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Primary aldosteronism: a common and important problem A practical guide to the diagnosis and treatment

Pierwotny aldosteronizm jako problem częsty i ważny: praktyczny przewodnik diagnostyki i leczenia

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Abstract

In view of the fact that primary aldosteronism (PA) is a problem that is more prevalent than previously thought and its diagnosis is of greater clinical significance than previously believed, the Endocrine Society has recently published recommendations on the diagnosis and management of PA. Due to the fact that the currently available tests cannot be considered the gold standard in the diagnosis of PA and the discrepancies in the results of determination of aldosterone levels and plasma renin activity (PRA) are considerable the authors of this document do not provide strict cutoff values, leaving the interpretation of results to clinicians. This paper, which focuses on screening and confirmatory tests and on the aetiological diagnosis and treatment of PA, is based on the experience of the Department of Endocrinology, Diabetes and Internal Diseases, Medical University in Bialystok, Poland, but it also takes into account other points of view presented in papers published in the past few years. **(Endokrynol Pol 2012; 63 (4): 324–336)**

Key words: *plasma aldosterone concentration, plasma renin activity, aldosterone–renin ratio, confirmatory tests*

Streszczenie

Biorąc pod uwagę fakt, że pierwotny aldosteronizm (PA) jest problemem występującym częściej niż wcześniej sądzono, a jego rozpoznanie ma istotniejsze znaczenie kliniczne niż dotąd uważano, Towarzystwo Endokrynologiczne opublikowało ostatnio rekomendacje dotyczące rozpoznawania i leczenia PA. Ze względu na to, że dostępnych obecnie testów nie można uważać za „złoty standard" w rozpoznawaniu PA, a rozbieżność uzyskiwanych wyników oznaczeń ALDO i PRA jest znaczna, autorzy tego dokumentu nie wskazali ścisłych poziomów odcięcia, pozostawiając interpretację wyników klinicystom. Dlatego niniejsze opracowanie, dotyczące badań przesiewowych i potwierdzających oraz diagnostyki etiologicznej i leczenia PA, oparto na doświadczeniu Kliniki Endokrynologii Uniwersytetu Medycznego w Białymstoku, ale uwzględniono także inne punkty widzenia, przedstawione w piśmiennictwie ostatnich lat. **(Endokrynol Pol 2012; 63 (4): 324–336)**

Słowa kluczowe: *osoczowe stężenie aldosteronu, aktywność reninowa osocza, iloraz aldosteron–renina, testy potwierdzające*

The history of discovering primary aldosteronism

Primary aldosteronism (PA) is commonly referred to in the medical literature as Conn's syndrome, because Jerome Conn, who described this syndrome in a female patient with aldosterone-secreting adenoma in 1955, is considered its discoverer [1]. However, two years earlier, Michał Lityński published, in Polish, a description of two cases of males who had died from renal failure in the course of malignant hypertension caused by adrenal cortex tumours [2]. In both cases the autopsy revealed adrenal tumours whose microscopic structure revealed large cells with foamy cytoplasm and small nuclei, typical of the glomerular layer of the adrenal cortex. Michał Lityński concluded his report with these words: "It must be assumed that in both cases the hypertension was caused by adrenocortical tumours, unilateral in one case and right-sided in the other case. The histology of the tumours revealed proliferation of cells resembling cells of the glomerular layer, i.e. the mineralocorticoid-producing layer. It allows us to believe that what we were dealing with was excessive production of these hormones".

Michał Lityński's report, almost unknown even in the Polish scientific literature, was brought to the attention of the Polish medical community by Walenty Hartwig [3] in 1983 and by Franciszek Kokot in 1984 [4]. A proposal was also put forward to rename the syndrome "the Lityński-Conn syndrome" (Figure 1) [5]. Michał Lityński's precedence in the discovery of PA was also recognised in "The Lancet" in 1991 [6] and in "Kaplan's Clinical Hypertension" in 2002 [7].

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Figure 1. *Michał Lityński (1906–1989) (reprinted from reference [5])*
Rycina 1. *Michał Lityński (1906–1989) (reprodukowano z [5])*

Introduction

Primary aldosteronism is characterised by an autonomous overproduction of aldosterone, a sodium-retaining hormone of the adrenal cortex. This process is caused by an adenoma composed of glomerular layer cells (aldosterone-producing adenoma, APA) or bilateral adrenal hyperplasia (BAH). Only exceptionally PA is caused by a carcinoma originating from glomerular layer cells. Retention of sodium and, secondarily, of water suppresses the secretion of renin by the juxtaglomerular apparatus in the kidneys, which in turn results in decreased serum levels of angiotensin II (AII) [7]. The main effects of aldosterone are reabsorption of sodium in the distal tubule of the nephron and secretion of potassium and hydrogen ions into the tubular lumen. Aldosterone excess leads to hypertension (HT) — as a result of increased volume of circulating blood and accumulation of sodium in smooth myocytes of the vascular walls (sodium is an important vasoconstriction factor) — and to hypokaliaemia and metabolic alkalosis [8]. Aldosterone receptor antagonists with or without other antihypertensive drugs are the treatment of choice in cases where BAH is identified as the cause of PA. If the diagnosis of aldosteronoma is established, unilateral adrenalectomy, most commonly laparoscopic, should be considered [9]. Surgery and drug treatment usually improves the quality of life by alleviating or, in some cases, eliminating HT and hypokaliaemia [10].

After Lityński's discovery until not very long ago PA was considered a very rare cause of HT, accounting, roughly, for a mere 1% of the cases. This point of view was largely determined by a belief that further evaluation for aldosterone excess was only justified when hypokaliaemia was present. In the recent years, however, the opinions on the epidemiology of PA and its role in the pathogenesis of cardiovascular disease have changed significantly for two reasons.

Firstly, due to the widespread use of the ratio of plasma aldosterone concentration to plasma renin activity — ALDO/PRA ratio — proposed by Hiramatsu et al. in 1983 [11, 12] PA is currently diagnosed in as many as 5–13% of hypertensive patients with most of them being normokalaemic [13, 14]. Based on the recent results the contribution of PA to the development of refractory HT is estimated at as much as 20% [15]. While some researchers have called this considerable "involvement" of PA in the aetiology of HT an epidemic, others, like Kaplan, question it, mainly due to the imperfection of aldosterone and PRA determinations [16].

Secondly, the reports published in the past few years suggest that aldosterone excess is a significant cardiovascular risk factor that predisposes to inflammation, fibrosis and remodelling of the vascular wall independently of HT *per se* [17, 18]. PA significantly increases mortality due to myocardial infarction, stroke and arrhythmia [19, 20]. Increased albumin secretion, which is more severe than in patients with essential HT, is a marker of vascular damage in the course of PA [18, 21]. It has been shown that restoration of normal aldosterone levels may suppress the process of adverse structural changes in vascular walls [22]. Therefore the diagnosis of PA not only offer an opportunity to provide effective treatment of HT but also a chance of reversing HT-independent adverse impact of aldosterone on the cardiovascular system.

In view of the fact that PA is a problem that is more prevalent than previously thought and its diagnosis is of greater clinical significance than previously believed, the Endocrine Society has recently published recommendations on the diagnosis and management of PA [23]. Due to the fact that the currently available tests cannot be considered the gold standard in the diagnosis of PA and the discrepancies in the results of determination of aldosterone levels and PRA are considerable the authors of this document do not provide strict cutoff values, leaving the interpretation of results to clinicians. This paper, which focuses on screening and confirmatory tests and on the aetiological diagnosis and treatment of PA, is based on the experience of the Department of Endocrinology, Diabetes and Internal Diseases, Medical University in Bialystok, Poland, but it also takes into account other points of view presented in papers published in the past few years.

Screening tests

Who should be screened?

The Endocrine Society recommends that screening based on the calculation of the ALDO/PRA ratio (ARR, aldosterone-renin ratio) should be performed in patients from groups in which the incidence of PA is increased (Table I). These groups are patients with moderate to severe HT, which may or may not be refractory, patients with hypertension co-existent with hypokaliaemia (spontaneous or induced by diuretics) and/or adrenal incidentaloma, and patients with a family history of HT or a cardiovascular event before the age of 40 years. The Endocrine Society also recommends screening in all hypertensive first-degree relatives of patients with PA [23]. Some authors believe that all hypertensive patients should be screened, including those without hypokalaemia and without the family history, as the delayed diagnosis of PA leads to irreversible sequelae of HT and aldosterone excess and the delayed treatment of PA reduces the chances of achieving normal blood pressure values [24]. These authors note that screening before initiation of drug therapy makes it possible to avoid the effect of antihypertensive agents on serum aldosterone and PRA. Kaplan questions such a wide range of indications for screening for PA [25]. In particular, he points out that patients with moderate HT (defined as BP 160–180/100–110 mm Hg) account for as many as 25% of hypertensive patients, while aldosteronoma accounts for about 1% of cases of adrenal incidentaloma [26, 27].

Screening for primary aldosteronism: the aldosterone–renin ratio

Although the determination of ARR is considered the most reliable method of screening for PA, its interpretation is complex, as it requires an individual assessment of the impact on numerous factors on the rennin–angiotensin–aldosterone system (RAAS). In order to reduce the percentage of false positive and false negative results first of all efforts should made to eliminate the influence of numerous interfering factors on the RAAS. Figure 2 depicts the RAAS along with the physiological and pharmacological factors that affect this system. It also helps to elucidate the different effect of these factors on the individual elements of the system. The RAAS plays a key role in maintaining water and electrolyte homoeostasis and blood pressure, keeping the volume of circulating blood constant mainly be regulating the level of sodium, an ion that shows a high osmotic potential. Potassaemia is the second to circulating blood volume significant factor co-dependent on the RAAS (it is both a regulated and a regulating factor). The level of hydration and kaliaemia are the most important factors that determine aldosterone secretion with the information on the level of hydration is transmitted through the RAAS and high potassium levels directly stimulate aldosterone secretion. The third factor that stimulates aldosterone secretion, especially under conditions of suppressed renin activity (e.g. in PA), is adrenocortico-

Table I. ***Characteristics of groups of hypertensive patients (NT) in which primary aldosteronism (PA) is more prevalent***

Tabela I. ***Charakterystyka grup chorych na nadciśnienie tętnicze (NT), u których częściej występuje pierwotny aldosteronizm (PA)***

Moderate to severe hypertension
Refractory hypertension
Hypertension and hypokaliaemia (spontaneous or induced by diuretics)
Hypertension and adrenal incidentaloma
Hypertension and a family history of hypertension or a cardiovascular event before the age of 40 years
Hypertension and first-degree relatives with PA

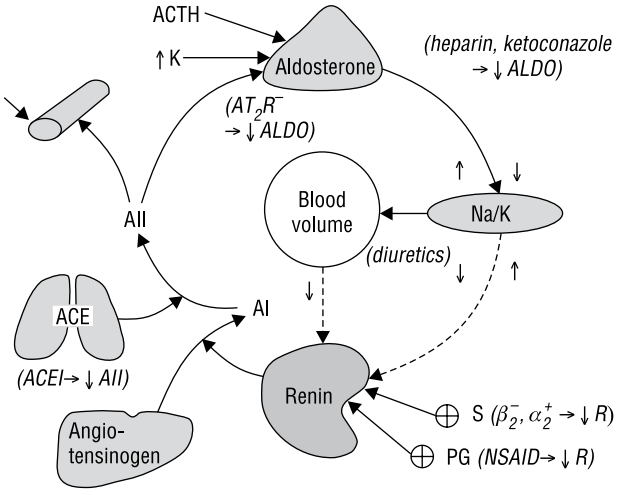

Figure 2. *The renin-angiotensin-aldosterone system along with the physiological and pharmacological factors affecting its homoeostasis; ALDO — aldosterone; R — renin; Na — sodium; K — potassium; S — sympathetic nervous system; PG — prostaglandins; NSAID — non-steroid anti-inflammatory drug; ACE — angiotensin converting-enzyme, ACEI — ACE inhibitors; AI/II — angiotensin I/II; AT_2R^- — inhibition of the angiotensin receptor type 2; ACTH — adrenocorticotropic hormone; ↑/↓ — increase/decrease; +/– — stimulation/inhibition*

Rycina 2. *Układ renina–angiotensyna–aldosteron oraz czynniki fizjologiczne i farmakologiczne wpływające na jego równowagę; ALDO — aldosteron; R — renina; Na — sód; K — potas; S — układ współczulny (sympatyczny); PG — prostaglandyny, NSAID — niesteroidowe leki przeciwzapalne; ACE — konwertaza angiotensyny, ACEI — inhibitory ACE; AI/II — angiotensyna I/II; AT_2R^- — inhibicja receptora angiotensyny typu 2; ACTH — kortykotropina; ↑/↓ — zwiększenie/zmniejszenie; +/– — pobudzenie/hamowanie*

tropic hormone (ACTH). Renin activity depends on the integration of three types of stimuli: a "flow-related" stimulus, an "electrolyte" stimulus and direct adrenergic stimulation. Reduced blood flow through the afferent arteriole of the juxtaglomerular apparatus results from systemic hypovolaemia, renal artery stenosis (the classic Goldblatt experiment) or intrarenal circulation abnormalities stimulate renin activity. Hyponatraemia and hyperkalaemia exert a similar effect, independently from each other. Stimulating factors transmitted through the sympathetic nervous system (stress and other states of hypercatecholaminaemia, e.g. phaeochromocytoma) are transmitted through stimulation of β_2-adrenergic receptors and inhibition of α_2-adrenergic receptors. Renin activity is also stimulated by locally secreted prostaglandins, which is important in terms of the influence of the commonly used non-steroid anti-inflammatory drugs (NSAIDs) on the RAAS. Angiotensin II (AII) is an important element of the RAAS. However, it is not the only mechanism whereby AII affects water and electrolyte balance and the regulation of blood pressure, as it is also an important vasoconstrictive factor, it increases antidiuretic hormone secretion and, independently from the RAAS, it increases sodium reabsorption [28].

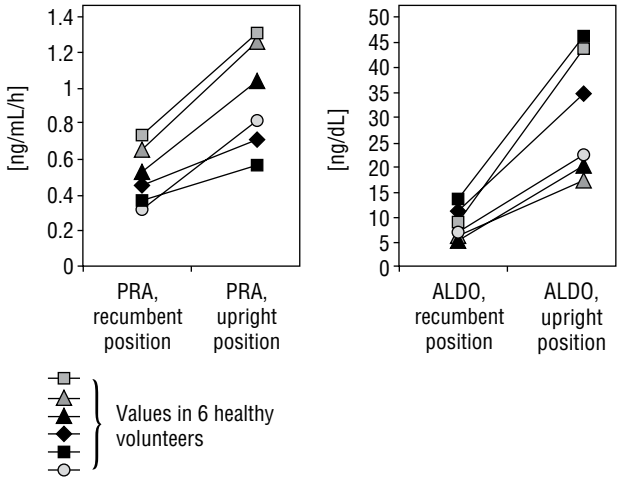

Figure 3. *The impact of upright posture on PRA and ALDO under physiological conditions (the authors' own studies)*

Rycina 3. *Wpływ pionizacji na aktywność reninową osocza (PRA) i stężenie aldosteronu w surowicy (ALDO) w warunkach fizjologicznych (baza — pozycja leżąca) — badania własne*

The impact of posture, time of day and dietary sodium content on the sensitivity of ARR

The assumption of upright posture results in the activation of the RAAS and an increase in aldosterone levels (Figure 3). The increased renin activity results from a reduced renal blood flow caused by redistribution of blood flow to the lower limbs. In the group of patients with AII-responsive forms of PA, which includes all cases of BAH and some cases of APA, normal increases in PRA and ALDO are observed upon the assumption of the upright position (a > 50% increase in ALDO compared to the level in the recumbent position). In most patients with APA, whose PA is AII-unresponsive, no significant effect of assuming the upright position on ALDO is observed [29, 30]. The head-up tilt test is not recommended for routine differentiation between BAH and APA due to its insufficient specificity. In a metaanalysis of 16 published reports the specificity of the tilt test in 246 patients with surgically confirmed APA was 85% [31]. In practice, in accordance with the recommendations of the Endocrine Society, blood for screening determinations of PRA and ALDO is collected in the morning after 5–15 minutes' rest in the sitting position and after 2 hours of keeping the chest in the upright position (the patient may stand, sit or walk during this time) [23]. The upright position ensures a higher sensitivity of the screening tests, as more than 2/3 of the cases of PA are AII-responsive forms [32].

As renin activity in patients with PA is constantly suppressed, aldosterone secretion is depends on ACTH stimulation to a greater degree than under physiological conditions. It also shows a diurnal rhythm with peak values between 8 and 9 o'clock in the morning [33]. Because of that morning measurements of ALDO for the purpose of determining PRA, in contrast to measurements performed at other times of the day, are considered more sensitive in the screening for PA [34].

Due to the fact that dietary salt restriction may lead to increased PRA values and the consequent reduction in ARR, salt restriction is not recommended in practice [29, 35].

The impact of gender, menstrual cycle, age and renal function on ARR

A relationship between the phase of the menstrual cycle and PRA and ALDO is observed in women [36, 37]. Falsely elevated ARR values are more common in women. In about 30% of women on the 7th day of the cycle and in as many as 70% of women on the 21st day of the cycle ALDO values exceed 15 ng/dL, which is considered significant for PA [37]. The higher ARR values in pregnancy and in the luteal phase compared to the follicular phase are associated with the effects of progesterone, although the underlying mechanism is unclear [36, 38]. The recommendations of the Endocrine Society do not contain suggestions regarding selection of the phase of the menstrual cycle in which ARR should be performed, although some authors indicate that the best time point for screening for PA is the beginning of the cycle, when estrogen and progesterone levels are the lowest [38].

In patients with chronic kidney disease, especially in patients with impaired filtration, false positive ARR results are more common due to the direct and indirect (sodium and water retention) decrease in renin secretion and the possible increase in ALDO as a result of hyperkalaemia resulting from renal dysfunction [39]. Similarly, in the elderly, renin activity decreases as renal failure progresses, which predisposes to false positive ARR results [40].

Significance of potassaemia and its correction in the screening for PA

Although it is not a prerequisite for the diagnosis of PA, hypokalaemia warrants further evaluation in terms of this diagnosis, particularly in hypertensive patients. On the other hand, decreased serum potassium levels before screening must be corrected, as potassium excess stimulates aldosterone secretion and hypokalaemia decreases ALDO, increasing the likelihood of obtaining false negative ARR results [29, 35].

Impact of drugs on ARR

Drugs that may cause false positive ARR results

The possible impact of drugs on ARR is summarised in Table II. Because sympathetic stimulation — through stimulation of β_2-adrenergic receptors and inhibition of α_2-adrenergic receptors — increases renin activity, inhibition of these receptors by β-blockers and stimulation by α-agonists, respectively, increases PRA. This may lead to falsely elevated ARR, as these drugs have potentially smaller effect on ALDO, which is independently regulated by potassaemia and ACTH [35, 41]. However, Young believes that β-blockers do not exert a significant effect on ARR due to the simultaneous decrease in ALDO, parallel to the suppression of PRA [42]. Mulatero et al. have demonstrated no effect of α-blockers on ARR [43].

NSAIDs may decrease PRA by inhibiting prostaglandin synthesis and, as a consequence, increase ARR. NSAIDs also contribute to sodium and water retention, which may further inhibit PRA, and they also predispose to potassium retention, which increases ALDO [44].

Drugs that may cause false negative ARR results

Drugs that may increase PRA include diuretics, which stimulate renin activity by increasing sodium and water excretion [30]. Dihydropyridine calcium antagonists stimulate renin secretion, both directly (by affecting calcium-dependent regulating mechanisms) and indirectly (by sympathetic stimulation and natriuretic effect caused by hypotension), and decrease ARR by 17% (with the exception of verapamil, which exerts no effect) [43]. Angiotensin converting enzyme inhibitors (ACEIs) and AT_2-receptor blockers (ARBs) both inhibit the RASS and decrease ALDO and, as a consequence, ARR, by 30% and 43%, respectively [43, 45]. Estrogen-containing oral contraceptives may slightly increase ARR by stimulating angiotensinogen synthesis in the liver and the subsequent increase in ALDO [46]. Progesterone and progestins, most likely through the mineralocorticoid receptor, cause natriuresis, which stimulates renin secretion by the juxtaglomerular apparatus [47].

Table II. *The impact of physiological and pharmacological factors on PRA and ALDO*
Tabela II. *Wpływ czynników fizjologicznych i farmakologicznych na PRA i ALDO*

Type of stimulus		PRA	ALDO	ARR
Physiological factors	Upright position	↑↑	↑↑↑	↑↑↑
	Time of day (morning effect of ACTH)	(↑)	↑	↑
	Dietary sodium content (salt restriction)	↑↑	↑	↓
	Menstrual cycle (luteal phase)	–	↑	↑
	Age-related (> 65 years) decline of renal function	↓	(↑)	↑↑
	Hypokalaemia	(↓)	↓↓	↓↓
Pharmacological factors	β-blockers, α_2-agonists	↓	↓/–	–/↑
	NSAIDs	↓	↑	↑
	Diuretics	↑↑	↑	↓
	Dihydropyridine calcium antagonists	↑↑	↑	↓
	ACEIs and AT_2-receptor blockers	–	↓	↓
	Progestins	↑↑	↑	↓

Practical comments on the measurement of ALDO and PRA for the purpose of determination of ARR

Blood should be sampled without the tourniquet (in order to avoid haemolysis) in the morning after 5–15 minutes of sitting and two hours of keeping the chest in the upright position (walking, standing or sitting) [23]. The impact of upright posture on ARR is illustrated in Figure 4.

Not all the patients can be switched to antihypertensives that do not affect PRA and ALDO (verapamil, α_1-blockers, hydralazine) and in some cases discontinuation of all the drugs that may affect ARR would simply be dangerous [48]. This does not, however, prevent the patient from being evaluated for PA, and taking into account the possible effect on the RAAS during interpretation of the screening test results may be an important factor in deciding whether to continue or discontinue evaluation for PA. Increased ARR values in patients managed with drugs that may decrease ARR values (drugs that predispose to false negative ARR results), such as diuretics, ACEIs, ARBs and dihydropyridine calcium antagonists, increase the likelihood of PA. Normal ARR in patients managed with drugs which that may cause false positive results, such as β-blockers, suggest ruling out the possibility of PA.

Practical comments on the interpretation of ARR

Another fact that should be taken into consideration is that PRA is very often decreased (in as many as every fourth patient with essential HT) and in 15% of the patients it is elevated (it is normal in 60% of the cases), which may significantly affect the value of ARR [49, 50]. It should also be borne in mind while analysing ARR that the ALDO/PRA ratio may be increased not only in PA but also in secondary aldosteronism (commonly) and hypercortisolaemia (less commonly) (Figure 5).

Secondary aldosteronism refers to conditions in which excessive secretion of aldosterone results from increased PRA. The causes of secondary aldosteronism are summarised in Table III. Stimulation of the RAAS is most commonly caused by the reduction of "effective" circulating blood volume as a result of fluid escape outside the vascular bed. This is observed in patients with heart failure, liver cirrhosis and proteinuria. An absolute decrease in circulating blood volume is most commonly caused by the use of diuretics. Renal artery stenosis is caused by atherosclerosis in about 90% of the patients (more commonly in patients over the age of 50 years) or by fibromuscular dysplasia (in younger patients, more commonly in women) and leads to HT (renovascular HT). Reninoma, which is rare, is a cause of refractory HT with hypokalaemia, and this diagnosis is established in patients with secondary aldosteronism

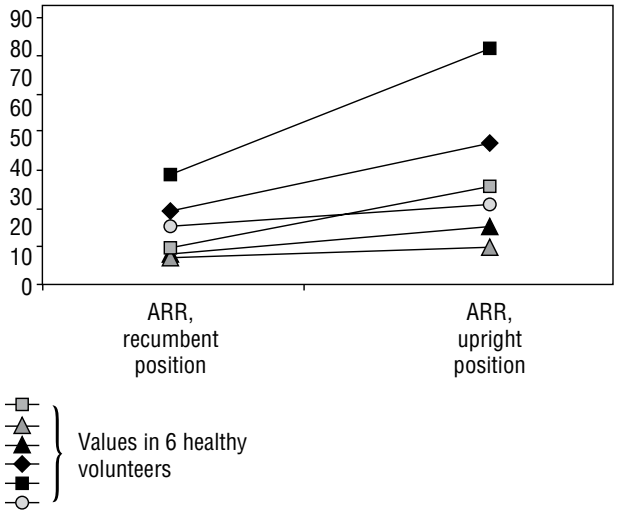

Figure 4. *The impact of upright posture on ARR under physiological conditions (the authors' own studies); ALDO in ng/dL; PRA in ng/mL/h*

Rycina 4. *Wpływ pionizacji na wskaźnik ALDO/PRA (ARR,* aldosterone–renin ratio*) w warunkach fizjologicznych (baza — pozycja leżąca) — badania własne*

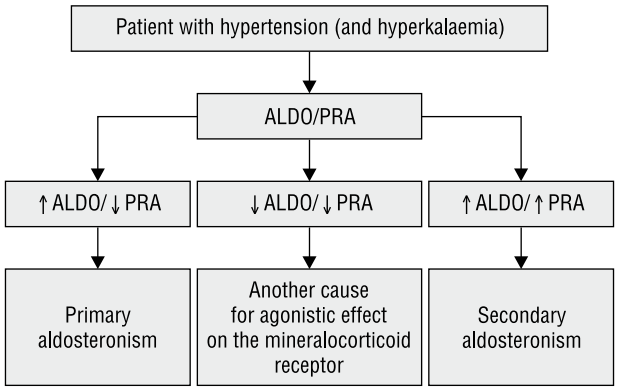

Figure 5. *Preliminary assessment of serum aldosterone (ALDO) and plasma renin activity (PRA) determinations*

Rycina 5. *Wstępna ocena wyników oznaczeń aldosteronemii (ALDO) i aktywności reninowej osocza (PRA)*

and unilateral overproduction of renin after renal artery stenosis has been ruled out [51].

What cutoff value of ARR rules out PA?

The variety of PRA and ALDO assays, their low repeatability and the plethora of factors affecting the RAAS results in the considerable variation in cutoff values adopted by individual laboratories. Depending on the laboratory, the ARR cutoff values range from 7.2 to 100 (ALDO expressed in ng/dL and PRA in ng/mL/h) [15, 52–57]. Another difficulty for the clinician is the use of different units for the measurement of ALDO (ng/dL, pg/mL, pmol/L), where 1 ng/dL = 10 pg/mL = 27.7 pmol/L.

Table III. *The causes of secondary aldosteronism (↑ALDO and ↑PRA and frequently ↑ARR) (the relatively common causes are in bold)*

Tabela III. *Przyczyny wtórnego aldosteronizmu (↑ALDO z ↑PRA i często ↑ARR) (względnie częste wyróżniono pogrubieniem)*

With reduced "effective" blood volume	**Congestive heart failure**
	Liver cirrhosis
	Nephrotic syndrome
With reduced circulating blood volume	**Diuretic treatment**
	Bartter syndrome
	Gitelman syndrome
	Pseudohypoaldosteronism type 1
With hypertension	**Malignant hypertension**
	Renal artery stenosis
	Coarctation of the aorta
	Reninoma

Mathematically, ARR values are determined by PRA to a greater degree than ALDO does, as the values of PRA may range from a hundredth to more than ten (four orders of magnitude) and those of ALDO from more than ten to several hundred (two orders of magnitude) [58]. In light of the above Young proposed to use ALDO values of > 15 ng/dL as the second essential criterion for a preliminary diagnosis of PA, in addition to ARR values of > 20 [56]. These criteria were met by 90% of Mayo Clinic patients in whom surgery confirmed the presence of adenoma [59]. According to other authors, this approach may result in missing the cases of PA also caused by APA [60]. A comparative analysis carried out by Schirpenbach et al. showed significant discrepancies between determinations of ALDO using 4 different assays [61]. Due to the more marked effect of PRA on ARR, particularly in view of the fact that the interpretation of ALDO determinations can be controversial, some authors attach more significance to the measurement of PRA as a stand-alone screening test [62].

In our studies, in the group of patients evaluated for PA, as many as 47% of the patients had ARR values exceeding 30 (the most commonly adopted cutoff value) and ARR values exceeding 50 were noted in as many as 28%, which points to the low usefulness of this marker in the selection of patients requiring further investigation [63]. These data are illustrated in Figure 6.

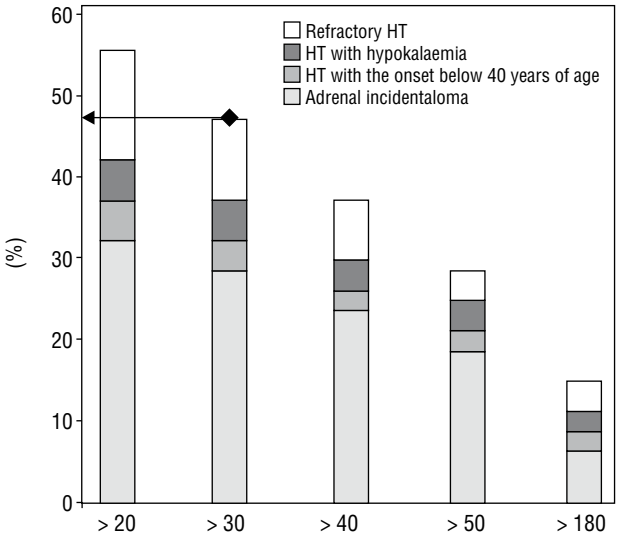

Figure 6. *Percentages of patients with individual indications for evaluation for primary aldosteronism (PA) (n = 81) in whom the aldosterone-to-renin ratio (ARR) (serum aldosterone [ng/dL]/ /plasma renin activity [ng/mL/h]) exceeded specific cutoff values. ARR exceeding 30 was observed in 47% of the patients (source [63]); HT — arterial hypertension*

Rycina 6. *Odsetek pacjentów z poszczególnymi wskazaniami do diagnostyki w kierunku pierwotnego aldosteronizmu (PA) (n = 81), u których wskaźnik ARR (aldosteronemia [ng/dL]/aktywność reninowa osocza [ng/mL/h]) przekracza kolejne poziomy odcięcia; ARR przekraczające 30 stwierdzono u 47% badanych (źródło [63]); HT — nadciśnienie tętnicze*

The role of tests for confirming autonomous aldosterone secretion

The aim of the tests confirming PA is to demonstrate the lack of suppression of renin activity and, secondarily, of aldosterone by stimuli that suppress the RAAS under physiological conditions. In practice, intravenous saline or the intravenous synthetic mineralocorticoid fludrocortisone are used. The lack of suppression of aldosterone secretion while using these agents confirms the autonomous nature of aldosterone secretion. The

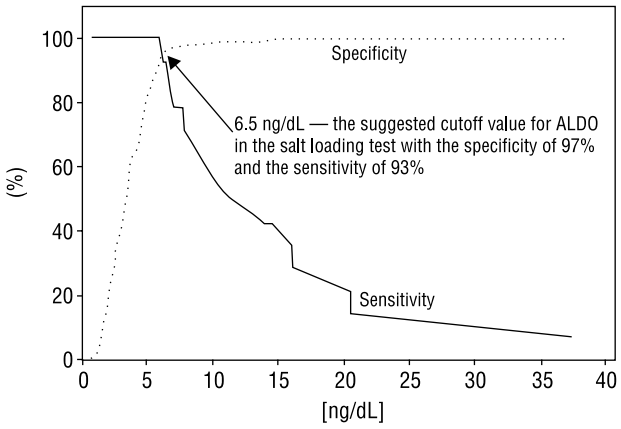

Figure 7. *The sensitivity and specificity of plasma aldosterone determination in the salt loading test (source [65]); ALDO — plasma aldosterone levels*

Rycina 7. *Czułość i swoistość oznaczeń aldosteronemii w teście z NaCl (źródło [65]); ALDO — stężenie aldosteronu w osoczu*

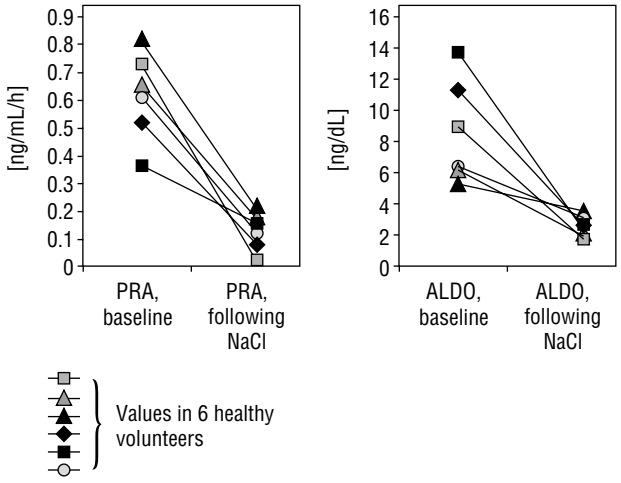

Figure 8. *The effects of 2 litres of 0.9% NaCl on PRA and ALDO under physiological conditions*

Rycina 8. *Wpływ 2 litrów 0,9-procentowego roztworu chlorku sodu (NaCl) na aktywność reninową osocza (PRA) i stężenie aldosteronu w osoczu (ALDO) w warunkach fizjologicznych*

captopril test is less useful clinically than these two tests [64].

The results of our study in 198 patients evaluated for PA show that the routine use of the salt loading test to demonstrate autonomy of aldosterone secretion effectively narrows down the group of patients for further investigation while only slightly increasing the cost of diagnostic evaluation. The lack of suppression of aldosterone secretion with salt below 6.5 ng/dL under conditions of suppressed PRA allows to confirm the diagnosis of PA with a high sensitivity and a high specificity (Figure 7) [65].

Intravenous saline infusion test

The commonly used protocol for this test involves intravenous administration of two litres of 0.9% NaCl over 4 hours, followed by measurement of ALDO. The patient should remain recumbent. The cutoff values for the confirmation of PA vary from laboratory to laboratory and range from 5 to 10 ng/dL (140–280 pmol/L) [65, 66]. This test is probably the most commonly used test for autonomous aldosterone secretion due the ease of performance and the short duration. Simultaneous determination of PRA is aimed to confirm that the potential lack of suppression of aldosterone secretion is observed under conditions of suppressed PRA (in contrast to secondary aldosteronism) and is not secondary to factors that stimulate renin activity (mainly antihypertensive drugs). The effects of 2 litres of 0.9% NaCl on PRA and ALDO under physiological conditions are illustrated in Figure 8.

In each case the individual risk of HT and hear failure worsening should be taken into account [67].

Oral salt loading test

In order to confirm PA, some authors, including Young et al., measure aldosterone levels in the urine following oral administration of salt [56]. In this protocol, after achieving normal blood pressure and normal serum potassium levels, the patient is asked to follow a high-sodium diet for 3 days. The diet should contain 5 g of sodium (12.8 g of sodium chloride) [31]. The sodium supply should be intensive enough to achieve urinary sodium excretion exceeding 200 mEq/day. As a high-sodium diet stimulates kaliuresis and, as a consequence, causes hypokalaemia, serum potassium levels should be monitored every day and corrected, if necessary. The lack of reduction in the 24-hour aldosterone excretion confirms PA. In each case the individual risk of HT and hear failure worsening should be taken into account [67].

Fludrocortisone suppression test

The test involves administration of 0.1 mg of fludrocortisone acetate every 6 hours and 2 g of sodium chloride (with main meals) 3 times daily — for 4 days. Serum aldosterone levels exceeding 5 ng/dL on day four confirms the diagnosis of PA. In some centres the fludrocortisone suppression test is considered the most reliable [30, 35], while in other centres, including the Mayo Clinic, it is not used, as it is considered to be unsafe due to the variability of the QT interval and worsening of left ventricular function observed during the test [67]. Mulatero et al. showed a comparable diagnostic value of this test and of the intravenous salt loading test [43].

Aetiological diagnosis of primary aldosteronism

Adenoma and bilateral adrenal hyperplasia are two most common causes of PA (both characterised by a similar prevalence). Unilateral adenoma is the cause of aldosterone excess in 30–60% of the patients with PA. PA is much less commonly (3–5% of the cases) caused by unilateral micro- or macronodular adrenal hyperplasia. Familial forms of PA — familial hyperaldosteronism (FH) types I and II — are even rarer [68]. FH type I, or glucocorticoid-remediable aldosteronism (GRA), is an autosomal dominant condition. This form of PA is characterised by manifestations of aldosterone excess of varying severity and increased levels of 18-hydroxycortisol and 18-oxocortisol, which result from expression of a hybrid gene, and by responsiveness to corticosteroid treatment [69]. Genetic testing for GRA should be performed in relatives of patients with GRA, relatives of patients with a history of stroke at a young age, and patients with diagnosed with PA before the age of 20 years [70]. FH type I in the Polish population is most probably sporadic, as evidenced by the lack of the hybrid aldosterone gene typical of GRA in 129 patients with PA [71]. FH type II predisposes to the familial occurrence of APA, BAH or both [72]. FH type II may be a monogenic or an autosomal dominant condition. FH type II should be suspected in cases of familial occurrence of PA after GRA has been ruled out. The incidence of FH type II is estimated to be higher than that of GRA [72].

The histopathological presentations of PA vary considerably (Figure 9) and contain in their spectrum the typical APA, APA co-existing with nodular hyperplasia (in various proportions) and the typical BAH, which may be micro- or macronodular [73]. Mixed forms, in which BAH overlaps with APA, are also common. The differentiation between the individual forms of PA is essential for the selection of conservative or surgical therapy in cases of aldosterone excess caused by BAH or APA, respectively. It is estimated that APA is the cause of HT in 2.5% of the patients. The percentage of candidates for adrenalectomy for PA is the same. In practice, the establishment of the cause of hyperaldosteronism is often impossible, as the demonstration of adenoma or hyperplasia is not decisive in establishing the aetiology of PA, particularly since non-functioning adrenal adenomas occur in 5–10% of the general population and their prevalence increases with age [74, 75]. Measurements of aldosterone levels in blood sampled during adrenal vein catheterisation (AVC) have shown that the cause of PA may be localised contralateral to the identified adenoma, may be caused by bilateral adenomas or by unilateral overproduction of aldosterone despite signs of hyperplasia in both adrenal glands [30, 76]. PA is only exceptionally caused by adrenal carcinoma, which is usually characterised by a diameter exceeding 4 cm an a heterogenous structure [74].

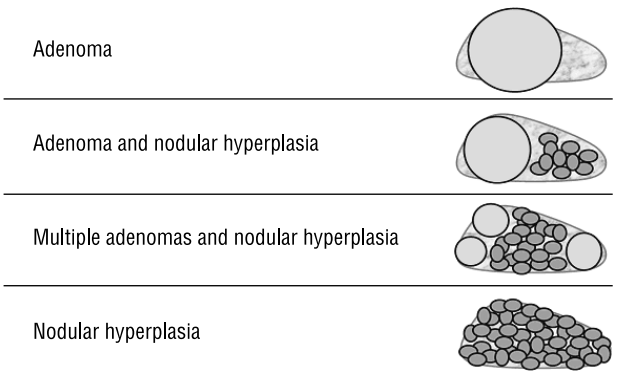

Figure 9. *The histopathology of primary aldosteronism*
Rycina 9. *Obraz histopatologiczny pierwotnego aldosteronizmu*

Detection of a solitary homogenous hypodense lesion of an adenomatous nature (density < 10 Hounsfield units [HU]) in the presence of an intact contralateral adrenal gland in a young (aged < 40 years) patient justifies adrenalectomy [23]. Patients with PA caused by APA are usually characterised by a higher grade of HT, hypokalaemia and higher ALDO values. Aldosteronomas can, however, be microadenomas (< 1 cm) and for this reason they may not be detected by CT and may erroneously suggest adrenocortical hypertrophy. In one of the studies CT revealed unilateral lesions only in 55 out of 111 patients with surgically confirmed APA and CT scans revealed only 25% of microadenomas [77]. In another study of 203 patients, APA was correctly differentiated from BAH in a mere 53% of the patients: 1/5 of the patients would have been incorrectly considered ineligible for adrenalectomy and 1/4 of the patients would have undergone unnecessary surgery [78]. For this reason AVC is necessary in most patients considered for adrenalectomy.

AVC is an invasive procedure and not an easy one to perform, mainly because of the small diameter of the right adrenal vein [31, 78, 79]. Hence the radiologist's experience and manual skills are of key importance. In order to minimise the impact of stress on aldosterone secretion the patients are often started on cosyntropin infusion at the dose of 50 mg/h 30 minutes prior to catheterisation with the infusion being continued until completion of the procedure. An ALDO gradient of more than 4:1 confirms a unilateral cause of PA (sensitivity 95%, specificity 100%), while a gradient of less than 3:1 indicates a bilateral cause of aldosterone excess [78]. In centres with expertise the incidence of complications is about 2.5%. The complications include: haematoma, adrenal haemorrhage and adrenal vein dissection [78, 79].

Treatment

The aim of the treatment of PA is to normalise blood pressure and serum potassium levels and to prevent cardiovascular damage.

Unilateral adrenalectomy is usually reserved for cases of PA caused by excessive secretion of aldosterone by one adrenal gland (APA or, rarely, hyperplasia). Laparoscopic adrenalectomy is recommended, as it makes it possible to shorten hospitalisation and reduce the number of complications [8, 9]. In the preparation of patients with PA for adrenalectomy pharmacotherapy with aldosterone antagonists and thiazide diuretics are used to normalise blood pressure and potassium levels. In patients with BAH, even bilateral adrenalectomy rarely results in blood pressure normalisation, which is why the treatment of choice involves the use of drugs which counteract aldosterone effects, especially since the removal of both adrenals is associated with the necessity of lifetime replacement treatment with adrenal cortex hormones [31]. Unilateral adrenalectomy in some selected patients with BAH may significantly reduce the severity of HT by reducing the mass of aldosterone-producing tissue [80]. Confirmation of lateralisation by means of AVC is usually a decisive factor in qualifying the patient for surgery, which leads to normalisation of potassaemia in nearly all of the patients and corrects HT in 30–60% or at least improves it in the remaining patients, making it possible to reduce the intensity of antihypertensive treatment [10, 68, 81, 82]. Therefore, in about 50% of the patients undergoing adrenalectomy, it is not possible to discontinue antihypertensive treatment [83, 84]. If permanent normalisation of blood pressure is achieved (without the use of antihypertensive medication) following laparoscopic adrenalectomy, it is the least expensive method of treatment in the long term [85]. Surgery fails to normalise blood pressure in older patients, in patients with a longer-standing HT, with a greater likelihood of the co-existence of essential HT (familial occurrence) and in patients with renal impairment [81, 82]. Patients with high ALDO and extremely decreased PRA have a better chance of achieving a complete resolution of HT after adrenalectomy causing PA [10].

The reason for the persistence of HT despite the correction of elevated serum aldosterone by adrenal surgery in the patient with PA is the usually co-existent primary HT and/or glomerulosclerosis resulting form long-standing uncontrolled HT in the arterial system [83, 84]. In some patients, the failure to fully correct HT following adrenalectomy may be associated with an incorrect classification of the cause of PA on the basis of imaging studies (without AVC) as unilateral, while in reality the PA is caused by BAH, which should be treated pharmacologically [10].

Table IV. *Aldosterone Resolution Score (ARS) (source [86])*

Tabela IV. *Skala oceny szansy na wyleczenie aldosteronizmu (źródło [86])*

Clinical feature	Points
≤ 2 antihypertensive drugs	2
BMI ≤ 25 kg/m^2	1
Hypertension of ≤ 6 years' duration	1
Female sex	1
ARS	**% patients cured**
0–1	27 (approx. 1/4)
2–3	46 (approx. 1/2)
4–5	75 (3/4)

BMI — body mass index

Young et al. proposed the aldosterone resolution score (ARS) to help clinicians to more correctly select patients most likely to achieve normal blood pressure following adrenalectomy [85]. Based on a study of 100 patients with PA at Mayo Clinic four clinical features characterised by the highest predictive value as regards the chances of complete resolution of HT after resection of the affected adrenal gland. Each of the four features of the ARS score was assigned 1 or 2 points to differentiate the predictive value (Table IV). According to the authors it may be predicted normalisation of blood pressure following adrenalectomy will be achieved by every only fourth patient with an ARS of 0–1, every second patient with an ARS of 2–3 and three fourths of patients with an ARS of 4–5. ARS requires verification in studies conducted by other centres.

For those patients with PA who are not eligible for adrenal surgery due to BAH, low ARS or the refusal of consent treatment with mineralocorticoid receptor agonists is a viable alternative [87]. Treatment used for more than 5 years also in patients with APA effectively maintains normal blood pressure and normal potassaemia. Important elements of the conservative treatment of HT, including HT caused by PA, is low-salt diet (< 100 mEq of sodium daily), maintaining normal body weight, not smoking, not abusing alcohol and regular aerobic exercises [68].

No randomised controlled studies have so far been conducted to assess the efficacy of various pharmaceuticals in patients with PA, although spironolactone is an effective, tried and tested first-line drug in these patients. The drug should be given at doses that make it possible to achieve normal potassium levels without the need for supplementation. Spironolactone is given

with food, which increases its absorption, starting from 25 mg daily and increasing the dose every 2 weeks [23].

The mineralocorticoid receptor antagonist class includes spironolactone (a non-selective antagonist) and eplerenone (a selective antagonist). Doses should be increased until normalisation of potassaemia is achieved. Normalisation of blood pressure is achieved later, after 4–8 weeks of pharmacotherapy. After normal blood pressure values have been achieved the doses of antihypertensive medication can be reduced in some patients. After initiation of treatment serum potassium and creatinine levels should be monitored, initially every month, particularly in patients with renal failure and diabetes mellitus. NSAIDs should not be combined with spironolactone, as they interfere with tubular excretion of its active metabolites, decreasing its efficacy. Spironolactone, on the other hand, prolongs the half-life of digoxin, potentiating its effects. As it is not a selective antagonist of the aldosterone receptor, spironolactone may also bind with the testosterone receptor, resulting in painful gynaecomastia, libido abnormalities in men and menstrual disorders in women, due to the stimulation of progesterone receptors. The frequency of gynaecomastia during spironolactone treatment depends on the dose: gynaecomastia affects 7% of patients receiving the dose of 50 mg/day and 52% of patients receiving the dose of 150 mg/day [87]. Eplerenone is a selective inhibitor of aldosterone receptors showing a 1000-fold lower affinity for the testosterone receptor and a 100-fold lower affinity for the progesterone receptor compared to spironolactone. In addition, the half-life of eplerenone is shorter, which is why it has to be given twice daily. It is recommended that the conservative treatment of PA should be initiated with spironolactone and if adverse effects develop, especially gynaecomastia, the patient should be switched to eplerenone. Despite head-to-head comparative studies of the potency of spironolactone and eplerenone the former is considered to be more effective. Eplerenone is more expensive. However, being more selective, eplerenone is not associated with such a high frequency of gynaecomastia as spironolactone [23].

Patients with BAH usually require long antihypertensive treatment before good blood pressure control is achieved. Taking into account that hypovolaemia is the most common reason for resistance to treatment, hydrochlorothiazide is often added at the daily dose of 12.5–50 mg. Potassium-sparing diuretics, amiloride and triamterene (sodium channel inhibitors), are not recommended as the principal drugs in PA, as they do not counteract the undesirable effect of aldosterone excess on the cardiovascular system, although they can supplement the effects of aldosterone antagonists in normalising blood pressure and potassaemia. The second group of antihypertensive drugs that can be used are ACEIs, which reduce the levels of serum AII, a stimulator of aldosterone secretion, especially in patients with BAH [87].

Before the initiation of treatment of GRA with a corticosteroid the diagnosis should be confirmed by genetic testing and the doses of the steroid should be optimised, while avoiding the occurrence of hypercortisolaemia.

Conclusions

Studies conducted in the past few years demonstrate that PA is a common, potentially curable cause of hypertension and an important cardiovascular risk factor. Taking this into consideration recommendations have been developed under the aegis of the of Endocrine Society for the diagnosis and treatment of PA, as a valuable guide for clinicians. While the diagnosis of PA is key, the evaluation of PA is associated with considerable errors, especially in terms of false positive results, due to the imperfection of laboratory assays and the influence of numerous factors. Hence the authors of the document recommend that each case should be considered individually. The demonstration of the au-

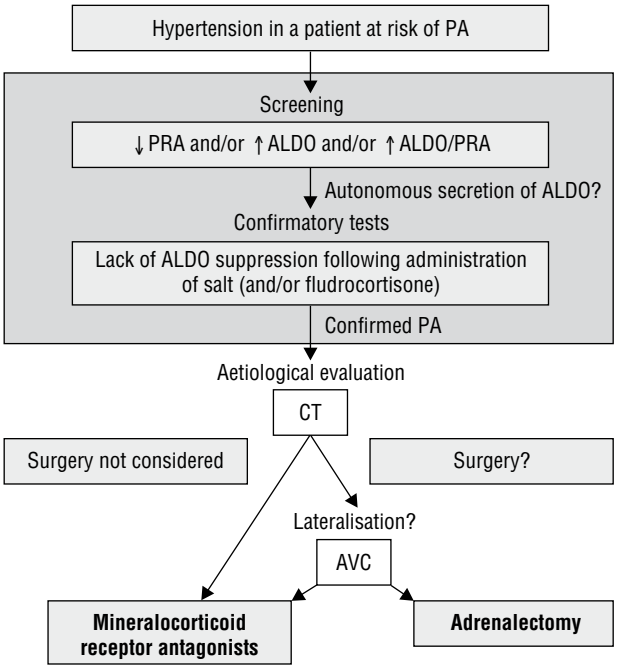

Figure 10. *A diagnostic and therapeutic algorithm in primary aldosteronism; PRA — plasma renin activity; ALDO — serum aldosterone levels; CT — computed tomography; AVC — adrenal vein catheterization*

Rycina 10. *Algorytm postępowania diagnostyczno-leczniczego w pierwotnym aldosteronizmie (PA); PRA — aktywność reninowa osocza; ALDO — stężenie aldosteronu w surowicy; CT — tomografia komputerowa; AVC — cewnikownie żył nadnerczowych*

tonomy of aldosterone secretion in a confirmatory test effectively selects patients for the much more expensive causative evaluation of PA without significantly increasing the costs of evaluation. From the therapeutic point of view, the causes of PA may be divided into unilateral (APA, unilateral adrenal hyperplasia and adrenal carcinoma), in which laparoscopic adrenalectomy is recommended, and bilateral (BAH and, rarely, GRA). As on the one hand aldosteronomas are often small tumours but on the other hand a considerable percentage of the population has non-functioning adenomas, the CT presentation is not conclusive as to the location of the source of excess aldosterone (with the exception of young patients). If the patient is a potential candidate for surgery, he should undergo AVC, which — in most cases — is conclusive as to whether the cause of PA is unilateral (and the patient is eligible for adrenalectomy) or bilateral (in which case the treatment should involve administration of aldosterone antagonists). Conservative treatment should also be offered to patients with PA who refuse to undergo surgery or are not appropriate candidates for it due to contraindications or little changes of benefitting from this modality. The aim of the treatment of PA, irrespective of the cause, is to achieve normal potassaemia, normal blood pressure and to minimise the adverse consequences of aldosterone effects on the cardiovascular system.

A diagnostic and therapeutic algorithm in PA is presented in Figure 10.

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