and vasodilatators have definite influence. Diabetes mellitus can have higher risk of false negative results. Urine sodium excretion is significantly correlated with plasma aldosteron and serum potassium. Plasma aldosteron and PRA are significantly correlated with concentrations of electrolites in urine.

Conclusion: Increased prevalence of primary aldosteronism necessitates need for accurate and better diagnostics.

Key words: primary aldosteronism drugs sodium potassium correlations

INTRODUCTION

Primary aldosteronism (PA) is a group of disorders in which aldosterone production is inappropriately high, relatively autonomous and non-suppressible by sodium loading (2). The most important disorders are aldosterone producing adenoma (APA), unilateral or bilateral adrenal hyperplasia (UAH and BAH, IHA), glucocorticoid-remediable aldosteronism (GRA) and aldosterone producing adrenal carcinoma (1, 2). Since the Conn first described, in 1954, the clinical syndrome of hypertension, hypokalemia and metabolic alkalosis as a result of the autonomous production of aldosterone from the adrenal adenoma, numerous studies are trying to determine the prevalence of this disorder (2). Primary aldosteronism was previously considered rare and the diagnosis was not practically possible without hypokalemia. Today, more than half of patients with PA have normal potassium (1). Recent studies point to the increasing prevalence - more than 10% of hypertensive patients, and from 5 to 20% in the case of type 2 diabetes and resistant hypertension (3). Primary aldosteronism is basically 36.4% of cases of hypertension with adrenal incidentaloma and 52% of adrenal incidentalomas, detected by examining the hypertension (4). It is estimated that APA makes 30% and BAH about 60% of cases of primary aldosteronism.

Clinical characteristics of aldosteronism are nonspecific and variable. They depend on the size of excess aldosterone and comorbidity. Hyperaldosteronism is usually indicated by hypertension, hypokalemia, edema, and hypervolaemia without metabolic alkalosis. Hypertension, frequently diastolic, can be severe and refractory to standard antihypertensive therapy. In BAH, patients may have a slight increase in blood pressure due to hypertension is not a *sine qua non* hyperaldosteronism diagnosis. Hypokalemia, if present, may cause muscle weakness, cramps, and paresthesias. Hypernatremia is rare. It is the consequence of sodium retention, polyuria and osmosat reset. Increased sodium retention follows starting increased natriuresis, a phenomenon known as a escape of aldosterone activity (*escape of aldosterone action)*. The result is activation of atrial natriuretic peptide. Metabolic alkalosis and increased serum bicarbonate, is usually mild, with no significant consequences and may pass unnoticed. Increased concentrations of aldosterone have direct toxic effects on the cardiovascular system and kidneys, independent of hypertension. Patients with PA may have left ventricular hypertrophy, impaired diastolic and endothelial function, carotid artery intima thickened, increased albuminuria and reduced intrarenal resistance, compared to the same level of increase in blood pressure in essential hypertension.

Hyperaldosteronism is associated with an increased risk of myocardial infarction and stroke. There is evidence of links between aldosteronism and metabolic syndrome, or insulin resistance and hyperglycemia.

Determination of aldosterone plasma renin activity ratio (ARR or postural aldosterone/PRA ratio) is a screening for primary aldosteronism in high risk groups. *Clinical guide of endocrine society for the detection, diagnosis and treatment of primary aldosteronism* defines high risk groups: 1) patients with moderate to severe hypertension (160-179/100-109mmHg - moderate,> 180mmHg /> 110mmHg - severe), 2) resistant hypertension (blood pressure > 140/90mmHg on therapy with three and / or more antihypertensive drugs), 3) hypertensive patients with spontaneous or diuretic-induced hypokalemia, 4) hypertension and accidentally discovered adrenal adenoma (incidentaloma), 5) hypertension and family history of early development of hypertension and cerebrovascular events before the age of 40, due to increased suspicion of GKA.

Many factors determine the secretion of aldosterone and/or renin and may affect the value of the ARR in terms of false positive and false negative results. ARR value is influenced by: age, posture, time of day, diet, medications, associated conditions and diseases. Older than 65 years have much lower values of renin compared to aldosterone which leads to a greater number of false-positive ARR. Sampling in tests of PA should be given in hospital, the morning after eight hours of lying in bed, two hours of sitting, standing and walking and sitting 5-15 minutes. A noteworthy fact about salt intake, because of restrictions, leads to a significant release of renin and aldosterone, or reduction in ARR and false negative results, while excessive intake has the opposite effect. Hypokalemia can lead to more false-negative ARR values , mainly influenced by the decrease in aldosterone, while excessive intake of potassium gives a possibility for false-positive results. It is necessary to know on which therapy patients and whether the test was conducted under less than ideal conditions. Of particular importance are the antihypertensive drugs, especially mineralocorticoid antagonists (MRA), and antidepressants, nonsteroidal anti-inflammatory drugs and preparations of estrogen (oral contraceptives, hormone replacement therapy). Beta-adrenergic blockers and central alpha agonists (clonidine, methyl-dopa) increase the possibility of false positive results by increasing the value of the ARR. Angiotensin converting enzyme inhibitors, diuretics sparing potassium (amiloride and triamterene), angiotensin receptor blockers and dihydropyridine calcium channel blockers, in their effects on the ARR, give the possibility of false negative results. In order to reduce the influence of drugs, their discontinuance is advised (*washout period*), for two weeks, or four to six weeks in the case spironalakton, eplerenone and diuretics. Reversal of antihypertensive drugs can be in mild hypertension, but can be dangerous in the event of severe hypertension. Drugs that have a minimal effect on the ARR and that can be used to control blood pressure during the screening and confirmation

tests of PA are: nondihydropyridine calcium channel antagonists, alpha adrenergic blockers (prazosin, doxazosin, terazosin) and hydralazine. Some other studies show that testing is possible when the blood pressure control is achieved through the use of fosinopril. Nonsteroid antyreumatics increase the value of the ARR and the number of false-positive cases of PA. In the case of renin inhibitors and oral contraceptives it is important whether to determine the direct renin concentration (DRC) in plasma or PRA. Both groups influence on increase of the values of DRC and false positive cases of PA. In addition, it was observed that the components of the renin-angiotensin system have the highest levels when estrogen concentrations are highest during the luteal phase of the menstrual cycle. Selective serotonin reuptake inhibitors with normotensive men can significantly lower the ARR, either the PRA or DCR is determined. Aldosterone and renin is influenced by renal failure, renovascular hypertension, diabetes and pregnancy.

Because of the lack of uniformity of diagnostic protocols and assay for measurement of aldosterone and PRA, there is variability of normal values for the ARR. Some authors suggest that those values should be between 20 and 100, while for others, acceptable range is 20 to 40. Some believe that it is essential that higher levels of aldosterone, > 15ng/dl, in addition to increased ARR, while others are against limit values of aldosterone. Ratio greater than 20 indicates a possible PA. ARR greater than 30, in conditions where aldosterone > 15ng/dl, has sensitivity of 90% and specificity of 91% for the diagnosis of PA, but ratio greater than 50 confirms the diagnosis. In the range between 25-35 there is a gray zone in which there is a higher incidence of false positive and negative results. Three repeated elevated ARR results require further confirmation or exclusion of autonomous aldosterone secretion by applying one of four tests: oral sodium load, acute intravascular volume expansion with isotonic saline solution, fludrocortisone and captopril test.

Once the biochemical diagnosis of PA is confirmed, further research is necessary to uncover the etiology of this disorder. In determining the etiology, the important role have radiological surveys and visualization methods. Serial sections at 3mm spiral CT are the best method for radiological visualization of the adrenal tumor and allow identification of the size of 5mm tumor. It is recommended that all patients with PA undergo CT of the adrenal gland that would, among other things, exclude presence of adrenocortical carcinoma. Magnetic resonance imaging of renal glands has no additional benefits in diagnosis. Adrenocortical scintigraphy with NP-59 (131I-6-B-19-jodomethyl norcholesterol) differentiate APA from IHA. Adrenal venous sampling is the gold standard for lateralization of aldosterone hypersecretion and differentiation of unilateral from bilateral PA variants. That was the most sensitive method for diagnosing IHA and APA. It is used when biochemical and radiological tests have not yielded conclusive results. The criteria for determining the lateralization of aldosterone hypersecretion depend whether sampling was conducted during the ACTH stimula-

tion. Cortisol corrected aldosterone ratio between the two sides continued during the ACTH stimulation, which is higher than 4:1 indicates on unilateral aldosterone excess, while the ratio lower than 3:1 match bilateral hyperplasia. With these reference values, adrenal vein sampling has a 95% sensitivity and 100% specificity in the diagnosis of unilateral aldosterone excess. Values between mentioned may indicate on unilateral or bilateral adrenal involvement. Without ACTH stimulation, lateralization ratio 2:1 is diagnostic for unilateral excess. In the differential diagnosis of PA, the most commonly performed test is postural response to aldosterone and PRA. It is desirable that the test is repeated two or three times. In the early beginning, before 20 years of age, a certified PA, or with a family history of PA and/or stroke at an early age, genetic testing is recommended at GKA.

Unilateral laparoscopic adrenalectomy is the method of choice for the treatment of patients with confirmed PA, either APA or UAH. Pharmacological treatment of mineralocorticoid receptor antagonists is advised for patients who cannot be, or refuse to be operated on. It is the treatment of choice in cases of IHA, bilateral APA and GKA. It is possible to use standard antihypertensive drugs. Patients with suspected PA it is not always possible to discontinue the use of antihypertensive drugs in the corresponding period and it is not known on what kind of diet they are. Patients with PA have a higher incidence of cardiovascular, cerebrovascular and renal complications. PA is the most common specifically treated and potentially curable cause of secondary hypertension. Determining the impact of various factors on the values of aldosterone and PRA has diagnostic significance. Identifying patients with whom the factors led to the changes of plasma aldosterone and PRA activities, the diagnosis of aldosteronism is improved.

OBJECTIVE

The aim of this study was to determine the impact of antihypertensive drugs and the concentration of potassium and sodium in the blood and urine on the values of aldosterone and plasma renin activity.

MATERIALS AND METHODS

In a retrospective study medical records of the patients admitted to the Department of thyroid disease Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia in the period since 2009. to 2011 were analyzed. The study included patients with hypertension and hypokalemia, adrenal tumors, detected incidentally (incidentalomas) or tested because of hypertension, adrenal hyperplasia and resistant hypertension. With all patients, of the importance for the research were body

weight, height, body mass index, concentrations of sodium and potassium in serum and urine concentrations in plasma aldosterone and plasma renin activity and history data on drugs in therapy and associated diseases.

Blood samples were taken in until 9am. Electrolyte concentrations in serum were determined by ISE unit of OLYMPUS apparatus for electrolytes. Twenty-four hours urine was collected in a plastic container without acid, discarding the first morning urine on the day of collection, ending with the first urine the next morning. Patients' blood samples were taken for determination of plasma concentrations of aldosterone and renin activity, at around 9am, after 8 hours of lying down and two hours of walking or standing. For the determination of aldosterone in serum, plasma and urine radioimmunoassay kit ALDO-RIACT was used (reference values for the normal population with a normal salt intake are: 5th percentile 97, 201 median, 95th percentile 626). For the quantitative determination of angiotensin REN-CT2 radioimmunoassay kit was used in human plasma. Plasma PRA activities were indirectly measured with this assay which is expressed in ng angiotensin I, which occurs in ml per hour. Reference values for this essay under salt intake of 100-150mmol/24h are: idle period from 0.2 to 2.8, 1.5 to 5.7 effort.

Medical history data were obtained on the second and antihypertensive therapy, diabetes, kidney failure and other diseases. Dichotomously, use of beta-adrenergic antagonists, ACE inhibitors, calcium antagonists, vasodilators, alpha adrenergic antagonists, diuretics, potassium was denoted. Data were analyzed using the methods of descriptive and analytical statistics (Student's T test and a single linear relationship). For processing, the software package SPSS 12.0.

RESULTS

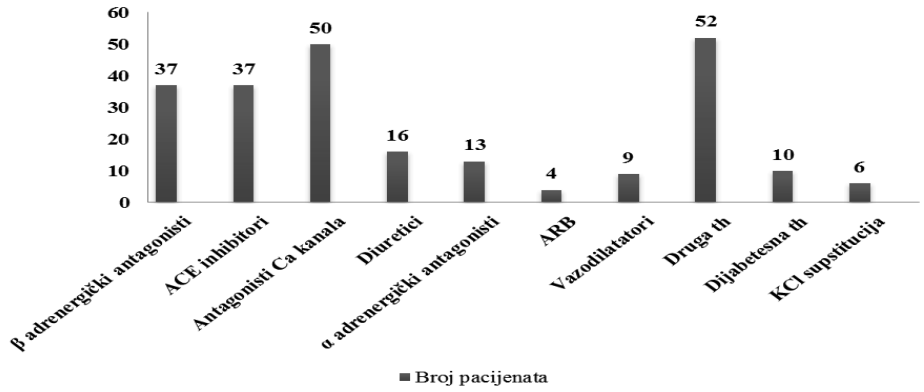
Total number of patients whose data were analyzed is 137.

Table 1 Representation of patients by gender and other anthropometric characteristics

	Ž	**M**	**Ukupno pacijenata**
Pol	**92** (67.15%)	**45** (32.85%)	**137**
ì TV	**81.36** ± 22.00		107
ì TM	**167.24** ± 10.32		111
ITM	**28.92** ± 7.47		107

The absolute frequency of patients in relation to treatment is shown in Chart 1.

Figure 1 Distribution of patients in relation to treatment



The highest mean value of plasma aldosterone were found in 13 patients treated with alpha adrenergic antagonists 221.8 (± 122.4). Ten patients with diabetes treated with insulin or oral hypoglycemic agents had at least mean aldosterone 110.4 (± 75.53). Patients who were not on therapy had similar mean values of plasma aldosterone, with the exception of slightly lower average value of alpha adrenergic antagonist groups and other therapies. The highest average PRA were in groups treated with vasodilators 4.64 (± 5.45) and the substitution of potassium 4.66 (± 5.45). Patients treated with alpha adrenergic receptor antagonists had the lowest mean PRA 2.659 (± 2.83). Ninety-three patients who were not treated with beta adrenergic receptor antagonists had the highest mean values of PRA 3.76 (± 3.91). The lowest mean PRA among patients who were not on therapy were in the second therapy group 3.21 (± 3.69). Mean values of plasma aldosterone were lower in the group of tumors of the adrenal 167.74 (± 109.8) compared to other diagnoses 208.59 (± 122.66), while the mean value of the PRA was lower in patients with hypertension and/or hypokalemia 3.88 (± 3.73) compared with the tumor that was 3.20 (± 3.52).

Results presented in Table 2 were obtained by the use of T test to assess the significance of difference of two independent samples.

Table 2 The significance of differences in the mean values of aldosterone, PRA and ARR in patients who were on therapy and some patients in the tumor group

	Aldosteron			**PRA**			**ARR**		
	DA	NE	**p**	DA	NE	**p**	DA	NE	**p**
â blokatori	158,4	198,1	**0,054**	2,8	3,7	**0,120**	169,5	232,3	**0,471**
ACE inhibitori	151,4	200,9	**0,032**	3	3,7	**0,300**	122,1	259,3	**0,052**
Ca antagonisti	174,9	193,2	**0,007**	3,4	3,5	**0,844**	253,8	189,5	**0,513**

Diuretici	145,1	192,7	**0,067**	2,8	3,6	**0,373**	94,5	231,7	**0,014**
á blokatori	221,8	182,9	**0,292**	2,7	3,6	**0,29**	237,9	212	**0,797**
Vazodilatatori	113,3	192,3	**0,017**	4,6	3,4	**0,522**	65,1	225,9	**0,005**
Dijabetes	196,2	180,6	**0,464**	2,9	3,5	**0,503**	122	222,5	**0,226**
KCL	161,6	188	**0,635**	4,6	3,4	**0,579**	99,9	220,3	**0,155**
Druga terapija	196,2	180,6	**0,465**	3,9	3,2	**0,281**	289,4	165,1	**0,237**
Tu nadbubrega	187,5	189,2	**0,943**	4,5	3,2	**0,105**	85,7	246,6	**0,005**

By using single linear regression analysis of the correlation and significance of correlation obtained results are detailed in Table 3.

Table 3 The correlation coefficient, sample size and significance of the association between different variables

	Aldo	PRA	ARR	BMI	Diureza	K serum	Kaliureza	K urin	Na serum	Natriureza	Na urin
Aldo	1 137	0.15 135 p 0.09	0.39 135 p 0.00	-0.03 105 p 0.73	0.1 28 p 0.60	0.12 69 p 0.31	0.15 28 p 0.44	0.55 12 p 0.06	-0.08 69 p 0.51	0.32 40 p 0.04	0.57 12 p 0.05
PRA	0.15 135 p 0.09	1 137	0.32 135 p 0.00	0.15 103 p 0.12	0.11 27 p 0.57	0.1 68 p 0.42	0.24 26 p 0.25	0.93 11 p 0.00	0.06 68 p 0.60	0.02 38 p 0.91	0.64 11 p 0.03
ARR	0.39 135 p 0.00	-0.32 135 p 0.00	1 135	-0.03 103 p 0.79	0.24 27 p 0.22	0.01 68 p 0.94	-0.1 26 p 0.63	-0.26 11 p 0.43	-0.16 68 p 0.19	-0.01 38 p 0.96	-0.09 11 p 0.80
BMI	-0.03 105 p 0.73	-0.15 103 p 0.12	-0.03 103 p 0.79	1 137	0.01 24 p 0.95	0.04 52 p 0.76	-0.13 20 p 0.59	-0.28 9 p 0.46	-0.17 52 p 0.22	0.19 31 p 0.30	0.11 9 p 0.78
Diureza	0.1 28 p 0.60	-0.11 27 p 0.57	0.24 27 p 0.22	0.01 24 p 0.95	1 137	-0.01 27 p 0.95	0.29 12 p 0.37	-0.29 12 p 0.37	-0.01 27 p 0.98	0.42 16 p 0.10	-0.16 12 p 0.61
K serum	0.12 69 p 0.31	0.1 68 p 0.42	0.01 68 p 0.94	0.04 52 p 0.76	-0.01 27 p 0.95	1 137	-0.04 18 p 0.86	-0.05 11 p 0.88	-0.02 69 p 0.87	0.46 26 p 0.02	-0.08 11 p 0.81
K-ureza	0.15 28 p 0.44	0.24 26 p 0.25	-0.1 26 p 0.63	-0.13 20 p 0.59	0.29 12 p 0.37	-0.04 18 p 0.86	1 137	0.79 12 p 0.00	-0.14 18 p 0.58	0.59 28 p 0.00	0.62 12 p 0.03
K urin	0.55 12 p 0.06	0.93 11 p 0.00	-0.26 11 p 0.43	-0.28 9 p 0.46	-0.29 12 p 0.37	-0.05 11 p 0.88	0.79 12 p 0.00	1 137	0.12 11 p 0.74	0.52 12 p 0.08	0.72 12 p 0.01
Na serum	-0.08 69 p 0.51	-0.06 68 p 0.60	-0.16 68 p 0.19	-0.17 52 p 0.22	-0.01 27 p 0.98	-0.02 69 p 0.88	-0.14 18 p 0.58	0.12 11 p 0.74	1 137	0.09 26 p 0.66	-0.12 12 p 0.74
Na-ureza	0.32 40 p 0.04	0.02 38 p 0.91	-0.01 38 p 0.96	0.19 31 p 0.30	0.42 16 p 0.10	0.46 26 p 0.02	0.59 28 p 0.00	0.52 12 p 0.08	0.09 26 p 0.66	1 137	0.81 11 p 0.00
Na urin	0.57 12 p 0.05	0.64 11 p 0.03	-0.09 11 p 0.80	0.11 9 p 0.78	-0.16 12 p 0.61	-0.08 11 p 0.81	0.62 12 p 0.03	0.72 12 p 0.01	-0.12 11 p 0.74	0.81 12 p 0.00	1 137

There is a medium strong, positive correlation between plasma aldosterone concentration of potassium and sodium in the urine. Correlation between plasma aldosterone and natriuresis was statistically significant ($p < 0.05$).

Plasma renin activity shows a strong positive correlation with the concentration of potassium in the urine and medium strong statistically significant correlation with the concentration of sodium in the urine ($p < 0.05$). The concentration of potassium in the urine shows a strong but not statistically significant correlation with PRA. Correlation with the concentration of aldosterone is medium strong, and with the concentration of sodium in the urine is also medium strong and statistically significant ($p < 0.05$).

The study found a significant relationship between the amount of sodium in the twenty-four hour urine, and plasma aldosterone ($p < 0.05$) and serum potassium concentrations ($p < 0.05$). The concentration of sodium in the urine indicates a strong connection of high marginal significance with plasma aldosterone ($p = 0.05$) and medium strong statistically significant association with the PRA ($p < 0.05$). Statistically significant correlation exists with kaliuresis ($p < 0.05$) and with the concentration of potassium in the urine ($p < 0.05$).

DISCUSSION

This study evaluated data from two times more females. This is important because there are differences based on gender in the physiological response of the renin-angiotensin system on the stimulatory and inhibitory effects, as demonstrated in research (22,27). Other authors (16) assert the effects of menstrual cycle phase, and that the components of the renin-angiotensin system reach highest values during the luteal phase of the menstrual cycle (a phenomenon known as “activation” of the renin-angiotensin system). Thus, in terms of determining the direct renin concentration, a higher incidence of false-positive ARR in hypertensive women is explained compared to men. Aldosteronoma show a higher prevalence in women (1,2). The mean body weight obtained in this study correspond to excessive nutritional status - mild obesity. Rossi et al (27) have shown that, besides a positive association of BMI and plasma aldosterone in essential hypertension, especially over-fed-obese subjects, there was no effect on plasma aldosterone and ARR in PA. Correlation analysis in this study showed that BMI is not associated with any of the variables relevant to the study, what partially agrees with the results of these authors. In this study, there were more patients with resistant and malignant hypertension, hypokalemia and hypertension than patients with adrenal hyperplasia or adrenal adenoma. In paper of D. A. Calhoun and associates (20) it is stated that resistant hypertension is present in 10-30% of persons with essential hypertension. Primary aldosteronism is a common cause of resistant hypertension.

The highest incidence of calcium antagonists in the treatment of patients in this study is a reflection of the fact that they are, according to the guides of World and the European Society of Hypertension, among the most widely prescribed drugs for the treatment of hypertension. This is especially referred to dihydropyridines. In addition, the fact that non dihydropyridine calcium antagonists can be used to control blood pressure during the test for primary aldosteronism, supports this frequency (2,3). Angiotensin converting enzyme inhibitors are often the first therapeutic choice in the treatment of hypertension, which may explain their higher prevalence. It is similar to the beta adrenergic receptor antagonists, especially in those indications in which they have an advantage. Unexpectedly, there is a small number of patients with diabetes mellitus in spite of the direct connection between diabetes and hypertension, especially resistant hypertension (8,10,11,13,14). A possible explanation for the small number of people with diabetes is that the data were obtained from patients admitted to the Department of thyroid disease. This can be explained by the greater number of patients in other therapies. Treatment of beta adrenergic receptor blockers resulted in a change in plasma aldosterone, in terms of lower mean values in the patients who were in therapy. There was no change in PRA and ARR. Despite the marginal significance of these changes, the beta adrenergic antagonist therapy could affect the results of the screening of PA. In the study of Mulateroa and associates (3), beta adrenergic antagonist therapy leads to a statistically significant decrease in PRA and plasma aldosterone and thus to increased ARR. In one study, it was found that propranolol reduces the aldosterone metabolic clearance and, it seems, increases the production of different mechanisms of the known stimuli. At the same time, the treatment with propranolol leads to reduction of PRA by 25% (37). Propranolol was common in the treatment of our patients. Patients who were treated with ACE inhibitors had a significantly lower mean plasma aldosterone. ACE inhibitors had no effect on PRA and ARR. These results partially agree with the results of other studies, where the use of ACE inhibitors significantly affect the ARR in terms of significantly higher PRA values. Some authors relate that to a higher risk of false-negative diagnoses of PA, while for others fosinopril therapy does not affect the diagnosis of PA. Calcium channel blockers had no effect on the concentrations of aldosterone, PRA and ARR. This does not exclude the possibility of false-negative diagnoses due to reduced ARR, which is a well-known effect of most used dihydropyridine calcium channel blockers (2,3). Diuretics had not influenced the individual and independent concentration of aldosterone and PRA, but they influenced the ARR. In patients which were taking diuretics, there is a significantly lower mean of ARR and the greater the possibility of false negative test results. In other studies, it is pointed out that the long-term use of thiazide diuretics acutely increases PRA, and that the time to reach maximum values is within two weeks since the beginning of the therapy. The results of this study, alpha adrenergic antagonist therapy did not affect the change in plasma concentration of aldosterone, PRA and ARR, which is

in agreement with results of other research and clinical guidelines for the diagnosis of PA (2). Vasodilators therapy resulted in a change in plasma aldosterone and ARR. Patients taking vasodilators had significantly lower mean values of aldosterone and ARR, without PRA changes, compared to patients who were not on this therapy. The use of vasodilators could, therefore, increase the risk of false-negative cases of PA during testing. In the literature, there is little data on the impact of organic nitrites on aldosterone, PRA and ARR. In the works of other authors, it is generally referred that a drug called hydralazine can be used during the screening, which means that it is without the influence on the components of the renin-angiotensin system. Substitution of potassium had no effect on the concentrations of aldosterone, PRA and ARR. This confirmed the importance of the correction of hypokalemia, which would affect a greater risk of false-negative cases of PA (2,3). Patients with diabetes mellitus have a significantly lower mean concentration of aldosterone than non-diabetics. The therapy for diabetes did not affect the change in PRA and ARR. N. K. Hollenberg and colleagues, in their work indicate that patients with diabetes mellitus show an increase in PRA, angiotensin II concentration and plasma aldosterone concentration (41). In the opinion of other authors, most patients with type 2 diabetes have normal circulating levels of plasma aldosterone. However, in patients with long-term diabetes and dysautonomia, conversion of precursors of renin may be disrupted in diabetes damaged kidney. The result of this situation is hyporeninemic hypoaldosteronism syndrome, in which the accumulated prorenin affects the formation of non- stimulated renin and aldosterone reduction and carries the risk of hyperkalemia. In patients with uncomplicated type 1 diabetes, plasma aldosterone is relatively lower compared to the PRA, independent of salt intake (42). Primary aldosteronism is common in diabetic patients with resistant hypertension with a prevalence of 14%.

There was no change in plasma concentrations of aldosterone, PRA and ARR depending on the clinical diagnosis. Therefore, before the screening of primary aldosteronism, based on clinical diagnosis, the outcome of the test cannot be predicted. Data from the literature, however, show an increase of the PA frequency in resistant hypertension. In the report of D. Clark and co-authors, it is noted that the PA prevalence in resistant hypertension ranges from 14 to 21% (45). As anatomical PA substrate in resistant hypertension, adrenal adenoma is more common, and hyperplasia is present in other hypertensive forms. It is estimated that the incidence of adrenal incidental is 8.4% of the population without hypertension, and from 18.9-24.4% in the hypertensive population(57). The results of this study showed that there was a significant correlation between natriuresis, as a measure of salt intake, and plasma concentrations of aldosterone and potassium levels. Plasma concentrations of aldosterone and PRA were significantly correlated with the concentrations of sodium and potassium in urine. In addition, kaliuresis and potassium concentrations in urine are correlated with the concentration of sodium in urine, and vice versa. W.G. Walker and colleagues in their

work demonstrated that there is a highly significant and strong association between aldosterone and urinary potassium, whether it is expressed through the concentration of potassium in urine or the relationship of potassium and creatinine in urine (as a measure of excretion of potassium) (46). They also showed a strong correlation between the concentration of potassium in urine and blood pressure, and weak associations between PRA and sodium. They stressed the importance of potassium for activity of the renin-angiotensin system, instead of sodium, which until then was considered the most responsible (46). Another study showed that the increased urinary excretion of sodium was strongly associated with low levels of plasma aldosterone, with the excretion of sodium expressed as an index of sodium/creatinine (47, 48, 49, 52, 54).

CONCLUSION

Patients with resistant hypertension may be more often subjected to testing. The least impact on the results of the test had administered alpha blockers and calcium antagonists. Beta-adrenergic receptor blockers and ACE inhibitors may have an impact. Diuretics and vasodilators have definite impact on ARR. Diabetes mellitus can affect, with a greater number of false negative results. Establishing the diagnosis of primary aldosteronism is possible by determining the concentration of electrolytes in urine instead of the total amount.

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