

Review Article

Diagnostic Modalities of the Most Common Forms of Secondary Hypertension

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Only 5-10% of hypertension cases are due to a definable cause. In general, a search for the cause of hypertension should be limited to patients with: a) new or sudden onset before the age of 20 or after the age of 50; b) markedly elevated blood pressure with severe end organ disease; c) resistant or refractory hypertension; or d) specific biochemical disturbances suggesting a secondary form of hypertension, and physical signs or a specific body habitus (central obesity, purple striae, abdominal bruits). There is a long list of diseases responsible for secondary hypertension, some of them rarely encountered in clinical practice. Three causes of secondary hypertension that merit special attention are renovascular hypertension, mineralcorticoid excess states and catecholamine excess states. Targeted testing and appropriate selection of diagnostic tests should allow prompt identification of patients with treatable causes of hypertension, avoidance of unnecessary radiation exposure, and cost minimization.

Renovascular hypertension

Renovascular hypertension (RVH) is among the most common forms of secondary hypertension. Its prevalence is estimated to range from 1% to 5% of all hypertensive patients in the general population and can reach 30% in a highly selected referral population.¹⁻⁷ RVH may be caused by a hetero-

geneous group of conditions but the most common is fibromuscular dysplasia and atherosclerotic renovascular disease.

Atherosclerotic renovascular disease (ARVD)

The diagnosis of ARVD should be considered if there is evidence of atherosclerosis affecting peripheral, cerebral or coronary arteries.⁸ In middle-aged and older patients ARVD accounts for approximately 90% of cases of renovascular hypertension.⁹ Other risk factors include all conditions that induce atheromatosis, i.e. age, male gender, smoking and history of hypertension, diabetes mellitus, and/or hyperlipidemia.¹⁰ Stenotic lesions of the renal circulation cause hypertension through ischemia-mediated stimulation of the renin angiotensin aldosterone (RAA) axis.⁸ Even if the systemic RAA activation is not sustained, an increase in endothelin production, local RAA activation, arterial wall remodeling and oxidative stress are responsible for maintaining the hypertension. All these structural and paracrine changes contribute directly, in addition to hypertension itself, to renal injury.¹¹⁻¹³

Renal parenchymal damage results not only from ischemia due to proximal renal artery stenosis (RAS), but also from small vessel atherosclerosis and atheroembolism of platelet and cholesterol thrombi derived from unstable atherosclerotic plaques.¹⁰

Fibromuscular dysplasia

Fibromuscular dysplasia is a non-atherosclerotic, non-inflammatory disease that affects renal arteries and is the second most common cause of RAS.¹⁴⁻¹⁷ It affects younger patients, especially women, between 15 and 50 years of age, and accounts for approximately 10% of causes of renovascular hypertension.⁹ Most commonly affected is the mid to distal part of the renal artery, but intra-renal segmental branches can also be involved. Fibromuscular dysplasia can also affect other arteries, such as the carotid, vertebral, iliac and mesenteric arteries.^{18,19} It is associated with cigarette smoking.²⁰ In contrast to ARVD, the renal microcirculation is normal; therefore, progressive renal atrophy is due to hemodynamically significant arterial stenosis, which needs to exceed 75-80%.

The clinical presentation of RAS is protean and its low prevalence makes universal screening of all patients with hypertension inappropriate. Clinicians should consider the diagnosis of RVD when there is a high index of clinical suspicion, as shown in Table 1.²¹⁻²⁶ The greater the number of clues, the more extensive the investigation should be (Figure 1). There are a number of invasive and noninvasive tests available that can aid the decision making.

Noninvasive renal artery diagnostic modalities

A number of noninvasive tests have been developed to avoid the potential risks of conventional contrast angiography; however, there might be a lack of accuracy. These tests can be divided into functional tests that seek to identify lesions that are hemodynamically and physiologically significant, and tests that rely upon direct imaging of the renal artery anatomy.

Table 1. Clinical clues to renovascular hypertension.

- Severe or refractory hypertension or abrupt acceleration of stable hypertension
- Severe hypertension in the setting of generalized atherosclerosis
- Early onset of severe hypertension with loss of physiological diurnal blood pressure variation
- Proteinuria, nephrotic syndrome, progressive or otherwise unexplained renal failure
- Asymmetric kidney size on routine renal ultrasound
- Systolic-diastolic bruit para-umbilically
- Recurrent and unexplained flash pulmonary edema
- ACE inhibitor- or ARB-induced renal dysfunction

ACE – angiotensin converting enzyme; ARB – angiotensin receptor blocker.

Plasma renin activity, captopril plasma tests

Peripheral plasma renin activity (PRA) measures the level of renin aldosterone axis activation. A high PRA is present in about 75% of patients with unilateral, uncomplicated RVH; however, many patients with essential hypertension also have elevated PRA.²⁷ Due to its low specificity, this test may be helpful in cases of a highly suppressed PRA (<1.0) – which makes uncomplicated RVH less likely – and in cases of extremely high values (>10.0) that should prompt a more careful workup.²⁸ The accuracy of this test can be increased by measuring the rise in PRA one hour after the administration of 25 to 50 mg of captopril.²⁹ Patients with RAS have increased PRA, possibly due to removal of the normal suppressive effect of high angiotensin II levels on renin secretion in the stenotic kidney. The sensitivity and specificity of this test ranged in different studies from 75% to 100% and 60% to 95%.^{30,31} In general, the utility of this test is limited by the need to discontinue antihypertensive medications (RAS inhibitors, diuretics). Renal vein sampling is time consuming and complicated. This test may be helpful in determining the functional significance of a renal artery lesion or “borderline angiographic appearance” and in predicting curability with revascularization.

Captopril renography (ACE inhibitor scintigraphy)

In normal kidneys there is a rapid uptake and excretion of the radioactive tracer. In the ischemic kidney, both glomerular filtration rate (GFR) and renal blood flow are dependent on angiotensin II mediated afferent arteriolar vasoconstriction. The administration of captopril (25 to 50 mg, 1 hour after the isotope is injected)³² induces a decline in GFR in the stenotic kidney, often accompanied by an equivalent increase in GFR in the contralateral kidney, due to the elimination of angiotensin II mediated vasoconstriction.³³ A decrease in relative uptake from one kidney accounting for less than 40% of the total GFR and a delayed peak uptake of the isotope to more than 10-11 minutes, above the normal value of 3 to 6 minutes, are the two major criteria for a positive captopril renogram.^{31,32} Baseline and angiotensin-converting enzyme (ACE) inhibitor scintigraphy are performed after intravenous injection of technetium-99m mercaptoacetyl triglycine (MAG3), iodine-131 orthoiodohippurate (OIH), or Tc-99m diethylenetriaminepentaacetic acid (DTPA). This test, like all functional tests

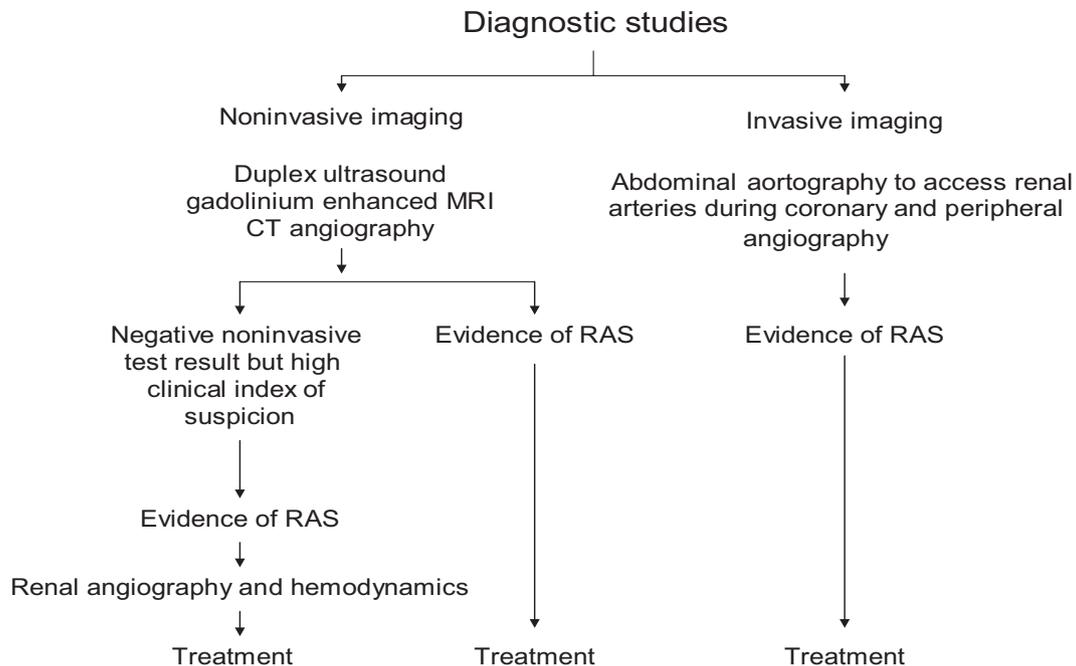


Figure 1. The diagnosis of renal artery disease (RAS).

for RVH, loses its accuracy in the setting of bilateral disease and renal insufficiency.³⁴ The sensitivity and specificity of this test can exceed 90% in high risk populations for high grade stenotic lesions and for a successful antihypertensive response to correction of stenosis,³⁰⁻³² with positive predictive value (PPV) 85% and negative predictive value (NPV) 90%. The utility of this test may also be limited by confounding factors such as volume depletion, concurrent medication and underlying renal dysfunction. The fact that ACE inhibitors or angiotensin receptor blockers should probably be withdrawn for several days prior to testing makes it less practical for some patients with severe hypertension.

Contrast angiography

Contrast angiography with aortography and selective renal artery cannulation has been considered the gold standard in assessing renal artery anatomy. Advantages of contrast angiography include good resolution, diagnosis of intra-renal branch artery stenosis, diagnosis in kidneys with complex anatomy, and the ability to simultaneously measure a pressure gradient across the lesion, while stent placement can be performed in the same session if necessary. Contrast angiography is indicated in patients with clinical clues in

whom definitive diagnostic noninvasive images cannot be obtained, and in patients where concomitant angiographic access has been obtained for peripheral angiography or coronary angiography.³⁵ However, conventional contrast angiography is invasive and associated with a risk of complications, including cholesterol embolization, pseudoaneurysm, hematoma,³⁶ arteriovenous fistula and contrast induced acute renal failure, that can occur in up to 20% to 50% of patients with both diabetes and chronic kidney disease.^{37,38} The use of alternative imaging agents, such as carbon dioxide or gadolinium, instead of iodinated contrast, as well as the use of oral acetylcysteine (600 mg twice per day), can decrease the incidence of nephrotoxic effects.^{39,40} The greatest limitation of conventional contrast angiography is that this imaging test looks for the anatomic presence of stenosis and not for the functional or clinical significance of the lesion, and cannot always differentiate between incidental RAS and stenosis producing hypertension.

Duplex ultrasonography

Duplex ultrasonography is the most widely studied method of noninvasive imaging of the renal arteries, having the advantage of providing both anatomic and functional assessment of the arteries. Doppler mea-

surements are taken along the entire length of the artery and significant stenosis is indicated by an increase in velocity through the narrowed lumen.⁴¹ Duplex ultrasonography compared with angiography has a sensitivity of 84% to 98% and a specificity of 62% to 99% for detecting RAS.⁴²⁻⁴⁸ An end-diastolic velocity of more than 150 cm/s predicts RAS greater than 80%.⁴⁹ Another ultrasonographic parameter, the vascular resistance index (RI), has been proposed as an adequate predicting tool. RI is calculated from the maximum systolic velocity (Vmax) and minimum diastolic velocity (Vmin) from a Doppler spectrum with the use of a formula, and it has been proposed as a functional equivalent of structurally altered vasculature. In the subset of patients with a favorable profile for revascularization, this method seems to be the first that should be applied, along with ultrasound.⁵⁰ Overall, duplex ultrasonography is useful for monitoring renal artery patency after endovascular treatment or surgical revascularization of RAS,^{51,52} unlike magnetic resonance angiography, where most stents cause artifacts. There are, however, certain limitations, including dependence on operator skill, duration of testing, difficulty in identifying the main renal artery due to overlying bowel gas, and the diminished ability to visualize accessory renal arteries.⁵² In an attempt to improve the reliability and reduce the difficulty of duplex sonography, the procedure has been performed after administration of captopril⁵³ and color coding,⁵⁴ which permits better discrimination of vascular structures.

Magnetic resonance angiography (MRA)

MRA is being increasingly used as the first-line screening test for RVH.⁵⁵⁻⁵⁸ Three-dimensional gadolinium-enhanced MRA uses a non-toxic contrast agent to visualize the vasculature in a manner similar to conventional contrast angiography. Comparisons with contrast angiography indicate a range of sensitivities from 90% to 100% and specificities of 76% to 94% for detection of RAS.³⁵ MRA does not require an arterial puncture, nor the use of nephrotoxic agents, and can therefore be used safely in patients with renal insufficiency. However, breath holding is required, which may make it difficult for patients with severe pulmonary, cardiac disease or claustrophobia to cooperate. In addition, MRA is contraindicated in patients with pacemakers or cerebral aneurysm clips. MRA best delineates the proximal renal vasculature and is therefore a useful diagnostic tool for patients suspected of hav-

ing atherosclerotic RAS, which more often involves the proximal renal artery⁵⁶ and not the distal, usually affected because of fibromuscular dysplasia, where MRA accuracy seems to be diminished.⁵⁹

Computed tomography angiography (CTA)

CTA is an accurate noninvasive screening test that combines the diagnostic accuracy of arteriography with the low risk of intravenous digital subtraction angiography.^{60,61} CTA produces excellent three-dimensional images of the aorta and renal arteries and, when compared with conventional contrast angiography, showed a sensitivity from 59% to 96% and a specificity from 82% to 99% for detecting significant RAS⁶²⁻⁶⁸ (the low sensitivity values comes from analysis that includes accessory renal arteries). The principle disadvantage of CTA is the need to administer significant amounts of potentially nephrotoxic intravenous iodinated contrast (100-500 cc) and it is therefore not an ideal screening method for patients with renal insufficiency, because of the risk of inducing nephropathy.

Overview of renal artery diagnostic modalities

At present there is no sufficiently accurate noninvasive radiologic or serologic screening test that, if negative, would completely exclude the presence of renal artery stenosis.^{26,69,70} Each of the diagnostic modalities mentioned above presents relative advantages and disadvantages. Thus, the primary determinant of the degree and type of evaluation remains the clinical index of suspicion and the presence or absence of renal insufficiency. A positive screening test result or very strong clinical clues call for more definitive confirmatory testing.

Primary aldosteronism

Primary aldosteronism (PA) is caused by autonomous production of aldosterone by the adrenal cortex. Its incidence is estimated to vary from 1% to 11%^{71,72} in patients with hypertension (Table 2). The various forms of primary aldosteronism are shown in Table 3. The syndrome was first described in 1955.⁷³ In 65-90% of patients, PA occurs as a result of one or more aldosterone producing adenomas (APAs). In 65-70% of patients, the aldosteronoma is solitary, while in 13% of patients multiple adenomas are present and in 6% of patients microadenoma exists.⁷⁴⁻⁷⁷

Table 2. Prevalence of unrecognized primary aldosteronism in patients with hypertension.

Author (Ref.)	Country	No. screened	Prevalence
Gordon et al ⁸⁸	Australia	199	8.5%
Kumar et al ⁸⁹	India	103	8.7%
Kreze et al ⁹⁰	Slovakia	115	13.0%
Lim et al ⁹¹	United Kingdom	465	9.2%
Loh et al ⁹²	Singapore	350	4.6%
Fardella et al ⁹³	Chile	305	9.5%
Schwartz et al ⁹⁴	United States	117	12.0%
Rossi et al ⁷¹	Italy	1046	6.3%

PA is characterized by moderate to severe hypertension without edema. The diagnosis of primary aldosteronism is based on the typical biochemical finding of hypokalemia, hypernatremia, depletion of magnesium, elevated bicarbonate levels, low plasma pH and elevated aldosterone levels in the serum and urine. However, in recent studies hypokalemia was reported only in one third of patients with PA. Thus, normokalemic hypertension constitutes the most common presentation of the disease, with hypokalemia probably present in the most severe cases. In hypokalemic patients daily potassium urinary excretion >30 mmol (off diuretics and under potassium supplementation for 4 days) is indicative of potassium wastage, usually driven by mineralocorticoid excess. With hypokalemic alkalosis, various symptoms, including muscular weakness, polydipsia, nocturia, paresthesia, headaches and abnormal ECG findings, may develop.⁷⁴⁻⁷⁸

The screening can be completed with plasma aldosterone concentration (PAC) to PRA ratio, (Figure 2)⁷⁹⁻⁸⁶ Suppressed PRA with concomitant elevations in plasma renin and aldosterone concentration and an elevated PAC/PRA ratio, point toward a diagnosis of PA. Using the PAC/PRA ratio as a screening test followed by aldosterone suppression confirmatory testing identifies 5-13% of all hypertensive patients as having primary aldosteronism,⁸⁷⁻⁹³ and the prevalence can reach 20% in patients with resistant hypertension.⁹⁴ A PRA ratio >30 is suggestive of PA, with a sensitivity of 91%, PPV 69% and NPV 98%, while some investigators suggest that aldosterone should

be above 15 ng/dl at the same time to establish a firm diagnosis and reduce false positive results. A suppressed PAC and PRA suggest more rare causes of secondary hypertension, including congenital adrenal hyperplasia, Cushing syndrome, deoxycorticosteroid-producing tumor and Liddle syndrome. In contrast, an elevated PRA and PAC, and a reduced PAC/PRA ratio indicate secondary aldosteronism, including RVH, malignant hypertension or a renin-secreting tumor. It has been suggested that captopril administration may optimize the PAC/PRA test characteristics.⁹⁵⁻¹⁰⁰

The PAC/PRA ratio is currently the most reliable available method of screening for PA. PAC/PRA seems to be superior to measurement of potassium or aldosterone alone (due to lack of sensitivity) or of renin (low specificity). Nevertheless, testing should be done under the proper conditions. A limitation of the test is the inherent variability of aldosterone secretion due to an intrinsic circadian rhythm. Sampling should be done in the morning after patients have been out of bed for at least 2 h, usually after they have been seated for 5-15 min. There should be no restriction in dietary sodium intake before testing, and restoration of normal serum potassium should precede it. It is better to perform this test while all antihypertensive drugs that affect RAS are withheld. This can be difficult to accomplish when severe hypertension dictates the continuation of some medications to control hypertension and hypokalemia during testing. However, mineralocorticoid receptor blockers (spironolactone or eplerenone) should be discontinued for at least 3 weeks. Beta-blockers should also be stopped, because they lower renin and spuriously alter the ratio.

A confirmatory test for establishing diagnosis of PA is oral sodium loading for 3 days and 24 hour urine collection of aldosterone. The 24-hour urine sodium must be >200 meq to document adequate sodium loading and a urinary aldosterone of >14 pg is suggestive of PA.¹⁰¹ Alternatively, 2 L of isotonic sa-

Table 3. Forms of primary aldosteronism.

Aldosterone-producing adenoma (APA)
Bilateral idiopathic hyperplasia (IHA)
Primary (unilateral) adrenal hyperplasia
Aldosterone-producing adrenocortical carcinoma
Familial hyperaldosteronism (FH):
Glucocorticoid-remediable aldosteronism (FH type I)
FH type II (APA or IHA)

line is infused over 4 hours to suppress aldosterone production and a plasma aldosterone level >10 ng/dl is considered diagnostic of hyperaldosteronism.

Following confirmation of aldosteronism, CT imaging of the adrenals should be performed to differentiate aldosterone-producing adenoma from idiopathic hyperaldosteronism (bilateral hyperplasia).^{85,102} If CT scan findings are equivocal, radionuclide studies and MRI should be performed.¹⁰³ As previously reported by Rossi et al, adrenal imaging is often insufficient to achieve discrimination between aldosterone-producing adenomas and idiopathic hyperaldosteronism, and CT results may lead to useless

and/or inappropriate adrenalectomy in many cases.¹⁰⁷ If doubt remains concerning the diagnosis, adrenal venous sampling is recommended.

Chemical shift imaging is another useful method for the characterization of adrenal masses. It is based on the principle that fat protons process faster than water protons. Benign adrenal tumors contain fat, while malignant adrenal tumors rarely do. Chemical shift MRI is highly sensitive and specific for the differentiation of benign from malignant adrenal tumors. MRI showed a sensitivity of 70-100% and a specificity of 64-100% according to several studies.^{103,108-110} A false positive diagnosis occurred in cas-

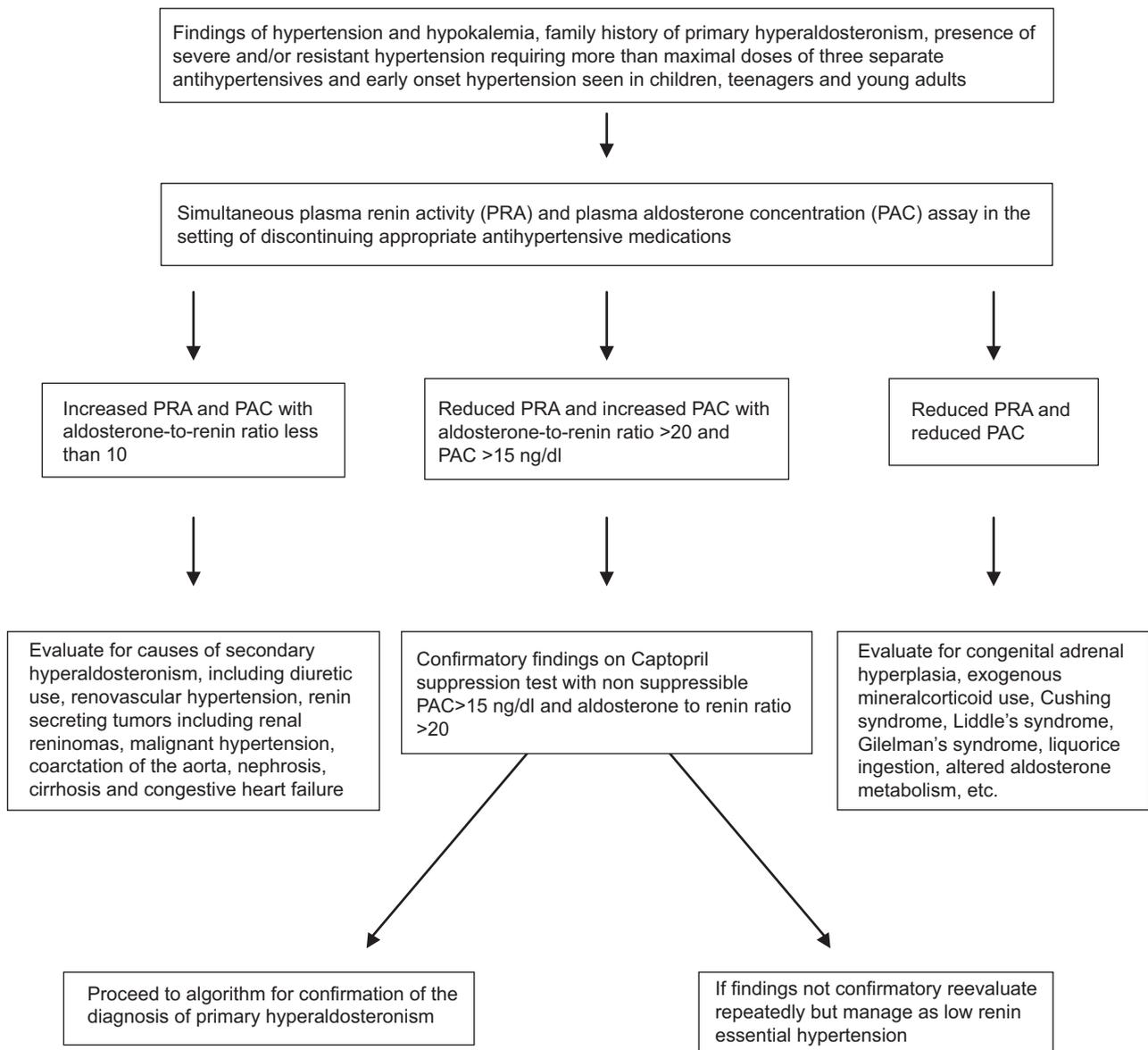


Figure 2. Algorithm for the identification and screening of possible secondary hyperaldosteronism.

es of idiopathic hyperaldosteronism, bilateral nodular hyperplasia, and primary hypertension associated with non-functional adrenal adenoma.

Radionuclide scanning with ¹³¹I-iodocholesterol (NP-59) has also been used. NP-59 is a cholesterol analog that binds low-density lipoprotein receptors of the adrenal cortex.¹⁰⁵ Imaging is usually performed after dexamethasone suppression to reduce high background tracer uptake by the *zona fasciculata*. Normal glands (showing uptake of the radionuclide) imply adrenal hyperplasia, whereas early unilateral depiction implies APA. NP-59 showed a sensitivity of 80-95% for the detection of adrenal hyperplasia. Smaller adenomas, which are not clearly depicted on CT scans, can be detected on NP-59.¹⁰⁶ However, it is cumbersome and has to be performed over 2 to 5 or more days. Moreover, secondary hyperaldosteronism produces bilateral tracer uptake that is indistinguishable from that of primary. All drugs that disturb the RAA axis must be withdrawn before imaging.

Imaging cannot reliably visualize microadenomas or distinguish incidentalomas from functional adenomas, making adrenal venous sampling the most accurate means of differentiating unilateral from bilateral forms of PA. Adrenal venous sampling has a sensitivity and specificity of 95% and 100%, respectively, for detecting unilateral aldosterone excess. Adrenal venous sampling is the standard reference test to differentiate unilateral from bilateral (idiopathic hyperaldosteronism) disease in patients with PA. However, it is an invasive procedure with the possible complications of adrenal infarction, hemorrhage, iliac venous thrombosis and adrenal insufficiency. Centers with experienced radiologists exhibit complication rates as low as 2.5%.^{104,108,111}

Pheochromocytoma

Pheochromocytomas are neuroendocrine tumors developing from adrenal medulla on the sympathetic ganglionic neurons. They occur in less than 0.2% of patients with hypertension.^{112,113} Most pheochromocytomas are sporadic, but 10% are familial. Familial syndromes^{114,115} include a simple autosomal dominant form not associated with other abnormalities, the multiple endocrine neoplasias (MEN) type IIA and IIB, neurofibromatosis and the Von Hippel-Lindau syndrome.^{114,115} Pheochromocytoma in these disorders is presumably a reflection of the genetic tendency towards tumor formation. These tumors produce catecholamines, generating different

symptoms and clinical responses. The classic crisis in patients with pheochromocytoma consists of episodic headache, sweating and tachycardia.^{112,116} About half have paroxysmal hypertension; most of the rest have apparently essential hypertension. However, not all patients have these symptoms,^{114,118} while patients with essential hypertension may have the same symptoms.¹¹⁹ When pheochromocytoma is associated with MEN 2 syndrome, symptoms are present in only about half of the patients and only one in three has hypertension.¹²⁰ A similar finding has been observed with pheochromocytoma and Von Hippel-Lindau disease, as 35% of patients have no symptoms, a normal blood pressure and normal catecholamine tests.¹²¹ Other signs and symptoms that can occur include pallor, orthostatic hypotension, visual blurring, papilledema, weight loss, hyperglycemia, leukocytosis, psychiatric disorders, a dilated cardiomyopathy that may reflect the toxic effects of excess catecholamines,¹¹⁶ and, rarely, secondary erythrocytosis due to overproduction of erythropoietin.¹²² Pheochromocytoma should be confirmed by biochemical testing in all patients suspected of having this tumor. The screening should be selective based on suggestive clinical features. Screening tests include measurement of catecholamines (epinephrine, norepinephrine, dopamine) and their metabolites (metanephrine, normetanephrine, venillmandelic acid) in the plasma and urine.

Measurement of plasma and urine catecholamines

Twenty-four-hour measurements of total urinary catecholamines and metanephrines have been the cornerstone of diagnosis for many years. A urinary collection should be made twice to avoid missing cases because of the episodic nature of pheochromocytoma. Urinary dopamine has a specificity of 99% but its use is limited due to the low sensitivity of 63%. Elevations in either urinary norepinephrine or epinephrine were found to have a sensitivity of 100% and a specificity of 97%; however, the collection may be cumbersome for some patients. In general, large tumors produce more catecholamine metabolites because the catecholamines are metabolized within the tumor before they are released, whereas small tumors are more likely to release free catecholamines. Alternatively, the measurement of plasma metanephrines is considered extremely sensitive, and some have advocated its use as a first-line test. Its sensitivity is nearly 99%, and its specificity has been reported to be in the

range of 85-89%. Because of its high NPV and quick results, many argue that a negative result is sufficient to exclude pheochromocytoma.¹¹⁶

Iodinated contrast dyes can interfere with some biochemical measurements. Tricyclic antidepressants, prochlorperazine, reserpine, clonidine, and clofibrate may interfere with urinary catecholamines and metabolite measurements. Such medications should be discontinued, preferably 2 weeks before collection. Measurement of fractionated 24-hour urinary metanephrines is less likely to be altered by drugs or certain foods.^{112,127} Urinary metanephrine and catecholamine excretion is unaffected by age or sex in normal subjects.¹³⁰

In order to differentiate between positive and false positive results, a clonidine suppression test can be performed. The clonidine suppression test consists of the oral administration of 0.3 mg clonidine given at least 12 hours after antihypertensive drugs have been discontinued. Patients without pheochromocytoma should have a fall in plasma total catecholamine concentration to less than 500 pg/ml after clonidine administration.^{123,124,125}

Radiologic tests

A positive screening test should prompt a search for the tumor, if sources of a false positive result have been excluded. Abdominal imaging with CT or MRI is the initial test of choice, given that 90% of pheochromocytomas are on the adrenal glands and 95% in the abdomen.¹³¹ Although any site containing paraganglionic tissue may be involved, the most common extrarenal locations are the superior and inferior para-aortic areas (75%), the bladder (10%), the thorax (10%), the head and neck, and the pelvis (5%).¹³²

CT and MRI are the most sensitive procedures (98-100%);¹²⁷ they can detect nodules >1 cm, although MRI lacks specificity (50%).¹²⁵ In patients with MEN 2 syndrome, CT may miss about 25% of the tumors.¹²⁰ The choice between CT and MRI depends upon the cost and certain other factors, such as exposure to radiation and exacerbation of hypertension if a radiographic contrast agent is given (which can be prevented by pretreatment with alpha adrenergic blockade).¹³³ However, gadolinium-enhanced MRI might be of help in detecting paragangliomas that are localized outside the abdomen and are often missed by CT or scintigraphy.

If CT or MRI is negative in the presence of clinical and biochemical evidence of pheochromocytoma, 123 I-metaiodobenzylguanidine (MIBG) scintigraphy or 111-in-pentetreotide scintigraphy (octreoscan) may be

done. These procedures can detect tumors missed by CT or MRI,¹¹⁶ or can be used in patients with large tumors (>10 cm) that have an increased risk of malignancy.¹³² A simplified algorithm for the diagnosis and localization of pheochromocytoma is shown in Figure 3.

A promising new modality for pheochromocytoma imaging seems to be 6-[18 F] fluorodopamine positron emission tomography.

The sensitivity and specificity of common diagnostic tests for identifiable causes of hypertension by cause are shown in Table 4.¹³⁴

Conclusions

Secondary hypertension accounts for some 10% of the cases of hypertension. Physicians should be quite selective about who to evaluate further for a potentially curable cause of hypertension. The last decade has brought major advances in noninvasive imaging of the renal vasculature. Ultrasound Doppler, MRA and CT angiography provide high specificity in selected centers. If primary aldosteronism is suspected, patients should undergo screening with plasma renin-to-aldosterone ratio and finally MRI for the detection of morphological adrenal abnormalities. Patients suspected of pheochromocytoma show an increase in plasma or urinary catecholamines, but sensitive examinations, such as CT and MRI, are needed to localize the tumor. Careful and thorough clinical evaluation

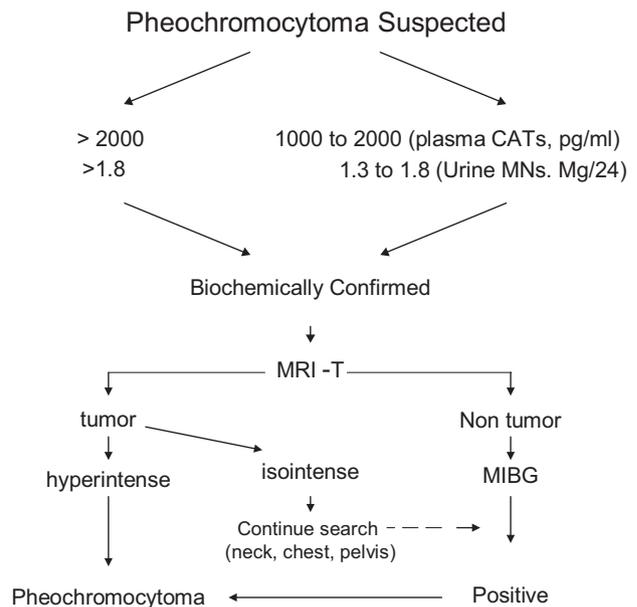


Figure 3. Algorithm for the diagnosis and localization of pheochromocytoma.

Table 4. Sensitivity and specificity of common diagnostic tests for identifiable causes of hypertension, by cause. (Modified from reference 134: The Diagnosis of Essential and Secondary Hypertension in Adults, The Journal of Family Practice, 2001, vol. 50, issue 8, pp. 707-712, Quadrant HealthCom. Reproduced with permission.)

Disorder/Test*	Sensitivity %	Specificity %
Renovascular:		
(conventional arteriography)		
Abdominal or flank bruit	65	90
MR angiography	93	95
Duplex sonography	98	98
Captopril renal scan	91	87
Pheochromocytoma:		
(tissue diagnosis)		
Plasma metanephrines	100	85
Plasma catecholamines	85	82
24-hour urine metanephrine	95	96
24-hour urine M-T-C ratio	100	98
Metaiodobenzylguanidine scintigraphy (localization)	88	89
Computed tomography (localization)	100	50
Hyperaldosteronism:		
(tissue diagnosis)		
PAC/PRA ratio and PAC	90	91
PAC/PRA ratio	100	95

*Test cutoff points: Plasma metanephrines, metanephrine >0.66 nmol/L or normetanephrine >0.30 nmol/L; plasma catecholamines, norepinephrine >3.00 nmol/L and epinephrine >0.54 nmol/L; 24-hour urine metanephrine, metanephrine >3.70 nmol/day; M-T-C ratio, urine metanephrine-to-creatinine ratio >0.354; 24-hour urinary cortisol, urinary cortisol >90 µg/day; DST, plasma cortisol >100 nmol; PAC/PRA ratio and PAC, plasma aldosterone/renin ratio >30 and plasma aldosterone level >20 ng/dL; PAC/PRA ratio, plasma aldosterone/renin ratio >25. MR – magnetic resonance; PAC – plasma aldosterone concentration; PRA – plasma renin activity.

and simple algorithms are needed to avoid unnecessary tests in making the diagnosis of secondary forms of hypertension more accurately and promptly.

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