Polish Society of Hypertension

2015 Guidelines for the Management of Hypertension

Part 8

Recommendations of the Polish Society of Hypertension

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Table XXV. Suggestive symptoms, signs and laboratory test results, and specific investigations for secondary forms of hypertension

Cause of hypertension	Symptoms, signs, and routine and additional laboratory test results suggesting a secondary form of hypertension				Investigations	
	History	Physical examination	Routine tests	Additional tests	First choice (screening) tests	Confirmatory tests
Obstructive sleep apnoea	Characteristic daytime and nocturnal symptoms* Symptom evaluation using questionnaires*	Abdominal obesity Increased neck circumference* Abnormalities of the splanchnocranium	Elevated glucose level, dyslipidaemia	Reduced or absent nocturnal BP fall in ABPM Elevated morning BP values in HBPM Arrhythmia and/or conduction disturbances in Holter ECG monitoring	Nocturnal study using a type IV device*	Nocturnal study using a type I–III device*
Parenchymal renal disease	History or urinary tract infection or abnormal anatomy, haematuria, overuse of analgesics, family history of kidney disease	Palpable enlarged kidneys (in cystic kidney disease)	Presence of protein, erythrocytes, or leukocytes in urine; reduced GFR	Albuminuria/proteinuria of varying severity	Renal ultrasound	Detailed investigations for kidney disease
Primary hyperaldosteronism	Muscle weakness, family history, particularly of severe hypertension or early onset hypokalaemia and cerebrovascular events < 40 years of age	Cardiac arrhythmia	Hypokalaemia (spontaneous or diuretic-induced)	Incidentally found adrenal lesion, severe target organ damage Reduced or absent nocturnal BP fall in ABPM	Aldosterone-renin ratio*	Confirmatory hormonal testing* Adrenal CT/MRI Adrenal venous sampling
Atherosclerotic RAS	Hypertension of sudden onset or increasing severity, worsening of BP control Resistant or malignant hypertension Recurrent flash pulmonary oedema	Vascular bruit in mid-abdomen	Rapid worsening of renal function (spontaneous or during treatment with RAAS inhibitors) Hypokalaemia	Renal ultrasound: kidney length difference > 1.5 cm Small kidney	Doppler renal ultrasound	CTA MRA Invasive angiography
RAS due to fibromuscular dysplasia	Hypertension of early onset (particularly in women) Increasing severity of hypertension, worsening of BP control Resistant or malignant hypertension History of fibromuscular dysplasia or arterial dissection in other vascular bed	Vascular bruit in mid-abdomen	Rapid worsening of renal function (spontaneous or during treatment with RAAS inhibitors) Hypokalaemia	Renal ultrasound: kidney length difference > 1.5 cm Small kidney	Doppler renal ultrasound	CTA MRA Invasive angiography

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Table XXV. Suggestive symptoms, signs and laboratory test results, and specific investigations for secondary forms of hypertension (continued)

Cause of hypertension	Symptoms, signs, and routine and additional laboratory test results suggesting a secondary form of hypertension				Investigations	
	History	Physical examinations	Routine tests	Additional tests	First choice (screening) tests	Confirmatory tests
Catecholamine-secreting tumour	Paroxysmal BP elevations Headaches, increased sweating, palpitations, pallor Family history of phaeochromocytoma	Skin lesions typical for neurofibromatosis (café au lait spots, neurofibromas)	Hyperglycaemia	Incidentally found adrenal (or sometimes extrad renal) lesion	Plasma free metanephrines or urinary fractionated metanephrines	CT or MRI of the abdomen and pelvis ^{123}I-MIBG scintigraphy Screening genetic testing for pathogenetic mutations
Cushing syndrome	Rapid increase in body weight, polyuria, polydipsia, psychological problems	Typical body physique (central obesity, moon face, buffalo hump), red striae, hirsutism, easy bruising	Hyperglycaemia	Incidentally found adrenal lesion	24-hour urinary free cortizol excretion Low-dose (1 mg) dexamethasone suppression test	Dexamethasone suppression tests
Coarctation of the aorta	Intermittent claudication, headaches, syncope, epistaxis	Murmur heard in the precordial or interscapular area Diminished and delayed femoral artery pulse and decreased blood pressure in the femoral artery compared to simultaneous arm measurement Blood pressure difference between the left and right arm	Reverse E sign and rib notching on chest X-ray	Abnormalities on echocardiography	Echocardiography	CTA MRA
Renin-secreting tumour	Severe/resistant hypertension, polydipsia, polyuria	Cardiac arrhythmia (in severe hypokalaemia)	Hypokalaemia	Incidentally discovered kidney lesion	Renin level or plasma renin activity and aldosterone level	Kidney CT or MRI

*details see text

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CT, computed tomography; CTA, computed tomography angiography; ECG, electrocardiographic; HBPM, home blood pressure monitoring; GFR, glomerular filtration rate; MIBG, metaiodobenzylguanidine; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; RAAS, renin-angiotensin-aldosterone system; RAS, renal artery stenosis.

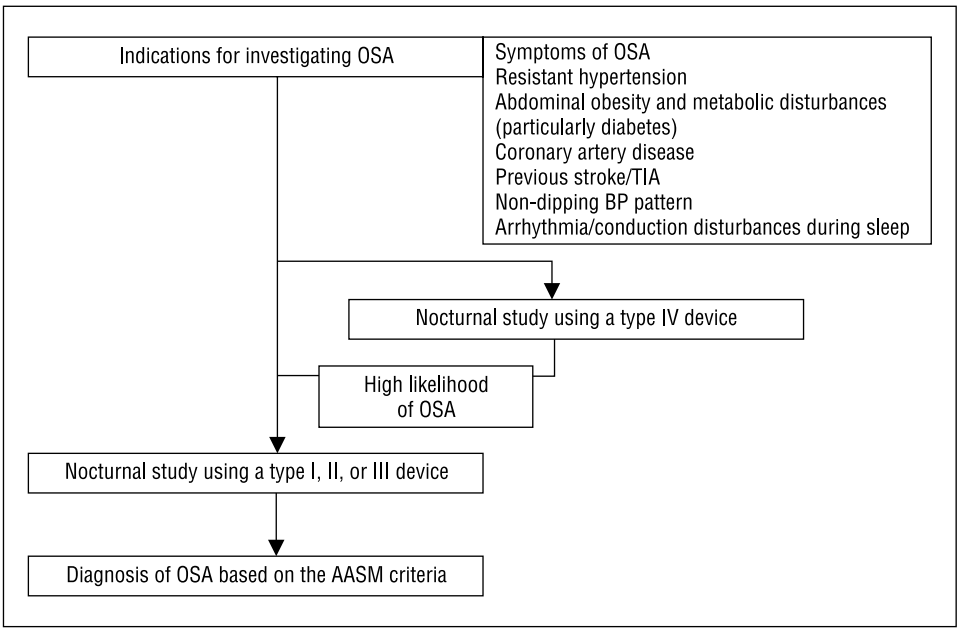


Figure 10. Diagnostic algorithm for obstructive sleep apnoea
AASM, American Academy of Sleep Medicine; BP, blood pressure; OSA, obstructive sleep apnoea; TIA, transient ischemic attack. Type I–IV devices: explanation see text

bances.

Available questionnaires, such as the Epworth Sleepiness Scale and the Berlin Questionnaire, lack specificity to allow excluding OSA. However, they may be helpful in identifying patients at an increased risk of OSA and should be included in the basic evaluation of a hypertensive patient.

Investigations for OSA include 4 types of devices and systems:

I. Complete polysomnography performed in a sleep laboratory.
II. Portable (unsupervised) polysomnography, recording a minimum of 7 channels, including all that are necessary to evaluate the sleep structure and the breathing pattern.
III. Polygraphy, or a limited recording of at 4 least parameters, including respiratory movements of the chest and abdomen, air flow through the upper airway, and oxygen saturation, without evaluation of the sleep structure.
IV. Recording of maximum 2 parameters, e.g., nocturnal pulse oximetry.

Use of different diagnostic devices and the diagnostic algorithm in cases of suspected OSA are summarized in Figure 10.

8.2.4. Diagnostic criteria

For a diagnosis of OSA, the criteria A, B, and D or only C and D must be fulfilled.

A. At least one of the following:
   a. inadvertent falling asleep, excessive daytime somnolescence, ineffective sleep, tiredness, or insomnia;
   b. awakenings with the feeling of breathing cessation, dyspnoea or choking;
   c. habitual snoring or episodes of apnoea noted by the partner of the patient.
B. Polysomnography findings:
   a. at least 5 disordered breathing events per hour of sleep (AHI ≥ 5);
   b. respiratory muscle activity noted during these episodes.
C. Polysomnography findings:
   a. at least 15 disordered breathing events per hour of sleep (AHI ≥ 15);
   b. respiratory muscle activity noted during these episodes.
D. The above findings are not related to other sleep disturbances, diseases (including neurological disease), or use of medications or other substances.

- Classification of the severity of OSA:
- Mild OSA (AHI ≥ 5 and ≤ 15);
- Moderate OSA (AHI > 15 and ≤ 30);
- Severe OSA (AHI > 30).

8.2.5. Management of obstructive sleep apnoea

The management of OSA includes the following:

- behavioural methods:

— body weight reduction (in all patients);
— avoidance of a supine position during sleep or sleeping in a semi-sitting position (in patients with mild or moderate OSA without severe obesity);
— avoidance of alcohol intake (in all patients);
— smoking cessation (in all patients);
— avoidance of sedative-hypnotics and narcotic analgesics (in all patients);

- mandibular advancement splints (simple snoring and mild OSA not responsive to behavioural treatment);
- continuous positive airway pressure (CPAP) therapy (all patients with AHI > 30; patients with AHI > 15 and excessive daytime somnolence [Epworth Sleepiness Scale score > 10] or cardiovascular disease)
- surgery (indications set individually).

Of the above methods, a beneficial effect on the reduction of cardiovascular risk and mortality has been shown only for the CPAP therapy. Published studies also indicate that regular use of CPAP for an appropriately long period of time during the night may be associated with BP lowering, particularly in patients with resistant hypertension.

8.2.6. Treatment of hypertension in patients with obstructive sleep apnoea

Limited data are available to develop recommendations regarding antihypertensive therapy in patients with OSA. Some evidence suggests benefits of aldosterone antagonists in terms of not only improvement of BP control but also reduction of the severity of OSA. However, these studies were performed in small groups of patients and further studies are required. Further research is also necessary to determine potential benefits of renal denervation in patients with resistant hypertension and concomitant OSA.

8.2.7. Care for patients with hypertension and concomitant obstructive sleep apnoea

The following issues should be evaluated during each visit related to the treatment of hypertension:

- in patients with previously undiagnosed OSA:
  — symptoms suggestive for, and the risk of OSA,
  — indications for investigations to diagnose OSA;
- in patients with established OSA without previous indications for CPAP therapy:
  — compliance regarding behavioural therapy for OSA,
  — indications for reassessment of the severity of OSA;
- in patients with established OSA and indications for CPAP therapy:
  — compliance regarding behavioural therapy for OSA,
  — compliance regarding CPAP therapy, and factors associated with noncompliance with this therapy,
  — frequency and duration of CPAP therapy during the night (data retrieved from the device memory).

8.3. Atherosclerotic renal artery stenosis

8.3.1. Introduction

Hypertension due to renal artery stenosis (RAS), also known as renovascular hypertension, is a secondary form of hypertension caused by excessive renin production in the ischemic kidney. Significant RAS does not only produce hypertension but also impairs excretory, endocrine, and homeostatic renal function and results in ischemic nephropathy. In some patients, RAS is a cause of end-stage renal disease and the need for renal replacement therapy. Most commonly, RAS is of atherosclerotic origin. The second most common cause of RAS is fibromuscular dysplasia, which is discussed in a separate section of the present document.

8.3.2. Indications for investigations to diagnose atherosclerotic renal artery stenosis

Investigations to diagnose atherosclerotic renal artery stenosis should be considered primarily in patients with:

- hypertension that is:
  — severe,
  — resistant,
  — malignant (accelerated);
- episodes of unexplained flash pulmonary oedema (Pickering syndrome) and/or unexplained congestive heart failure;
- unexplained renal failure (including patients in whom renal replacement therapy is initiated);
- new-onset azotaemia or worsening of renal function following administration of a RAAS inhibitor;
- hypokalaemia, particularly in patients treated with diuretics;
- an abdominal bruit;
- difference in kidney length > 1.5 cm or a small kidney.

Atherosclerotic RAS should also be suspected in hypertensive patients with atherosclerosis in other vascular beds, including coronary arteries. The rates of atherosclerotic RAS correlate with the severity of atherosclerosis in other vascular beds.

8.3.3. Diagnostic methods for renal artery stenosis

8.3.3.1. Doppler renal ultrasonography

Doppler renal ultrasonography is recommended as the first-line noninvasive diagnostic test in patients with suspected RAS. It allows evaluation of the extra- and intrarenal arteries, localization of the stenosis, and assessment of its aetiology.

In patients with a suspicion of RAS based on Doppler renal ultrasonography and clinical indications for revascularization, computed tomography angiography (CTA), magnetic resonance angiography (MRA), or invasive renal angiography should be performed before the revascularization procedure.

Renal CTA or MRA should be also performed in case of normal Doppler renal ultrasonography findings in patients with a significant clinical suspicion of RAS.

Doppler renal ultrasonography allows long-term follow-up of patients after correction of RAS and evaluation of disease progression in medically treated patients. Follow-up examinations in revascularized patients should be performed immediately after the revascularization procedure and 6-12 months afterwards. Follow-up examinations to evaluate progression of borderline lesions treated medically should be performed annually. In these patient groups, urgent Doppler renal ultrasound reevaluation should be performed in case of acute worsening of BP control and/or renal function.

8.3.3.2. Computed tomography angiography

Computed tomography angiography is indicated to confirm the diagnosis of RAS (in patients with normal or moderately impaired renal function, defined as eGFR > 30 mL/min).

Normal CTA findings exclude a hemodynamically significant stenosis of the main renal artery. Advantages over MRI include better spatial resolution and fewer artifacts in patients with renal stents. CTA should include urographic phase images in patients with a small kidney or a critical RAS.

Disadvantages of CTA include the risk of adverse effects related to intravenous administration of an iodine contrast agent and the effects of ionizing radiation absorbed by the patients. Another disadvantage of CTA is a limited ability to evaluate the significance of stenoses in accessory renal arteries and intrarenal arterial branches.

8.3.3.3. Magnetic resonance angiography

Magnetic resonance angiography is indicated to confirm the diagnosis of RAS. The most effective imaging sequence is three-dimensional gradient echo (3D GRE) following intravenous administration of a contrast agent. Evaluation should include both primary images and multiplanar reconstructions. Contrast-enhanced MRA allows excluding a hemodynamically significant stenosis of the main renal artery.

Magnetic resonance angiography is also useful for imaging of kidney transplant vessels. Nephrotoxicity of paramagnetic contrast agents in doses used for MRI is low and occurs infrequently but a possibility of nephrogenic systemic fibrosis in patients with renal dysfunction should be taken into consideration. In patient with significant renal dysfunction, MRA may be performed without contrast enhancement (using techniques such as true fast imaging with steady state precession [true-FISP], time-of-flight [TOF] angiography, and phase contrast [PC] imaging), with somewhat lower image quality compared to contrast-enhanced images.

Disadvantages of MRA include somewhat lower spatial resolution, a tendency to overestimate the degree of vessel stenosis, unreliable evaluation of the patency of some stents due to artifacts, and poor ability to evaluate small arteries (with a diameter of < 2 mm), including accessory renal arteries and intrarenal arterial branches.

8.3.3.4. Invasive renal angiography

Invasive renal angiography is performed to image the renal artery and its branches. It involves introduction of a pigtail catheter to the aorta at the level of renal arteries and injecting an iodine contrast agent. This method allows very good visualization of both the main renal artery and accessory renal arteries, and particularly their origin from the aorta. Selective renal angiography using catheters with appropriately curved tips is also recommended.

The indication for invasive renal angiography is the presence of clinical findings suggesting significant RAS, if the diagnosis cannot be definitively established based on noninvasive testing only.

Disadvantages of this method include an invasive nature of the procedure, exposure to ionizing radiation, and use of a potentially nephrotoxic contrast agent.

If the aetiology of the lesion is unclear, conventional angiography may be supplemented with intravascular ultrasound (IVUS).

In the recent years, it has been suggested to use translesional pressure gradient measurements using a special guidewire to identify hemodynamically significant RAS. The ratio of the mean pressure distal to the stenosis to the mean aortic pressure at basal conditions below 0.9 was associated with increased renin production. This ratio correlates with papaverine-induced systolic pressure gradient of more than

Table XXVI. Indications for revascularization of atherosclerotic renal artery stenosis (RAS)

Angioplasty may be considered (rather with stent implantation) in symptomatic RAS > 60% secondary to atherosclerosis
If angioplasty is indicated, stenting is recommended to treat ostial RAS of atherosclerotic aetiology
Interventional RAS treatment may be considered in patients with renal dysfunction
Balloon angioplasty with or without stenting may be considered in patients with RAS and recurrent congestive heart failure of undetermined aetiology, or with flash pulmonary oedema with preserved left ventricular ejection fraction
Surgical revascularization may be considered in patients undergoing aortic repair surgery, patient with complex renal artery anatomy, and following failure of interventional treatment

21 mm Hg under the conditions of maximal hyperaemia. Dopamine-induced pressure gradient above 20 mm Hg was associated with a favourable response to renal artery stenting.

Use of invasive renal angiography is limited to imaging before angioplasty and quantitative evaluation of the stenosis. This method may also be considered in patients with a significant clinical suspicion of RAS who undergo other invasive angiographic imaging (e.g., coronary angiography).

8.3.3.5. Other investigations

Captopril renal scintigraphy, renal vein catheterization, measurements of plasma renin activity, and the captopril challenge test are not recommended as screening tests for the diagnosis of RAS.

8.3.4. Management of atherosclerotic renal artery stenosis

Until now, no randomized study showed a significant effect of interventional treatment on the course of hypertension. The decision to implant a stent into a renal artery with an atherosclerotic stenosis should be based on multiple additional clinical factors and laboratory parameters. The arbitral stenosis threshold at 60% is worryingly low and may result in too hasty consideration of the intervention. Taking into account often erroneous estimation of the stenosis degree by angiography, and the effect of additional clinical and nephrological parameters on the decision to proceed with the intervention, patient selection and stent implantation should be performed in experienced hypertension units.

In a large randomized study published in 2013 (CORAL), it was found that revascularization in patients with atherosclerotic RAS was not associated with additional benefits in regard to a reduction in the mortality rate due to cardiovascular or renal events, cardiovascular event rate reduction, improvement of renal function, and a reduced rate of renal events compared to medically treated patients. In both groups, a significant BP — lowering effect was seen, obtained by intensification of the drug treatment using a combination of ARB + calcium antagonist + thiazide diuretic (mean SBP reduction throughout the study was 16–17 mm Hg). SBP lowering was more pronounced in the revascularization group (between-group difference of 2.3 mm Hg).

Indications for revascularization of atherosclerotic RAS are shown in Table XXVI.

8.3.5. Treatment of hypertension in patients with atherosclerotic renal artery stenosis

In patients with unilateral RAS, ACEI and calcium antagonists are effective in the treatment of hypertension and may decrease progression of nephropathy. Even in unilateral RAS, treatment with ACEI or ARB requires caution and monitoring of renal function parameters. A significant decrease in eGFR (by ≥ 30%) or an increase in plasma creatinine level (by > 0.5 mg/dL) may indicate the need to consider revascularization. ACEI and ARB are contraindicated in bilateral RAS and RAS in the single kidney.

Available evidence indicates that thiazide/thiazide-like diuretics, ARB, and beta-blockers are also effective in lowering BP to target values in patients with RAS.

The CORAL study showed that a combination of an ARB, a calcium antagonist, and a thiazide diuretic is effective antihypertensive drug therapy in patients with atherosclerotic RAS and difficult-to-control hypertension.

All patients with atherosclerotic RAS should be treated in accordance with the guidelines on cardiovascular disease prevention.

8.3.6. Care for patients with hypertension and concomitant atherosclerotic renal artery stenosis

In patients with end-stage renal disease, life expectancy is the shortest among patients with RAS. However, life expectancy is also significantly reduced in RAS patients without end-stage renal disease. Two-year mortality in patients with baseline serum creatinine concentrations before revascularization below 1.2 mg/dL,

1.2–2.5 mg/dL, and above 2.5 mg/dL was 5%, 11%, and 70%, respectively. More than 80% patients die due to cardiovascular disease. Thus, patients with atherosclerotic RAS should be considered a very high cardiovascular risk population.

8.4. Renal artery stenosis due to fibromuscular dysplasia

Fibromuscular dysplasia (FMD) most commonly involves renal arteries and leads to the development of hypertension. Carotid arteries are the second most common location of FMD. FMD may be present in virtually all vascular beds, and is often concomitantly present in several areas in the vascular system. In a French registry of patients with FMD in the renal arteries, the rate of FMD in other vascular beds was 25% in the carotid arteries, 9% in the lower limb arteries, and 31% in other abdominal arteries. The arterial wall affected by FMD is prone to dissection and the development of aneurysms. Dysplastic changes located in the carotid and vertebral arteries may coexist with cerebral aneurysms. Renal artery dissection may have serious clinical consequences, leading to an acute development of severe, resistant, or malignant hypertension, loss of kidney function, and renal infarction. In patients with FMD, dissection may also involve other arteries, including carotid and coronary arteries.

8.4.1. Definition of fibromuscular dysplasia

Fibromuscular dysplasia is an idiopathic, segmental, non-atherosclerotic, and non-inflammatory vascular disease that leads to the development of stenoses in small- and medium-sized arteries.

8.4.2. Indications for investigations to diagnose fibromuscular dysplasia

The indications for investigating a possibility of RAS due to FMD in hypertensive patients include:

- age below 30 years, particularly in women;
- grade 3 hypertension (≥ 180 and/or 110 mm Hg), accelerated or malignant hypertension;
- resistant hypertension;
- small kidney without a previous history of uropathy;
- abdominal bruit without evidence of atherosclerosis;
- established FMD in at least one other vascular bed.

Indications for investigations to diagnose FMD in the neck and head arteries and other vascular beds:

- investigations for FMD in the craniocervical arteries should be considered in patients with a history of retinal or cerebral ischemic events, intracranial aneurysms, subarachnoid haemorrhage, craniocervical arterial dissection, or pulsatile tinnitus;
- in patients with FMD in the renal arteries, investigations for FMD in the craniocervical arteries should be considered if identification of such lesions is likely to affect future patient management;
- in patients with FMD within renal and/or craniocervical arteries, investigations for FMD lesions in other vascular beds (which are less frequent) should be considered in patients with suggestive symptoms or past medical history;
- investigations for FMD are also indicated in patients with spontaneous coronary artery dissection, particularly with the presence of hypertension or other suggestive symptoms;
- in patients with FMD in the craniocervical arteries, investigations for intracranial aneurysms are indicated if identification of such a lesion is likely to affect future patient management.

In patients with FMD, it is recommended to take family history regarding early development of hypertension and the occurrence of intracranial dissection, aneurysm or bleeding in first-degree relatives. In case of any positive family history, the patient may inform his or her relatives about the possibility of hereditary FMD.

8.4.3. Investigations for renal artery stenosis due to fibromuscular dysplasia

- Doppler renal ultrasonography:
  - — is a screening test to detect most cases of RAS;
  - — a positive result requires confirmation by other diagnostic modality, as does a negative result in a patient with a significant clinical suspicion of RAS.
- Magnetic resonance or computed tomography angiography (preferred);
  - — is recommended to confirm FMD in the renal arteries;
  - — is recommended as a screening (first-line) test if Doppler renal ultrasonography may be expected to be suboptimal (obese patients, withholding breath difficult or impossible, low echogenicity, little ultrasonographer experience);
  - — is recommended as a screening (first-line) test if the suspicion of FMD is very strong and/or the diagnosis has significant clinical consequences (very young age, malignant or complicated hypertension, complications in other vascular beds, increased creatinine level).

- Invasive renal digital subtraction angiography is recommended in patients with FMD confirmed by CTA or MRA if revascularization is clinically indicated:
  — in patients with a high degree of suspicion of RAS due to FMD;
  — in patients with uncertain diagnosis based on non-invasive studies.

8.4.4. Management of renal artery stenosis due to fibromuscular dysplasia

- In hypertensive patients with RAS due to FMD, revascularization is indicated:
  — in patients with a recent-onset hypertension, as the treatment of choice to normalize BP;
  — in patients in whom drug treatment is unsuccessful (due to drug resistance or intolerance);
  — in patients with renal failure or renal function worsening, particularly after administration of an ACEI or ARB;
  — in patients with a smaller kidney supplied by a significantly stenosed artery.
- Renal angioplasty is the treatment of choice for significant RAS due to FMD. Stenting is not recommended, except for periprocedural dissection.
- Surgical treatment of significant RAS due to FMD should be considered in patients with:
  — stenosis associated with a complex aneurysm;
  — recurrent stenosis after two unsuccessful angioplasty procedures;
  — a lesion involving renal artery bifurcation and its branches.
- In hypertensive patients with RAS due to FMD in whom revascularization is not indicated, appropriate follow-up is recommended, including:
  — clinical follow-up (monthly BP evaluation until target values are obtained, followed by further regular follow-up);
  — biochemical follow-up (yearly measurements of creatinine level);
  — imaging (yearly evaluation of kidney length by ultrasonography).
- In patients after revascularization for RAS due to FMD, recommendations include:
  — evaluation of BP and eGFR at one month after the procedure;
  — renal imaging at 6 months after the procedure or earlier in case of BP elevation or creatinine level rise.
- Patients with FMD should be strongly urged to stop smoking. They should be engaged in smoking cessation programs using all available agents recommended in the respective guidelines.

8.5. Primary hyperaldosteronism

8.5.1. Definition and prevalence

Primary hyperaldosteronism (PHA) is defined as a hormonally mediated form of hypertension caused by autonomous aldosterone production. Using this definition, PHA is diagnosed by showing that aldosterone level is unaffected by factors that affect its production in physiological conditions.

Primary hyperaldosteronism is not a pathogenetically uniform condition, and several forms of PHA are distinguished depending on the hormonal profile and the management approach:

- bilateral adrenal hyperplasia;
- adrenal cortex adenoma;
- familial hyperaldosteronism type I;
- familial hyperaldosteronism type II;
- familial hyperaldosteronism type III;
- aldosterone-producing adrenal carcinoma;
- ectopic aldosterone production (by neoplastic tissue).

The prevalence of PHA in hypertensive patients depends on BP values. In the general hypertensive population, PHA is present in up to 7% of patients (depending on the definition of PHA), while the prevalence of PHA in patients with resistant hypertension has been estimated at 6–23%.

8.5.2. Clinical presentation

Clinical symptoms of PHA result from excessive autonomous aldosterone production. An increased aldosterone level results in elevated urinary potassium excretion and reduced plasma potassium level, leading to hypokalaemia which is the cause of most PHA symptoms. Reduced potassium level induces muscle cell polarization disturbances, manifesting clinically as muscle weakness. Loss of the urine concentrating function of the kidney, resulting from hypokalaemic nephropathy, may lead to polyuria and polydypsia. In some patients, potassium levels may be in the normal range, and BP elevation may be modest.

It has been suspected that by inducing hypokalaemia and directly affecting cardiomyocytes and the cardiac conduction system, increased aldosterone level may contribute to cardiac arrhythmia and conduction disturbances. In patients with PHA, hypertensive target organ damage is more severe compared to patients with essential hypertension. ABPM in PHA patients may reveal elevated BP during the night with a reduced nocturnal BP fall, or even no nocturnal BP fall and BP rise during the night. Primary hyperaldosteronism may also coexist with OSA, particularly in patients with metabolic syndrome.

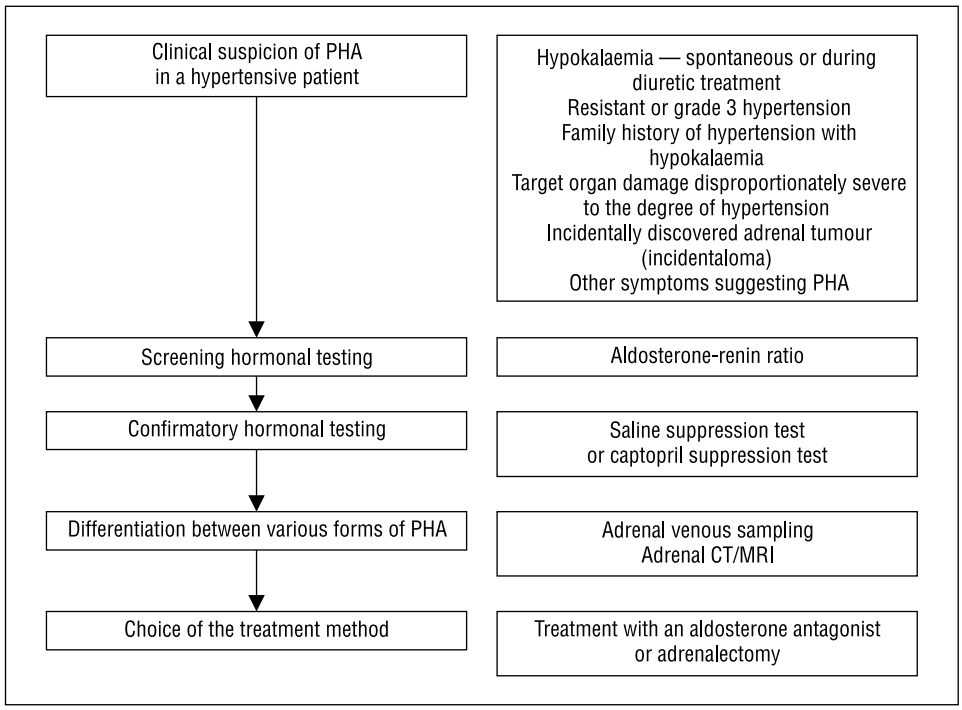


Figure 11. Diagnostic algorithm for primary hyperaldosteronism
CT, computed tomography; MRI, magnetic resonance imaging; PHA, primary hyperaldosteronism

Indications for investigations for PHA are summarized in Figure 11.

8.5.3. Screening for primary hyperaldosteronism

The primary screening test for PHA is evaluation of the aldosterone-to-renin ratio (ARR). When evaluating and interpreting ARR, the following should be taken into consideration:

- in patients with hypokalaemia, potassium level should be brought to normal values by adequate supplementation, and dietary sodium intake should also be controlled (normal sodium diet);
- antihypertensive drug therapy should be appropriately modified:
  - — drugs that significantly affect ARR should be withdrawn 4 weeks before testing, including spironolactone, eplerenone, triamterene, amiloride, thiazide/thiazide-like diuretics, and loop diuretics,
  - — if ARR is nondiagnostic and hypertension may be adequately controlled using drugs that do not affect ARR (see below), the following medications should be withdrawn 2 weeks before testing: beta-blockers, central alpha$_2$-agonists (clonidine, methyldopa), nonsteroidal antinflammatory drugs (false-positive ARR), and ACEI, ARB, renin inhibitors, and dihydropyridine calcium antagonists (false-negative ARR),
  - — drugs that have the least effect on ARR should be used to control hypertension, including verapamil, hydralazine, doxazosin, prazosin, and terazosin,
  - — in some situations, due to high BP values and concomitant conditions, appropriate modification of antihypertensive drug therapy is not possible and may be even associated with an increased cardiovascular risk; in these circumstances, the effect of drug therapy used in the patient should be taken into account;
- blood sampling for ARR should be performed in a sitting position between 9 and 10 AM, with the patient remaining upright (sitting, standing, walking) for 2-4 hours before blood collection, and the collected blood samples should be handled appropriately as agreed with the laboratory;
- due to the fact that interpretation of ARR is based on values considered abnormal in previous research studies and not reference ranges for the assays used in the laboratories, ARR should be determined in laboratories in which the assays for aldosterone and plasma renin activity or renin level were validated against the laboratories that have appropriate experience in the diagnosis of PHA;
- most commonly, the ARR value suggesting PHA is defined as:
  - — above 30 (aldosterone level in ng/dL and plasma renin activity in ng/mL/h); or

— above 830 (aldosterone level in pmol/L and plasma renin activity in ng/mL/h),
— for an elevated ARR to suggest PHA, plasma aldosterone level must be at least moderately increased (e.g., > 15 ng/dL or > 10 ng/dL),
— ARR is also much affected by the lower limit of detection of plasma renin activity by a given assay, which may be different for different assays and laboratories (plasma renin activity value used for calculating ARR should not be lower than 0.2 ng/mL/min),
— in the recent years, commercial assays to determine plasma renin level have been introduced; ARR conversion coefficient for renin level should be determined separately for each assay;

- other factors that may affect ARR value interpretation should also be taken into account, including age (low-renin essential hypertension in the elderly), creatinine level, concomitant conditions, difficult blood sampling, and use of hormonal drugs (oestrogen-containing preparations are associated with false-positive ARR values).

8.5.4. Confirmatory tests

The diagnosis of PHA is confirmed by establishing no effect of factors that normally decrease plasma aldosterone level or 24-hour urinary aldosterone excretion. Biochemical tests used to confirm the diagnosis of PHA include:

- oral salt loading test;
- saline suppression test;
- fludrocortisone suppression test;
- captopril suppression test.

When performing these tests, the same principles apply as described above for the screening tests (normalization of potassium level, normal sodium diet, appropriate modification of antihypertensive drug therapy). In Poland, the two tests that are currently most commonly used are the saline suppression test and the captopril suppression test:

- saline suppression test involves intravenous infusion of 2 litres of normal saline (0.9% NaCl) during 4 hours in a patient remaining in a semi -recumbent position. Plasma aldosterone level below 5 ng/dL at the end of the test indicates a low likelihood of PHA, and the level above 10 ng/dL indicates very likely PHA. Values in the range of 5–10 ng/dL should be interpreted individually. Due to a risk of complications such as worsening of BP control or exacerbation of heart failure, caution is necessary during this test;
- captopril suppression test involves measuring plasma aldosterone level (along with plasma renin activity or renin level) at baseline and 2 hours after administration of 25–50 mg of captopril. Normally, aldosterone level is reduced in these circumstances by more than 30%, and in patients with PHA it remains elevated, and plasma renin activity or renin level remains unsuppressed. The test is performed after assuming an upright position for more than one hour. During the test, the patient remains in the sitting position and BP should be evaluated frequently.

In patients with suspected familial PHA type I, possible investigations include genetic testing, urinary excretion of 18-oxocortisol and 18-hydroxycortisol, and the dexamethasone suppression test.

8.5.5. Differentiation between various forms of primary hyperaldosteronism

After the diagnosis of PHA has been established based on clinical symptoms and biochemical test findings, it is necessary to assess the nature and location of adrenal lesions. Various forms of PHA, in particular bilateral adrenal hyperplasia and adrenal adenoma, should also be differentiated.

8.5.5.1. Computed tomography

Computed tomography (CT) is currently the standard method to evaluate adrenal lesions. Its sensitivity for detecting adrenal tumours exceeds 90%. CT allows assessment of the morphology of detected adrenal tumours and identification of adrenal hyperplasia (anatomic evaluation). Varying reference ranges for normal thickness of the adrenals and their crura have been reported in the literature: an abnormal finding is segmental thickening of a single crux above 5–7 mm or the whole gland above 7–10 mm.

8.5.5.2. Magnetic resonance

Magnetic resonance imaging (MRI) has a similar sensitivity for detecting adrenal tumours compared to CT (> 90%). Evaluation of the nature of detected lesions is based on the application of chemical shift for the detection of lipids in adrenal adenomas. MRI is a second-line method to evaluate adrenal tumours that could not be adequately characterized by CT.

8.5.5.3. Adrenal scintigraphy

Adrenal scintigraphy is of little usefulness in differentiating between PHA forms. A new technique is positron emission tomography (PET)-CT using 11C-methomidate. Initial data suggest a potential utility of this method for distinguishing between various forms of PHA.

8.5.5.4. Adrenal venous sampling

Adrenal venous sampling (AVS) is the method of choice for differentiating between various forms of PHA (Figure 11). It should be performed only in adequately experienced centres. The success of this procedure in such centres, based on the proportion of diagnostically useful results, is more than 90%. In some patients, the finding of lateralized aldosterone secretion by AVS allows the diagnosis of adrenal adenoma smaller than 1 cm which is not detectable by CT. During AVS, blood samples are collected from both adrenal veins and from the vena cava inferior below the entry of renal veins, and aldosterone and cortisol levels are measured in the collected samples. Appropriate blood collection is confirmed by a higher cortisol level in the samples from the adrenal veins compared to the inferior vena cava sample (selectivity index). This should be done intraprocedurally, allowing further blood sampling in case the previous samples were not drawn from the adrenal veins. Interpretation of the aldosterone level requires determination of the aldosterone to cortisol level ratio in a given sample. Currently, it is generally accepted that lateralized aldosterone secretion is indicated by this ratio of at least 4:1. The test may be performed during ACTH infusion or without administration of ACTH.

Adrenal venous sampling should be performed in patients with the diagnosis of PHA in whom adrenalectomy is considered, except for patients:

- below 35 years of age, with significantly elevated aldosterone level, spontaneous hypokalaemia and clear CT/MRI findings of a unilateral adenoma (with the additional lesion size criterion of > 10 mm according to some authors) and a normal contralateral adrenal gland (in some centres, however, AVS is performed in all patients regardless of their age and imaging study findings);
- with an unacceptably high risk associated with adrenalectomy (e.g. elderly patients with significant comorbidities);
- with a suspicion of adrenal carcinoma;
- with the diagnosis of familial PHA type I or III;
- with 11C-methomidate PET-CT findings indicating a unilateral lesion, if it is not possible to perform AVS;
- with severe PHA, including high aldosterone level and hypokalaemia, if CT shows a unilateral lesion, familial PHA type I or III has been excluded, and it is not possible to perform AVS.

8.5.6. Management of primary hyperaldosteronism

In documented unilateral PHA due to an aldosterone-producing adenoma or unilateral adrenal hyperplasia, the treatment of choice is unilateral laparoscopic adrenalectomy, while patients with bilateral adrenal disease (idiopathic adrenal hyperplasia or bilateral adenomas) should be treated with aldosterone antagonists. Glucocorticoid-remediable aldosteronism should be treated with low doses of a long-acting glucocorticosteroid, e.g., dexamethasone.

In patients with bilateral adrenal disease and those with unilateral PHA who did not undergo adrenalectomy for various reasons, aldosterone antagonists are indicated. The initial spironolactone dose should be 12.5–25 mg once daily. The lowest effective dose should be determined by a gradual dose increase to 100 mg per day or more. To avoid high spironolactone doses, which may result in adverse effects, a thiazide diuretic, amiloride, or triamterene may be added. Eplerenone is a newer, selective mineralocorticoid receptor antagonist characterized by a weaker antiandrogenic effect and a weaker agonist effect on the progesterone receptor, and thus it is associated with a lower rate of adverse effects. The strength of its mineralocorticoid receptor antagonist effect has been estimated at 60% of that of spironolactone. Due to a shorter duration of action, this drug should be administered more frequently than once daily (initially 25 mg bid). However, eplerenone has not been licensed to treat PHA in the European Community.

8.6. Catecholamine-producing tumours

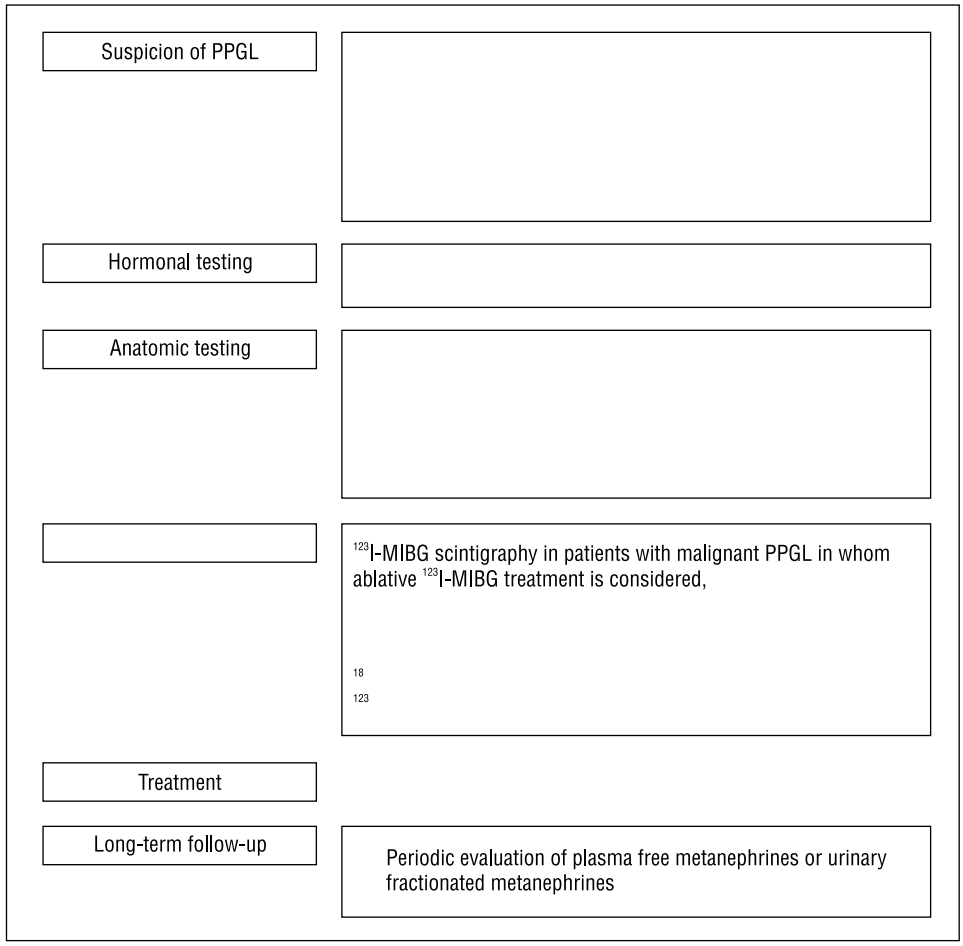
8.6.1. Definition

Adrenal catecholamine-producing tumours are known as phaeochromocytomas, and the remaining extra-adrenal chromaffin cell tumours, which may also be hormonally active, are known as paragangliomas. Collectively, these are called phaeochromocytomas-paragangliomas (PPGL).

It has been estimated that 80–85% of chromaffin cell tumours are located in the adrenal glands (phaeochromocytomas), and the remaining 15–20% are extra-adrenal.

8.6.2. Clinical presentation

Rich and variable clinical symptomatology of PPGL is related to the proportion of noradrenaline and adrenaline released by the tumour. Paroxysmal occurrence of symptoms which may have varying severity and recur with varying frequency is a characteristic feature. The provoking factors include exercise, abdominal pressure, large meals, some medications (ephedrine, phenylephrine, ACTH, phenothiazines, amphetamine, metoclopramide, tricyclic antidepressants, some anaesthesia drugs), stress, and alcohol intake. Catecholamine release by the tumour may also be induced by glucocorticosteroid administration.



Phaeochromocytomas may also remain asymptomatic (also with normal BP values).

The most common symptoms, usually paroxysmal in nature, include:

- paroxysmal BP surges (with typically large BP variation) which may last from several minutes to several hours;
- chronic hypertension;
- headache;
- excessive sweating;
- palpitation;
- pallor;
- tremor;
- anxiety;
- orthostatic hypotension.

On physical examination, skin may be pale and sweaty and pupils dilated, but most commonly, no characteristic PPGL signs are present. Elevated glucose level may be found on biochemical testing. ABPM may show large BP variation and a decreased nocturnal BP fall, or even a non-dipping BP pattern and BP elevation during the night.

8.6.3. Investigations for phaeochromocytoma-paraganglioma

The major diagnostic criterion for a hormonally active PPGL is the finding of an elevated urinary catecholamine metabolite excretion (or, less reliably, of catecholamines themselves) or their elevated serum level, with tumour localization by imaging studies. The final diagnosis is based on histopathologic assessment of the resected tumour. The diagnostic algorithm is summarized in Figure 12. The diagnosis of a hormonally non-functioning PPGL is based on imaging and functional studies, and the final diagnosis is again based on histopathologic assessment of the tumour.

Plasma free metanephrines and urinary fractionated metanephrines are considered the most useful (i.e., most sensitive) biochemical tests. The highest

sensitivity was reported for plasma free metanephrines (sensitivity 97–99%, specificity 82%). Urinary adrenaline and noradrenaline excretion is characterized by lower sensitivity and specificity, and the least diagnostic utility was shown for measurements of urinary vanillylmandelic acid and dopamine and plasma catecholamines. In rare cases, the clonidine suppression test may be performed (with determination of plasma normetanephrine level before and at 3 hours after clonidine administration).

Anatomical imaging studies in patients with PPGL should be performed after excessive catecholamine metabolite levels have been identified in plasma or urine (Figure 12). Localization studies for PPGL are also performed in PPGL gene mutation carriers. Useful imaging methods for PPGL include CT and MRI.

8.6.4. Management of phaeochromocytoma--paraganglioma

Paroxysmal BP surges caused by catecholamine -producing PPGL may be best managed by administering phentolamine intravenously, usually at the dose of 2–5 mg repeated as needed.

Surgical removal of catecholamine-producing PPGL is the treatment of choice.

Appropriate preoperative patient preparation is important to reduce BP values, lower the heart rate, and control paroxysmal BP surges and other symptoms related to the excess of circulating catecholamines. For this purpose, alpha-blockers are administered orally for 2–3 weeks, including phenoxybenzamine (in increasing doses starting from 10 mg b.i.d. up to 1 mg/kg/day in 2–3 divided doses) or doxazosin (in gradually increasing doses starting from 2 mg up to 32 mg/day in 1–2 divided doses). If alpha-adrenergic receptor blockade is unsuccessful at controlling BP, a calcium antagonist (nifedipine or amlodipine) may be added as the second antihypertensive medication. In patients with significant tachycardia, addition of a cardioselective beta-blocker is desirable but only after alpha-adrenergic receptors have been blocked. Catecholamines released by PPGL act on both alpha- and beta-adrenergic receptors. Administering a beta--blocker without previous alpha receptor blockade is contraindicated as it may lead to excessive alpha receptor activation and a significant BP rise. Drugs acting on both alpha- and beta-adrenergic receptors (labetalol and carvedilol) should not be used. Correcting hypovolemia by adequate sodium and fluid intake is also important during preoperative patient preparation to avoid orthostatic hypotension.

8.6.5. Long-term care of patients with phaeochromocytoma-paraganglioma

Following surgical removal of PPGL, long-term patient follow-up is needed that should include monitoring of BP values and plasma or urinary metanephrines. The initial postoperative evaluation to allow early identification of a possible tumour recurrence or development of hormonally active metastases should be undertaken depending on the overall clinical picture (genetic predisposition, tumour size, multiple tumours) after 6–12 months and then repeated annually.

8.6.6. Genetic testing in patients with phaeochromocytoma-paraganglioma

Each year, molecular biology advances in regard to the diagnosis of PPGL bring discoveries of new genes predisposing to this disease. In addition to 8 genes responsible for the most common hereditary PPGL syndromes (*RET*, *VHL*, *NF1*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*), new predisposing genes have also been identified, including *MEN1*, *MAX*, *TMEM127*, *EGLN1/PHD2*, *KIF1β*, *IDH1*, and *HIF2α*. The proportion of genetic forms of PPGL is currently estimated at 30–40%. In addition, a founder *SDHD* gene mutation has been identified in Poland. For this reason, genetic testing for known mutations associated with PPGL is recommended in all PPGL patients.

8.6.7. Other rarer forms of secondary hypertension

Other rarer forms of secondary hypertension, such as renin-secreting tumours, coarctation of the aorta, and Cushing syndrome, are summarized in Table XXV.

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