

# RENOVASCULAR HYPERTENSION: CLINICAL FEATURES, DIFFERENTIAL DIAGNOSES AND BASIC PRINCIPLES OF TREATMENT

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## RENOVASKULARNA HIPERTENZIJA: KLINIČKE KARAKTERISTIKE, DIFERENCIJALNA DIJAGNOZA I OSNOVNI PRINCIPI LEČENJA

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### ABSTRACT

Renovascular hypertension is caused by renal artery stenosis. Its prevalence in populations of hypertensive patients is 1-8%, and in populations of patients with resistant hypertension, it is up to 20%. The two main causes of stenosis are atherosclerosis and fibromuscular dysplasia of the renal artery. The main clinical consequences of renal artery stenosis include renovascular hypertension, ischemic nephropathy and "flash" acute pulmonary oedema. Unilateral stenosis of the renal artery causes angiotensin II-dependent hypertension, and bilateral stenosis of the renal arteries produces volume-dependent hypertension. Renovascular aetiology of hypertension should be questioned in patients with resistant hypertension, hypertension with a murmur identified upon auscultation of the renal arteries, and a noticeable side-to-side difference in kidney size. Non-invasive diagnostic tests include the determination of concentrations of peripheral vein plasma renin activity, the captopril test, captopril scintigraphy, colour Doppler ultrasonography, computed tomography angiography, and nuclear resonance angiography. Renovasography represents the gold standard for the diagnosis of renovascular hypertension. The indications for revascularization of the renal artery include haemodynamically significant renal artery stenosis (with a systolic pressure gradient at the site of stenosis of  $\Delta P \geq 20$  mmHg, along with the ratio of the pressure in the distal part of the renal artery (Pd) and aortic pressure (Pa) less than 0.9 ( $Pd/Pa < 0.9$ )), resistant hypertension, loss of renal function after administration of ACE inhibitors or angiotensin receptor II blockers, and recurrent flash pulmonary oedema associated with bilateral renal artery stenosis. The contraindications for renal artery revascularization include a longitudinal diameter of the affected kidney that is less than 8.0 cm, the resistance index measured from the segmental arteries peak blood flow (RI)  $> 0.8$ , chronic kidney disease ( $GFR < 30$  ml/min/1.73 m<sup>2</sup>) and negative captopril scintigraphy (lack of lateralization).

**Keywords:** renovascular hypertension, plasma renin activity, captopril test, resistance index

### SAŽETAK

Renovaskularna hipertenzija nastaje zbog stenozе renalne arterije. Njena prevalencija u populaciji bolesnika sa hipertenzijom iznosi 1-8%, a u populaciji bolesnika sa rezistentnom hipertenzijom i do 20%. Dva glavna uzroka stenozе su ateroskleroza i fibromuskularna displazija renalnih arterija. Glavne kliničke posledice stenozе renalne arterije su: renovaskularna hipertenzija, ishemijska nefropatija i "flash" akutni edem pluća. Stenoza jedne renalne arterije izaziva hipertenziju zavisnu od angiotenzina 2, a stenoza obe renalne arterije za posledicu ima hipertenziju zavisnu od volumena. Na renovaskularnu hipertenziju treba posumnjati kod bolesnika sa: rezistentnom hipertenzijom, hipertenzijom sa nalazom šuma pri auskultaciji arterija bubrega i sa razlikom u veličini bubrega. U neinvazivne dijagnostičke testove spadaju određivanje koncentracije plazma-reninske aktivnosti u uzorku krvi iz periferne vene, kaptoprilski test, kaptoprilska scintigrafija, kolor dopler ultrasonografija, kompjuterizovana tomografska angiografija i nuklearna rezonantna angiografija. Zlatni standard za dijagnostikovanje renovaskularne hipertenzije je renovazografija. U indikacije za revascularizaciju renalne arterije spadaju: hemodinamski značajna stenoza renalne arterije (gradijent sistolnog pritiska na mestu stenozе  $\Delta P \geq 20$  mmHg i odnos pritiska u distalnom delu renalne arterije (Pd) i aorte (Pa) manji od 0.9 ( $Pd/Pa < 0.9$ )), rezistentna hipertenzija, gubitak funkcije bubrega posle primene blokatora konvertaze angiotenzina 1 ili blokatore receptora za angiotenzin 2, rekurentni "flash pulmonary oedema", povezan sa obostranom stenozom renalne arterije. U kontraindikacije za revascularizaciju renalne arterije spadaju: uzdužni dijametar zahvaćenog bubrega manji od 8.0 cm, indeks rezistencije izmeren iz krive protoka krvi kroz segmentne arterije  $- RI > 0.8$ , hronična bolest bubrega ( $JGF < 30$  ml/min/1.73m<sup>2</sup>) i negativna kaptoprilska scintigrafija (odsustvo lateralizacije).

**Кljučne reči:** renovaskularna hipertenzija, plazma-reninska aktivnost, kaptoprilski test, indeks rezistencije



## INTRODUCTION

Renovascular hypertension is defined as hypertension caused by renal artery stenosis (RAS). In the hypertensive patient populations (blood pressure >140/90 mmHg), renovascular hypertension prevalence is 1-8%. In the population of patients with resistant hypertension (defined as increased blood pressure despite the use of three antihypertensive drugs at the optimal dosage, including a diuretic), the prevalence of renovascular hypertension is higher, 2.5-20% (1-4).

### Aetiopathogenesis of renovascular hypertension

#### *The aetiology of renal artery stenosis*

Renal artery stenosis may manifested as either unilateral or bilateral. The two most common causes of renal artery stenosis are atherosclerosis and fibromuscular dysplasia (5, 6). Atherosclerosis of the renal artery (ARAS) is the cause of stenosis in 90% of cases, and it usually involves the ostium and proximal third of the renal artery trunk. It usually affects patients over 65 years of age with known cardiovascular risk factors (obesity, hypertension, hyperlipidaemia, hyperglycaemia) and ranges from 30% among patients with coronary artery disease to 50% among the elderly and those with diffuse atherosclerotic vascular diseases (5). The one-year progression rate of renal artery stenosis caused by atherosclerosis is 0.5% (5, 6). Clinical features of renal artery stenosis include renovascular hypertension, ischemic nephropathy, and recurrent flash pulmonary oedema (bilateral atherosclerotic renal artery disease) (5, 6). In the USA, 12 - 14% of new patients entering dialysis programs have ARAS (a significant cause of end-stage chronic kidney disease) (5, 6).

Fibromuscular dysplasia (FMD) is a non-atherosclerotic, non-inflammatory disease, most commonly affecting the renal and internal carotid arteries (7, 8). It implicates renal artery stenosis in 5-10% of cases and affects the distal part of the renal artery. Any layer of the renal artery wall may be affected: the intima, media or adventitia (7, 8). The most common form is fibromuscular dysplasia of the media (fibroplasia of the media occurs in 70-95% of cases), which has been shown by pathognomonic angiography to cause slight stenosis along a vessel with intervening areas of dilatation (small aneurysms) creating a "string of beads" appearance (7, 8). It occurs most often in women 15-50 years of age. In most cases, the disease is asymptomatic, exhibits latency for several years, and is difficult to clinically recognize and diagnose. Clinical appearance often involves renovascular hypertension and irreversible kidney damage, such as ischemic nephropathy (the severity of the clinical outlook depends on the degree of stenosis and the type of fibromuscular dysplasia) (7, 8).

### Pathogenesis of the development of renovascular hypertension and Pickering syndrome

#### *Pathogenesis of renovascular hypertension*

Unilateral stenosis (stenosis of one renal artery) induces increased renin release and activation of the renin-angioten-

sin-aldosterone system (RAAS). As the condition progresses, angiotensin II is increasingly produced and released, causing the development of angiotensin II-dependent hypertension (9). Perfusion of the other, unaffected, kidney is increased due to increased renal perfusion pressure, and this results in RAAS inhibition and increased excretion of sodium (natriuresis is dependent on pressure) (9).

In patients with bilateral stenosis (stenosis of both renal arteries), or in patients with only one active kidney that is affected by stenosis, renal perfusion pressure is decreased, causing increased renin release, increased RAAS activity, increased production of angiotensin II and aldosterone, and reduced excretion of sodium and water. Due to retention of sodium and water, blood volume in arterial circulation is increased, leading to the development of volume-dependent hypertension (9).

#### *Pathogenesis of ischemic nephropathy*

Renal artery stenosis causes kidney tissue hypoxia, increased local production of renin and angiotensin II, increased production of free oxygen radicals (reactive oxygen species (ROS)), platelet-derived growth factor- $\beta$  (PDGF- $\beta$ ) and transforming growth factor  $\beta$  (TGF- $\beta$ ). These mediators cause glomerulosclerosis and tubulointerstitial injury, which results in a decrease of glomerular filtration rate (GFR) and the development of chronic kidney disease (ischemic nephropathy). In the last decade, ischemic nephropathy was recognized as an important cause of end-stage chronic kidney disease (9, 10).

#### *Pathogenesis of sudden acute pulmonary oedema (flash pulmonary oedema)*

Flash pulmonary oedema (FPO) or Pickering syndrome is defined as an unexpected and sudden form of acute heart failure (acute pulmonary oedema) in patients with bilateral renal artery stenosis (11). In patients with renovascular hypertension and unilateral RAS, prevalence of a FPO is 3.5%, compared to 14.3% in patients with renovascular hypertension and bilateral RAS (11). In patients with bilateral RAS, the activity of RAAS and the sympathetic nervous system is enhanced and hypertension is volume-dependent (hypervolemia) (11).

Hypervolemia with other predisposing factors, such as left ventricular hypertrophy, impaired left ventricular diastolic function, or increased systemic vascular resistance, lead to a sudden increase in end-diastolic pressure of the left ventricle (EDPLV), which is transferred to the left atrium and pulmonary capillaries. Increased hydrostatic pressure in the capillaries of the lungs and increased permeability of the alveolar-capillary membrane (allowing for transport of angiotensin II (Ang II), endothelin 1 (ET-1), catecholamines, and nitrous oxide (NO)) result in an unexpected development of FPO (11).

### Clinical features of renovascular hypertension

Renovascular hypertension should be suspected in patients with moderate (diastolic blood pressure  $\geq$  105 mmHg) or severe hypertension (diastolic blood pressure  $\geq$  120



**Table 1.** The probability of the existence of renovascular hypertension

Probability	Clinical features
<b>Low</b> (RAS: < 1.0%)	Borderline or moderate hypertension (diastolic blood pressure $\geq 105$ mmHg), without clinical signs
<b>Moderate</b> (RAS: 15-30%)	Severe hypertension (diastolic blood pressure $\geq 120$ mmHg) Resistant hypertension (use of $\geq 3$ antihypertensive drugs) The sudden appearance of hypertension in people younger than 30 years (fibromuscular dysplasia) or persons over 50 years old (atherosclerosis). Hypertension with the finding of a murmur at auscultation of the renal arteries Moderate hypertension (diastolic blood pressure $\geq 105$ mmHg) in patients with atherosclerotic disease (CAD, PAD)
<b>High</b> (RAS: 30-40%)	Severe hypertension (diastolic blood pressure $\geq 120$ mmHg) with progressive renal impairment Accelerating hypertension (an increase of SAP $> 15$ mmHg for six months) or malignant hypertension (retinopathy grade III and IV) Hypertension with an increase in serum creatinine concentration after administration of ACE I or ARB [ $\uparrow$ serum creatinine 0.5-1.0 mg/dL (44.2-88.4 $\mu$ mol/L)] Moderate (diastolic blood pressure $\geq 105$ mmHg) or severe hypertension (diastolic blood pressure $\geq 120$ mmHg) with difference in the longitudinal diameter of the right and left kidney $>1.5$ -2.0 cm

RAS - renal artery stenosis, CAD - coronary artery disease, PAD - peripheral arterial disease, ACEI - angiotensin-converting enzyme inhibitor, ARB - angiotensin II receptor blockers

mmHg), resistant hypertension (increased BP despite the use of three antihypertensive drugs including a diuretic), a murmur found by renal artery auscultation, when the difference in the longitudinal diameter between the right and left kidney is  $> 1.5 - 2.0$  cm, and an increase in serum creatinine concentration after administration of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor II blockers (ARB) (increase in serum creatinine of 0.5-1.0 mg/dL (44.2-88.4  $\mu$ mol/L)) after ACEI/ARB administration, (Figure 1) (12).

### Diagnosis of renovascular hypertension

The diagnosis of renovascular hypertension is performed by detecting and demonstrating the haemodynamic significance of RAS. Tests for the diagnosis of renovascular hypertension can be divided into three groups. The first group includes functional tests, proof and assessment of the haemodynamic significance of stenosis, and assessment of renin-angiotensin system activation. The functional tests include direct measurement of plasma renin concentration and plasma renin activity (PRA) from a peripheral vein, the captopril test (measurement of plasma renin activity from a peripheral vein after administration of captopril), and measuring the concentration of renin from a renal vein sample and determining the side-by-side ratio of plasma renin activity (lateralization estimation). For assessment of individual renal function, radio isotopic techniques are used (scintigraphy and captopril renal scintigraphy). The second group consists of tests that assess the morphology of the renal artery. Non-invasive versions of these tests include: colour Doppler of the renal arteries, computed tomography angiography (CTA), and nuclear magnetic resonance angiography (NMRA), while invasive tests include angiography with contrast medium, or reno-vasography. A third group of tests judge the benefit of RAS revascularization (using colour Doppler ultrasonography and lateralization tests) (6, 9, 12).

### Peripheral blood plasma-renin activity measurements

Peripheral blood plasma-renin activity (PRA) measurement and the captopril test play an important role in the diagnosis of renovascular hypertension (6, 9, 12). Low levels of plasma renin activity (PRA  $< 0.65$  ng/mL/h), in association with hypokalaemia ( $K^+ < 3.5$  mmol/L), indicate primary aldosteronism. When moderate levels of plasma renin (PRA = 0.65-3.2 ng/mL/h) are observed, additional tests for the detection of renovascular hypertension are required (such as the captopril test, colour Doppler of the renal artery, captopril scintigraphy, CT angiography, and NMR angiography). High plasma renin activity (considered to be PRA  $\geq 3.2$  ng/mL/h) strongly suggests existence of renovascular hypertension and requires direct reno-vasography (6, 9, 12).

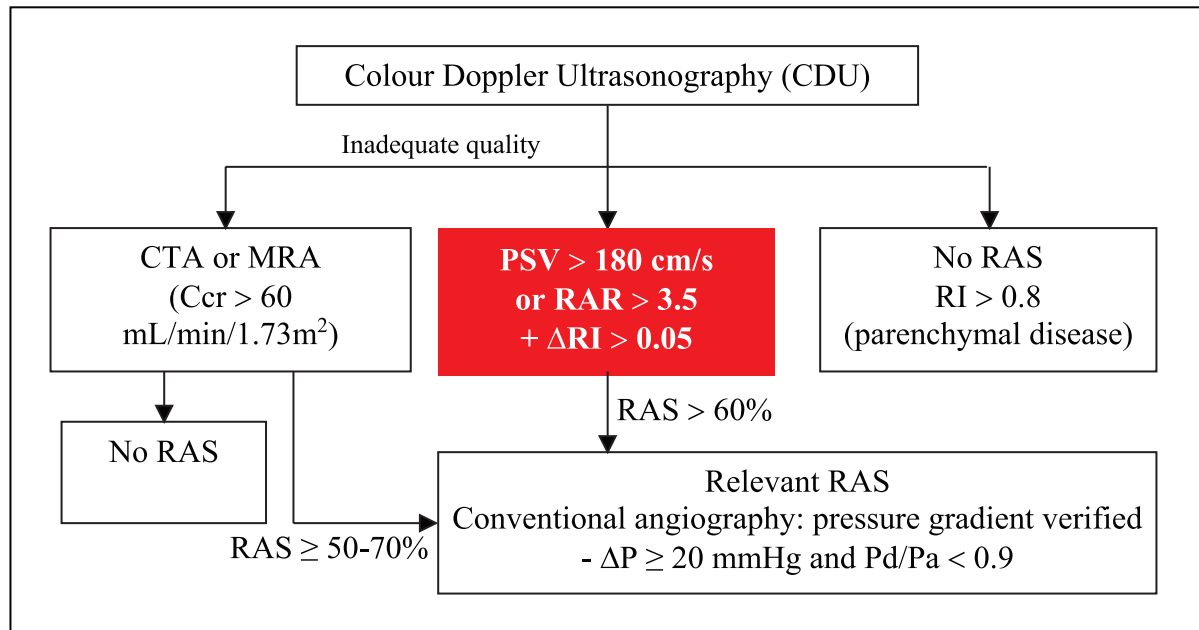
The captopril test is the most sensitive test for the detection of RAS. Before the test is administered, adequate preparation of patients is required. Patients must have a normal salt intake. Additionally, three weeks prior to the test the use of several classes of drugs must be discontinued (i.e., drugs that affect the PRA such as angiotensin converting enzyme inhibitors, angiotensin receptor II blockers, beta blockers, and direct renin blockers). Thirty minutes prior to the blood sampling, the patient should rest and be relaxed. Alpha-1-blockers (doxazosin) have no influence on the concentration or the PRA. To determine the initial PRA, a blood sample is taken at 20, 25 and 30 minutes before the test. After that, a 25 mg captopril tablet is given to the patient and blood pressure is recorded after 15, 30, 45 and 60 minutes. After 60 minutes, a blood sample is taken for determination of stimulated PRA. The test is positive if PRA measures at  $\geq 12$  ng/mL/h, or if the absolute increase of PRA is  $\geq 10$  ng/mL/h (6, 9, 12).

### Renal vein plasma renin activity

A good response after revascularization is indicated if the PRA ratio of the renal vein sample taken from a kidney affected by RAS to one without RAS is  $> 1.5$ .



**Figure 2.** Flow chart of renal artery stenosis assessment (*duplex sonography*)



RAS - renal artery stenosis, CTA - computed tomography angiography, MRA - magnetic resonance angiography, Ccr - endogenous creatinine clearance, PSV - peak systolic velocity, RAR - renal aortic ratio, DRI - resistance index difference, side to side, Pd - pressure in distal part of renal artery, Pa - aortic pressure.  
Modified by reference [5].

Lateralization of plasma renin activity indicates haemodynamically significant stenosis. Generally, the higher the degree of lateralization, the greater the likelihood of optimal blood pressure control after revascularization of RAS (6, 9, 12).

### Colour Doppler of renal arteries

Colour Doppler ultrasonography is a cheap, safe (no ionizing radiation) and non-invasive diagnostic procedure for detection and assessment of the severity of RAS (evaluating haemodynamic significance), and it is used to select patients who are good candidates for successful revascularization (12 -15). Colour Doppler ultrasonography of the renal arteries should be performed in all patients with a moderate to high probability for renovascular hypertension in which the PRA is  $\geq 1.6$  ng/mL/h (6, 9, 12).

Flow curve is a biphasic, low resistance colour Doppler technique with systolic and diastolic components. From the curve of blood flow through the renal artery, Doppler parameters can be calculated directly from blood flow through the main trunk and indirectly from intrarenal blood flow through the blood vessels (12 -15). The direct criteria for renovascular hypertension include peak systolic blood flow velocity (PSV)  $> 180$  cm/s, end-diastolic flow velocity (EDFV)  $> 50$  cm/s, reno-aortic ratio (RAR)  $> 3.5$  and reno-renal ratio (RRR)  $> 4.0$ , (Figure 2) (12 -15). The indirect criteria for renovascular hypertension include loss of early systolic peak (ESP), resistance index (RI)  $< 0.45$ , acceleration time (AT)  $> 70$  ms, acceleration (Acc)  $< 300$  cm/s<sup>2</sup>, and the difference in the resistance index (DRI)  $> 0.05$  or 5% (Figure 2) (5, 12-15). In renal transplant patient

groups, the presence of RAS is indicated by a PSV  $> 200$  cm/s, intrarenal artery blood flow curve AT  $> 100$  ms, and a PSV ratio between the renal artery and kidney transplant external iliac artery of  $> 1.8$  (16).

In cases where colour Doppler ultrasonography is not feasible or its findings are incomplete, either a CTA or NMRA is indicated. These two diagnostic methods require contrast mediums (such as the ionic contrast agent, gadolinium) and are not indicated in the group of patients with a reduced glomerular filtration rate (less than 30 mL/min/1.73 m<sup>2</sup>), due to hazard of contrast nephropathy (CN) and nephrogenic systemic fibrosis (NSF) (17, 18).

The gold standard in RAS diagnostics remains a conventional intra-arterial digital subtraction angiograph (DSA). It directly assesses the haemodynamic significance of RAS (peak systolic pressure gradients (DP)  $\geq 20$  mmHg) (5). The threshold for significant RAS is defined by a ratio of distal renal pressure to aortic pressure (Pd/Pa)  $< 0.90$  (5).

### Differential diagnosis

Renovascular hypertension should be distinguished from primary aldosteronism and pheochromocytoma (resistant hypertension) (19-21).

Primary aldosteronism is the most common form of secondary hypertension. The main causes of primary aldosteronism are adrenal adenoma that produces aldosterone and idiopathic bilateral adrenal hyperplasia (19, 20). The prevalence of primary aldosteronism in a hypertensive patient population is 3.5% (19, 20). Screening for primary aldosteronism should be performed in



patients with resistant hypertension, moderate or severe hypertension and hypertension associated with hypokalaemia and in patients younger than 40 years with cerebrovascular events due to hypertension. Measurement of plasma aldosterone concentration (PAC) and the ratio of PAC/PRA are used as screening tests for the diagnosis of primary aldosteronism (19, 20). Adequate preparation of patients is required. Two weeks before the test, antihypertensive drugs that affect renin and aldosterone concentrations in plasma are terminated (such as angiotensin converting enzyme inhibitors, angiotensin receptor II blockers, beta blockers, and direct renin blockers). Spironolactone should be excluded at least two months before blood sampling for screening tests (19, 20). Alpha-1-blockers (doxazosin), hydralazine, and calcium channel blockers have the least impact on the plasma concentrations of renin and aldosterone (19, 20). The test is considered positive if the PAC/PRA ratio is  $> 20$  and the PAC is  $> 15$  ng/dL ( $> 416$  pmol/L). In patients with a positive screening test, confirmatory testing, such as a captopril suppression test (CST) should be conducted (19, 20). When a CST is performed, serum aldosterone concentration is measured prior to, and two hours after, administration of a 25 mg dose captopril. The test is positive if the PAC is  $> 15$  ng/dL ( $> 416$  pmol/l) (19, 20). If the screening and confirmation tests are positive, then additional diagnostic procedures for adrenal visualization are indicated (such as: an adrenal ultrasound, CT, or NMR of the adrenals), as well as tests to assess lateralization (such as measuring the concentration of aldosterone in adrenal vein blood samples). In patients with adrenal adenomas (identified from a positive lateralization test), unilateral laparoscopic adrenalectomy is indicated, and in patients with idiopathic bilateral hyperplasia, medical therapy should be applied (such as the mineralocorticoid receptor antagonists spironolactone and eplerenone) (19, 20).

A pheochromocytoma is a rare, catecholamine-secreting tumour derived from chromaffin cells (21). It is also designated as an intraadrenal or intraglandular paraganglioma, unlike extraadrenal sympathetic, parasympathetic, and extraglandular paragangliomas (21). The prevalence of a pheochromocytoma in hypertensive patients is 0.2-0.5%. Due to paroxysmal release and increased concentration of catecholamines in serum, its clinical features are characterized by the "5Ps": paroxysmal hypertension (hypertension jumps), palpitations (due to tachycardia), perspiration, paleness (vasoconstriction due to decreased blood flow) and a pulsating headache (21). Screening for pheochromocytoma should be applied in patients with: resistant hypertension, characteristic "5P" clinical features, positive family history of pheochromocytoma, and genetic syndromes that are known to be associated with pheochromocytoma (such as MEN 2, von Hippel Lindau syndrome, and neurofibromatosis). Two screening tests are available: assessment of the plasma and 24 h urine sample concentrations of metanephrine and normetanephrine. Plasma concentrations of metanephrine  $> 0.31$  nmol/L and

normetanephrine  $> 0.61$  nmol/L suggest increased catecholamine secretion. A concentration of urine metanephrine  $> 0.7$   $\mu$ mol/24 h and normetanephrine  $> 1.7$   $\mu$ mol/24 h confirms the presence of pheochromocytoma (21). If the screening test is positive, additional diagnostic procedures for visualization of the adrenals should be conducted (abdomen and pelvis CT or NMR). If test is negative,  $^{123}$ I-metaiodobenzylguanidine (MIBG) adrenal scintigraphy should be performed (21). Treatment of pheochromocytoma is surgical, with adequate patient preoperative preparation. Adrenoceptor antagonists (doxazosin,  $\alpha_1$ -blocker) are used to prevent the effects of catecholamines suddenly liberated (preventing the development of hypertensive crisis and cardiac rhythm disorders) (21).

### Treatment of renovascular hypertension

In patients with a stenosis of one renal artery, use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs), with appropriate monitoring of serum creatinine concentration is feasible (22). These drugs are contraindicated if stenosis of both renal arteries is present, due to high risk of developing acute kidney injury (5, 23-25). In patients with atherosclerosis due to RAS, primary prevention of progression of stenosis with statins and secondary prevention of the development of renal and cardiac events with low-dose aspirin are indicated (23-26).

Revascularization of RAS (which includes angioplasty with or without stenting or surgical bypass) is indicated by the following: RAS  $\geq 50\%$  (systolic pressure gradient (DP)  $\geq 20$  mmHg and a Pd/Pa ratio  $< 0.9$  indicates haemodynamically significant stenosis (RAS)  $> 60\%$ ), resistant hypertension, loss of renal function after administration of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor II blockers (ARBs) ( $\geq 30\%$  decrease in GFR compared to the values measured before ACEI/ARB administration, an increase in serum creatinine concentration of 0.5 - 1.0 mg/dL (44.2 - 88.4  $\mu$ mol/L) after administration of ACEI/ARB), or recurrent flash pulmonary oedema associated with bilateral renal artery stenosis (5, 23-26).

The contraindications for renal artery revascularization include longitudinal diameter of the affected kidney  $< 8.0$  cm, resistance index measured from the blood flow curve through the segmental arteries (RI)  $> 0.8$ , chronic kidney disease (GFR  $< 30$  ml/min/1.73 m<sup>2</sup>) or negative captopril scintigraphy (lack of lateralization) (23-26).

### CONCLUSION

Early diagnosis of renovascular hypertension and timely implementation of appropriate therapeutic procedures ensures optimum control of blood pressure, prevents ischemic nephropathy progression and prevents the development of cardiovascular morbidity and mortality in the hypertensive patient population.



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