RENOVASCULAR HYPERTENSION - DIAGNOSTICS AND THERAPY

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SAŽETAK
Reno-vaskularna hipertenzija nastaje zbog stenozne renalnih arterija. U populaciji bolesnika koji boluju od povoljnijeg arterijalnog krvnog pritiska, prevelačenja renaovaskularne hipertenzije iznosi 0.2–5.0%. Dve najčešće primarne bolesti renalnih arterija su aterosklerošička stenoza i fibromuskularna displazija. Za stenozi renalnih arterija ateroskleroz je odgovorna u 90% slučajeva. Zahvata ostvranje i proximalnom trinaciju. Glavne glavne inevazivne dijagnostičke metode koje omogućavaju dijagnostiku renaovaskularne hipertenzije, kao i procesu stenozu renalnih arterija. Spinalna komputernozoraanom tomografija (CTA), magnetna rezonantna angiografija (MRA) i subtrakcija digitalna angiografija (SLA) su dijagnostičke metode koje imaju veliku senzitivnost i specifičnost u dijagnostiku renaovaskularne hipertenzije. Angiotensin II, with its multiple mechanisms, causes renovascular hypertension. Although renovascular hypertension represents the risk factors contributing to development of fibromuscular dysplasia (3). Fibromuscular dysplasia causes stenosis of renal arteries in <10% of cases, but in 90% it affects renal arte- rial sclerosis. It usually involves osti um and the proximal third of the main renal artery, as well as perirenal part of renal artery stenosis. Prevalence of atherosclerotic renal artery and fibromuscular dysplasia (3). Atherosclerosis accounts for 90% of cases of renal arterial sclerosis. It usually involves ostium and the proximal third of the main renal artery, as well as perirenal part of abdominal aorta. Prevalence of atherosclerotic stenosis in renal arteries increases with time principally with diabetes, coronary artery diseases, aortic-iliac occlusive disease or hypertension (3). Stenosis of renal arteries without atherosclerosis of abdominal aorta is almost always a consequence of fibromuscular dysplasia (4, 5). Fibromuscular dysplasia is the primary disease of renal arteries and affects intimae, median and adventitial segments of blood vessel wall. The cause of fibromuscular dysplasia is unexplained, but hereditary predisposition, smoking, hormonal factors and vasa varorum damage represent the risk factors contributing to development of fibromuscular dysplasia (3). Fibromuscular dysplasia causes stenosis of renal arteries in <10% of cases, but in 90% it affects renal vascular hypertension. Although renovascular hypertension usually contributes to development of accelerated renal arterial stenosis begins as a result of renal artery stenosis. Prevalence of renovascular hypertension amounts to 0.2–5.0% in the hypertensive population. Two most common primary diseases of the renal arteries are atherosclerotic renal artery and fibromuscular dysplaasia. Atherosclerosis accounts for 90% of cases of renal artery stenosis. Usually involves the ostium and proximal third of the main renal artery. Fibromuscular dysplasia accounts for less than 10% of cases of renal artery stenosis. Most commonly involves the distal two thirds of the renal artery and its branches. Uncorrected renovascular hypertension is a progressive disease which in 15 to 20% of patients drives to development of the end stage of chronic renal failure. Captopril test is the good screening method for detection of patients with renal artery ste- nosis. Colour Doppler sonography is the new, noninvasive method for diagnostics renovascular hypertension, and possible estimation degree of renal artery stenosis. Spiral computed tomography (CTA), magnetic resonance angiography (MRA) and digital subtraction angiography (DSA) are diagnostic methods with good sensitivity and specificity. Renal angiography is the gold standard for the definitive diagnostic of renal artery stenosis. Antihypertensive therapy, therapy which lowers concentration of lipid in serum, and balloon angiosclerosis (with or without stent placement) is of the biggest therapeutic importance. Regular time diagnostics and adequate therapy (revascularization), drive to normalization of blood pressure.

Key words: renovascular hypertension, diagnostic methods, diagnostic strategy, revascularization

INTRODUCTION
Renal arterial stenosis is one of the leading causes of secondary hypertension. Prevalence of renovascular hyperten- sion in population suffering from arterial hypertension reaches 0.2–5.0% (1). In 10–15% of patients >50 years of age, renovascular hypertension causes progression to terminal stage of chronic renal deterioration (2). The most frequent primary diseases of renal arteries include atherosclerotic renal artery and fibromuscular dysplasia (3). Atherosclerosis accounts for 90% of cases of renal arterial sclerosis. It usually involves ostium and the proximal third of the main renal artery, as well as perirenal part of renal arteries in <10% of cases, but in 90% it affects renal arterial sclerosis. It usually involves ostium and the proximal third of the main renal artery, as well as perirenal part of renal arteries in <10% of cases, but in 90% it affects renal arterial sclerosis. It usually involves ostium and the proximal third of the main renal artery, as well as perirenal part of abdominal aorta. Prevalence of atherosclerotic stenosis in renal arteries increases with time principally with diabetes, coronary artery diseases, aortic-iliac occlusive disease or hypertension (3). Stenosis of renal arteries without atherosclerosis of abdominal aorta is almost always a consequence of fibromuscular dysplasia (4, 5). Fibromuscular dysplasia is the primary disease of renal arteries and affects intimae, median and adventitial segments of blood vessel wall. The cause of fibromuscular dysplasia is unexplained, but hereditary predisposition, smoking, hormonal factors and vasa varorum damage represent the risk factors contributing to development of fibromuscular dysplasia (3). Fibromuscular dysplasia causes stenosis of renal arteries in <10% of cases, but in 90% it affects renal arterial sclerosis. It usually involves ostium and the proximal third of the main renal artery, as well as perirenal part of abdominal aorta. Prevalence of atherosclerotic stenosis in renal arteries increases with time principally with diabetes, coronary artery diseases, aortic-iliac occlusive disease or hypertension (3). Stenosis of renal arteries without atherosclerosis of abdominal aorta is almost always a consequence of fibromuscular dysplasia (4, 5). Fibromuscular dysplasia is the primary disease of renal arteries and affects intimae, median and adventitial segments of blood vessel wall. The cause of fibromuscular dysplasia is unexplained, but hereditary predisposition, smoking, hormonal factors and vasa varorum damage represent the risk factors contributing to development of fibromuscular dysplasia (3). Fibromuscular dysplasia causes stenosis of renal arteries in <10% of cases, but in 90% it affects renal arterial sclerosis. It usually involves ostium and the proximal third of the main renal artery, as well as perirenal part of abdominal aorta. Prevalence of atherosclerotic stenosis in renal arteries increases with time principally with diabetes, coronary artery diseases, aortic-iliac occlusive disease or hypertension (3). Stenosis of renal arteries without atherosclerosis of abdominal aorta is almost always a consequence of fibromuscular dysplasia (4, 5). Fibromuscular dysplasia is the primary disease of renal arteries and affects intimae, median and adventitial segments of blood vessel wall. The cause of fibromuscular dysplasia is unexplained, but hereditary predisposition, smoking, hormonal factors and vasa varorum damage represent the risk factors contributing to development of fibromuscular dysplasia (3). Fibromuscular dysplasia causes stenosis of renal arteries in <10% of cases, but in 90% it affects renal arterial sclerosis. It usually involves ostium and the proximal third of the main renal artery, as well as perirenal part of abdominal aorta. Prevalence of atherosclerotic stenosis in renal arteries increases with time principally with diabetes, coronary artery diseases, aortic-iliac occlusive disease or hypertension (3). Stenosis of renal arteries without atherosclerosis of abdominal aorta is almost always a consequence of fibromuscular dysplasia (4, 5).
or malignant hypertension (D'Ta ≥ 120 mmHg), it is not possible to differentiate it from essential hypertension. Reliable classic features, such as hypo K⁺, abdominal murmur, absence of hereditary predisposition for essential hypertension, duration of hypertension <1 year, and onset of hypertension after 40’s, provide differentiation between renovascular hypertension and other types of hypertension (table 1).

Table 1. Index of clinical suspicion on existence of renovascular hypertension.

<table>
<thead>
<tr>
<th>Index of Clinical Suspicion</th>
<th>RAS (in 10–30%)</th>
<th>Non-invasive diagnostic methods</th>
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<tr>
<td>Low index (patients not to be tested)</td>
<td>-Borderline or moderate renal artery hypertension without clinical signs</td>
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<tr>
<td>Moderate index (RAS in 15–30%, non-invasive diagnostic methods)</td>
<td>-expressed hypertension (diastolic pressure ≥120 mmHg) -hypertension refractory to standard therapy (therapy with ≥3 medications) -sudden occurrence of significant hypertension in persons under 20 years old (fibromuscular dysplasia) or older than 50 years (atherosclerotic stenosis of renal arteries) -hypertension with murmur finding above renal arteries (abdominal murmur, murmur in lumal and lateral regions of abdomen) -moderate hypertension (diastolic pressure &gt; 105 mmHg) in smokers or in patients deceased of cardiac coronary, coronary of peripheral vascular disease -normalization of arterial pressure with application of ACE inhibitors or ARBs in patients with moderate or marked hypertension</td>
<td></td>
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<tr>
<td>High index (RAS in 40–40%, angio-therapy should be considered immediately)</td>
<td>-marked hypertension (diastolic pressure ≥120 mmHg) with progressive renal insufficiency -accelerating hypertension (increase of median arterial pressure over 15 mmHg within 6 months) or malignant hypertension (retinopathy III or IV) -hypertension with de novo increase in creatinine of unexplained origin or after application of ACE inhibitors in treatment of arterial hypertension -moderate or marked hypertension with detected asymmetry in kidney size (difference in longitudinal diameter &gt;1.5–2.0 cm)</td>
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RAS – renal artery stenosis

DIAGNOSTICS

Patients with moderate to high indices of clinical suspicion on renovascular hypertension should have corresponsive investigations performed. These investigations include global renal function estimate, renin-angiotensin system estimation, renal blood flow evaluation and morphologic examination to prove renal artery stenosis. Besides basic biochemical investigations, a significant place in renovascular hypertension diagnosis is given to determination of plasma renin activity level that significantly affects the order of further investigations (figure 1).

Low plasma renin level (PRA ≤ 0.65 ng/ml/h) and low K⁺ level (K⁺ ≤ 3.6 mmol/l) in majority of cases indicate the possible existence of primary hyperaldosteronism and require additional investigations. Moderate plasma renin level (PRA = 0.65–3.2 ng/ml/h) requires application of non-invasive tests for detection of renovascular hypertension such as Captopril test, Captopril renography, pulsed Doppler of renal arteries, determination of plasma renin activity in renal vein plasma, and renovasography. Marked plasma renin level (PRA ≥ 3.2 ng/ml/h) in 75% of patients is a sign of renovascular hypertension and with high index of clinical suspicion on renovascular hypertension requires application of angiography (4–6).

Captopril test is the most sensitive screening test in differentiation of patients who require complete diagnostics. Basic indications for the test are onset of hypertension before 20 or after 50 years of age, hypertension resistant to antihypertensive therapy, accelerated or malignant hypertension with retinopathy grade III-IV, diastolic murmur in epigastrium, rapid decrease of renal function after application of ACE inhibitors, acute pain in groin and hypertension with diastolic pressure ≥120 mmHg (4–6). Basic principles of the test are following: nutrition with normal salt intake, patients should not take antihypertensive medications before 20 or after 50 years of age, hypertension resistant to antihypertensive therapy, accelerated or malignant hypertension with retinopathy grade III-IV, diastolic murmur in epigastrium, rapid decrease of renal function after application of ACE inhibitors, acute pain in groin and hypertension with diastolic pressure ≥120 mmHg (4–6). Normal plasma renin activity (PRA) is 0.65

- 3.2 ng/ml/h. the test is positive if all mentioned criteria are present: stimulated PRA ≥ 12 ng/ml/h, absolute PRA rise of 10 ng/ml/h or more, and PRA increase of 150%, or 400% with basal PRA <3 ng/ml/h, the test is less reliable in patients with chronic renal insufficiency (4–6).

Pulsed Doppler of renal arteries enables measurement blood flow velocity in renal arteries. This diagnostic method is inexpensive, widely available, but greatly depends on ultrasonographer’s experience. It is less convenient in comparison to invasive angiography in diagnosis of fibromuscular dysplasia and demonstration of accessory renal arteries (3). It is indicated in patients with moderate and high indices of clinically suspected existence of renovascular hypertension, and in patients with plasma renin activity (PRA) ≥ 1.6 ng/ml/h (1, 4, 7, 8).
Curve of blood flow through renal arteries is biphasic (peak systolic velocity, end-diastolic flow velocity), low-resistance type. Under physiologic conditions, normal peak systolic flow velocity in main branches of renal arteries is 100–180 cm/s, and normal end-diastolic flow velocity is 25–50 cm/s (9).

The most significant Doppler parameters for diagnosis of renovascular hypertension in extrarenal arteries include peak systolic velocity (VmaxS>180–200 cm/s) and ratio of renal and aortic peak of systolic velocity n RAR index (RAR>3.5), and the most significant Doppler parameters for intrarenal arteries are resistance index (RI<0.45) and difference in resistance index of intrarenal arteries of both kidneys - ∆RI (∆RI>5–10%) (table 2) (1, 7–10).

Table 2. Doppler criteria for diagnosis of renovascular hypertension

<table>
<thead>
<tr>
<th>Direct criteria</th>
<th>Indirect criteria</th>
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<tr>
<td>VmaxS&gt;180 cm/s (VmaxS&gt;200 cm/s)</td>
<td>acceleration time AT&gt;70 ms</td>
</tr>
<tr>
<td>Reno-aortal index-RAR index&gt;3.5</td>
<td>acceleration A-As1.0 ms²</td>
</tr>
<tr>
<td>Reno-renal index-RRR index&gt;4.0</td>
<td>peak systolic velocity VmaxS&lt;180 cm/s</td>
</tr>
<tr>
<td>End-diastolic blood flow velocity</td>
<td>RESISTANCE index RI&lt;0.45</td>
</tr>
<tr>
<td>&gt;50 cm/s</td>
<td>difference in RESISTANCE indices ARI&lt;5%</td>
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Combining of intra- and extrarenal Doppler parameters significantly increases sensitivity and specificity of Doppler sonography in diagnosis of renovascular hypertension. Peak systolic velocity measured from the extrarenal flow curve >200 cm/s and ∆RI>5% show sensitivity of 89% and specificity of 92%. Resistance index measured from blood flow curve in intrarenal arteries RI<0.45 + ∆RI>5% shows sensitivity of 92.5% and specificity of 95.7% in diagnosis of renovascular hypertension (1, 4, 7–9).

Besides diagnosis of renal artery stenosis, it is possible to evaluate the degree of stenosis. Ratio of peak systolic blood flow velocity at the site of stenosis and distally of the stenosis site is denoted as reni-renal ratio index (RRR index). RRR index>4.0 indicates hemodynamically significant stenosis of renal arteries (14). Peak systolic velocity measured from blood flow curve at the site of stenosis VmaxS>180 cm/s and acceleration time measured from the segmental flow curve at the side of stenosis AT>70 ms indicate a stenosis degree of 70–99% (1, 9).

Selective sampling of renal venous blood for PRA determination is necessary for simultaneous evaluation of functional kidney characteristics. The technique includes catheterization of vena cava inferior and each renal vein. The samples from vena cava inferior are drawn under the origin of renal veins so that PRA concentrations in both blood vessels can be equal. Afterwards, secretory index is determined on both sides: SI=(V-A)/A, where V=v. renalis, A=v. cava inferior. Existence of renovascular hypertension is indicated by renin concentrations at least twice greater than in contra lateral sample (4–6). Ratio of renin activities in plasma of both renal veins >1.5–2.0 indicates existence of renal artery stenosis on the side with greater plasma renin activity (4–6). PRA lateralization predicts improvement of blood pressure after revascularization (3–6).

Captopril scintigraphy is a better method for diagnosis of renovascular hypertension in comparison to classic scintigraphy. Sequential scintigram with ⁹⁹ᵐTc-DTPA (diethylen-triaminopenta-acetate acid) is performed and represents indicator of glomerular filtration, possible and in combination with ¹₃₁I-hipuran, an indicator of renal blood flow. Marker is applied two times: before and one hour after 25–50 mg of katopril. ACE inhibitors are not to be used a week before the test. The test is positive in all cases with unilateral stenosis of renal artery and asymmetry in size and function of kidneys. Normal finding excludes renovascular hypertension. This diagnostic method has limited application in patients with advanced atherosclerosis or creatinine >177 µmol/l (4–6, 11).

Minute intravenous urography is used as a screening method for detection of renovascular changes and selection of patients for further investigations. After 30 minutes, a healthy kidney excretes the contrast material, but on the side of renal artery stenosis the contrast material is retained in the kidney after that time (4, 5).

Spiral CT angiography (CTA) is a novel technique for investigation of renal blood vessels; it is superior and more precise in comparison to arteriography. The main risk of CTA is nephrotoxicity related to large amount of contrast medium (150 ml). Spiral CTA is not recommended in patients with altered renal function (serum creatinine concentration ≥265 µmol/l) (3, 10–13).

MR angiography (MRA) is used in diagnosis of renal artery stenosis in patients with altered renal function (serum creatinine concentration ≥265 µmol/l). This method is not nephrotoxic (gadolinium-contrast medium), but it is less reliable than invasive angiography in diagnosis of fibromuscular dysplasia (10, 12).

Digital subtraction angiography (DSA) with contrast medium of low osmolarity and small volume (15–20 ml) is a gold standard in diagnosis of renal artery stenosis. It provides information on anatomic lesion, but does not show its functional significance (3–6).

TREATMENT

Patients with fibromuscular dysplasia sometimes show disturbance of renal excretory function, and hypertension in these patients usually responds well to application of angiotensin I convertase blockers, i.e. in patients with refractory hypertension, on balloon angioplasty (4, 6, 14). For patients with hypertension and atherosclerotic stenosis of renal arteries, the risk factor therapy includes quitting smoking and application of aspirin, plasma lipid lowering drugs and anti-hypertensive therapy, and it gives basis for retardation of atherosclerotic process (3). Patients wit stenosis greater than 50% of renal artery luminal diameter are usually treated with angioplasty (with or without stent) or surgical procedure (figure 2).
Figure 2. Algorithm for differentiation of patients with indicated revascularization

Both angioplasty and surgical procedures are associated with complications, including possibility of cholesterol embolization and permanent renal failure (3). However, in 20–40% of patients the applied therapy does not lower blood pressure nor improves renal function. One of the reasons for poor response to applied therapy could be functional and structural change in small renal arteries and arterioles distal from the stenosis of renal artery, which could provoke prolonged hypertension. Such hypertension can induce nephrosclerosis or glomerulosclerosis, decreasing intrarenal vascular area and increasing vascular resistance in affected kidney and kidney that is not affected by pathologic process. In patients with renal artery sclerosis (>50%), improvement of renal function and reduction of increased blood pressure do not occur after correction of stenosis if resistance index of segmental arteries on the side of stenosis is RI≥80%, measured by Doppler ultrasonography (14). Value of renal resistance index RI≥80% before revascularization is a clear indicator of renal function worsening and absence of blood pressure reduction despite correction of renal artery stenosis (9, 14). Investigation of the degree of relationship between resistance index and clearance of endogenous creatinine showed statistically highly significant negative correlation. High resistance index (RI≥0.80) is a predictor for progression of chronic renal failure and in patients without renal artery stenosis (15).

Resistance index of segmental arteries of both kidneys should be measured at least three times in upper, middle and lower third of kidney, followed by calculation of median value. Estimation of different risk factors should enable differentiation of patients suitable for improvement of renal function and lowering blood pressure after correction of renal artery stenosis, and patients not suitable for that. Urinary protein loss≥1.0 g/24h, hyperuricemia (>7.3 mg/dl), endogenous creatinine clearance<40 ml/min, age above 65 years, pulse pressure≥70 mmHg, presence of coronary arterial disease, arterial occlusive disease and/or cerebrovascular disease, lack of lowering blood pressure over night, plasma renin activity PRA>5.7 ng/ml/h and kidney size<9.0 cm are useful indicators in identification of patients with poor protective action of revascularization (14).

REFERENCES