



# Clinical Issues in Hypertension

Canadian Coalition for High Blood Pressure Prevention and Control

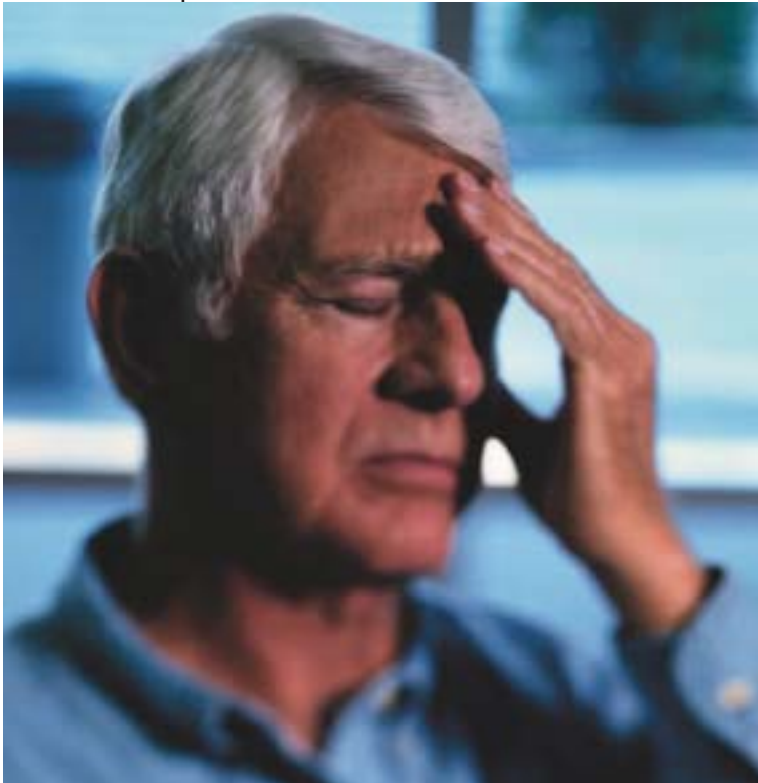
Coalition Canadienne pour la Prévention et le Contrôle de l'Hypertension Artérielle

## Secondary Hypertension: Diagnosis and Management Options

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Secondary hypertension is defined as being present when there is an identifiable cause contributing to high blood pressure (BP), as opposed to the primary form, also known as “essential hypertension.”

Secondary hypertension is identified in approximately 10-20% of patients evaluated for resistant hypertension.<sup>1</sup> Resistant hypertension is defined as persistently elevated BP, > 160/100 mmHg, in a compliant patient on therapeutic doses of three antihypertensives.<sup>2</sup> The most common causes of secondary hypertension are outlined in Table 1.

Most cases of secondary hypertension can be detected by the primary-care physician.<sup>3</sup>

The most important secondary causes, their diagnoses and treatment options are discussed in this article.

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Table 1

## Causes of Secondary

Renal	Endocrine	Other
Renal artery stenosis	Primary hyperaldosteronism	Sleep apnea
• Fibromuscular Dysplasia	Pseudohyperaldosteronism	
	• Liquorice ingestion	
	• Liddle's syndrome	
	• Congenital adrenal hyperplasia	
• Atherosclerotic renal artery stenosis	Cushing's syndrome	Coarctation of aorta
Renal parenchymal disease	Pheochromocytoma Hyperthyroidism Hyperparathyroidism Acromegaly	

### 1. Renal Artery Stenosis (RAS)

RAS can be classified into two varieties, fibromuscular dysplasia (FMD) and atherosclerotic RAS.

**History and clinical clues:** FMD is uncommon, occurs predominantly in young women and is usually unilateral. Clinical presentations of atherosclerotic RAS include abrupt onset of hypertension before age 40 or after age 50, renal or carotid artery bruits, lack of obesity, resistance to triple drug therapy, recurrent "flash pulmonary edema," diabetes and deteriorating renal function.

**Screening:** RAS greater than 75-80% is usually associated with excess renin secretion and renovascular hypertension. A good initial screening test is angiotensin converting enzyme inhibitor (ACEI) renal scintigraphy where administration of oral captopril or enalapril decreases glomerular filtration of the affected kidney (reflected by decreased radio-tracer uptake). The test has a sensitivity and specificity of 81-91% and 93-94% respectively

when angiography is used as the gold standard.<sup>4</sup> Duplex ultrasonography is useful but operator dependant and limited by superimposed arteries and bowel gas. Spiral computed tomography (CT) and magnetic resonance angiography (MRI) are promising modalities. The limitations of MRI are inadequate visualization of segmental arteries, overestimation of stenosis severity, high cost and low availability.

**Treatment:** Fibromuscular variant of RAS is best treated by percutaneous balloon angioplasty (PTA). Although PTA is being widely performed by many for atherosclerotic RAS, it has the same problems as in coronary disease with a restenosis rate of 30% in one year. Recently, renal artery stenting has been advocated to avoid restenosis. Medical therapy is an important aspect of hypertension control in these patients. ACEIs and angiotensin receptor blockers are contraindicated in patients with bilateral severe RAS. Most patients with RAS are best treated with three or more antihypertensives or combination drugs and intervention



should be considered probably only for those with refractory hypertension and progressive worsening of renal function.

## 2. Renal Parenchymal Disease (RPD)

Glomerular diseases are more frequently associated with hypertension than tubular disorders. An exception is the adult polycystic kidney disease in which hypertension is an early feature.<sup>5</sup>

**History and clinical clues:** Findings include presence of polycystic kidney disease in family history, resistant hypertension, and palpable, enlarged kidneys.

**Diagnosis:** Urinalysis is always abnormal and serum creatinine is elevated in RPD. If these two tests are abnormal one should proceed to renal ultrasonography to further delineate the pathology and assess renal size and asymmetry.

**Treatment:** Hypertension is difficult to control with RPD often requiring 2-4 drugs. Diuretics are cornerstone and loop diuretics should be used if creatinine is above 2 mg/dL (180 mmol/L). Multidrug therapy based primarily on ACEIs are better than those based on calcium channel blockers (amlodipine) in slowing progression of renal failure.<sup>6</sup>

## 3. Sleep Apnea

Sleep apnea or sleep disordered breathing is associated with hypertension even after controlling for variables such as anthropometrics.<sup>7</sup> The etiology of hypertension is a catecholamine excess, which could mimic pheochromocytoma, although a CT scan of the adrenals will be normal within limits.

**History and clinical clues:** Findings include obesity, male gender, gaspy nocturnal breathing with prominent snoring (elicit history from spouse), daytime somnolence, hypertension.

**Diagnosis:** Screening tests include home

oximetry monitoring and Berlin questionnaire.<sup>8</sup> Sophisticated tests such as polysomnography (sleep laboratory) may be necessary to confirm diagnosis.

**Treatment:** Continuous positive airway pressure (CPAP) is commonly used. Selected patients may require oral appliances, uvulopalatopharyngoplasty, or other surgical procedures. Effective CPAP is associated with an appreciable improvement in BP control.

## 4. Primary Aldosteronism

Two major varieties of this condition include adrenocortical adenoma (60%) and bilateral adrenocortical hyperplasia (40%). The disease often presents between 30-50 years of age.<sup>9</sup>

**History and clinical clues:** Findings include resistant hypertension; however, more striking is unexplained hypokalemia or dramatic hypokalemia to low dose diuretics.

**Diagnosis:** Screening begins with measurement of plasma renin activity (PRA) and plasma aldosterone (PA) levels; an elevated ratio (PA/PRA) suggests the diagnosis which can be confirmed with elevated PA levels following saline loading test. Adrenal adenomas are very often small, such that CT or MRI detects only 60-75% of these. Laboratory confirmation should prompt referral to a hypertension specialist or endocrinologist.

**Treatment:** Open surgical or laparoscopic removal of adenomas is the standard therapy although medical treatment has been reported to be effective. For adrenocortical hyperplasia, medical therapy with potassium sparing diuretics (spironolactone or amiloride hydrochloride) is recommended.

## 5. Cushing's Syndrome:

Cushing's syndrome is hypersecretion of cortisol usually due to pituitary microadenomas



## Clinical Issues in Hypertension

Table 2

### Summary of Suggested Screening Tests and

	Diagnostic Tests	Intervention
<b>Renal artery stenosis</b>	Captopril renogram (preferred) Duplex ultrasound Spiral CT MRI Renal angiogram	PTA ± stent Surgical correction Aggressive medical treatment of hypertension
<b>Renal parenchymal disease</b>	Urinary analysis Electrolytes Renal ultrasound	If abnormal, refer to nephrology
<b>Sleep apnea</b>	Oxygen pulse oximetry Berlin questionnaire Polysomnography	CPAP Uvulopalato pharyngoplasty
<b>Primary aldosteronism</b>	Serum potassium 24-hour urinary potassium excretion PA, PRA, PA/PRA (ratio) Saline suppression test CT, MRI	Aldosterone antagonists Surgical removal of adrenal adenomas
<b>Cushing's syndrome</b>	DST 24-hour excretion of urinary free cortisol MRI of brain	Transsphenoidal microadenectomy Pituitary irradiation Adrenalectomy mitotane
<b>Pheochromocytoma</b>	24-hour urinary excretion of metanephrines and creatinine  Plasma catecholamine and free metanephrine levels Imaging with MRI or CT or MIBG	Alpha blockade with phenoxybenzamine  Metyrosine  Surgical therapy
<b>Hyperthyroidism</b>	TSH	Radioiodine Beta blockers Thiouracils
<b>Hyperparathyroidism</b>	Parathyroid hormone level	Surgery

(Cushing's disease) in about 80%, but can also be caused by adrenal adenomas or hyperplasia.

**History and clinical clues:** Findings include truncal obesity, acne, plethora, fat pads, striae, easy bruising, hyperglycemia and resistant hypertension.

**Diagnosis:** The two best screening tests for Cushing's syndrome are the overnight dexamethasone suppression test (DST) and the 24-hour urinary excretion of free cortisol and creatinine.<sup>10</sup> If these tests are abnormal, then referral to an endocrinologist to further delineate



adrenocorticotrophic hormone (ACTH) dependency is needed. Identification of pituitary microadenomas is preferably done by MRI, although extremely small tumors can be missed.

**Therapy:** Transsphenoidal microadenectomy is the treatment of choice. Pituitary irradiation is reserved for young women who wish to have children and those who failed to respond to surgery.

## 6. Pheochromocytoma

This is a very rare cause of secondary hypertension (< 1% of cases of secondary hypertension).

### **History and clinical clues:**


Findings are associated with the triad of headaches, palpitations and sweating in patients with volatile blood pressure; association with multiple endocrine neoplasia syndromes (MEN); and situations where hypertension was made worse with beta blockers, monoamine oxidase inhibitors or positional changes.

**Diagnosis:** Screening tests include 24-hour excretion of metanephrines and creatinine. Plasma catecholamine levels and free metanephrine levels can also be measured particularly during a hypertensive episode.<sup>11</sup> If these tests raise suspicion for pheochromocytoma, localization should be performed with MRI or CT and /or I-131 meta-iodobenzylguanidine (MIBG).

**Treatment:** Acute preoperative therapy involves use of a phentolamine drip. Beta blockers should be avoided before alpha blockade due to the potential for severe unopposed alpha adrenergic surge after beta blockade. Surgical treatment consists of removal of tumor after several weeks of therapy with phenoxy-

benzamine and metyrosine to block and deplete catecholamines. Hypertension is cured by surgery in 75-80% of patients with lingering BP issues in the remainder.

## Conclusion

Secondary hypertension occurs only in 5-10% of patients diagnosed with hypertension. Using history, clinical exam and appropriate diagnostic testing (Table 2), a specific etiology for hypertension can be identified and effectively treated. 

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