

INTRODUCTION

Worldwide statistics show that one in three adults have hypertension. Most of these patients have no clear etiology and are classified as having essential hypertension. However, 5 to 10 percent have secondary hypertension, in which an underlying, potentially correctable etiology can be identified.

GENERAL APPROACH TO THE PATIENT

The physician should confirm that the patient's blood pressure has been accurately measured using correct positioning with an appropriately sized cuff. Ambulatory blood pressure monitoring can be useful to rule out white coat hypertension, if suspected. It is also important to review the patient's diet and medication use for other potential causes of elevated blood pressure. The clinical features of secondary hypertension are enumerated in Table 1. Many drugs affect blood pressure (Table 2) and a trial period off of a potentially offending medication may be all that is needed to reduce blood pressure. If these potential contributors to hypertension have been excluded and concern for secondary hypertension remains, the physician can investigate for potential physiologic causes.

MOST COMMON CAUSES OF SECONDARY HYPERTENSION BY AGE (TABLE 3)**Young adults (19 to 39 years of age)****Renal artery stenosis**

In young adults, particularly women, fibromuscular dysplasia is one of the most common causes of secondary hypertension. Patients with renal artery stenosis may have an audible high-pitched holo-systolic renal artery bruit.

Although angiography is the diagnostic standard for detecting renal artery stenosis, it is invasive and should not be used as an initial diagnostic test. MRI with gadolinium contrast media and computed tomography (CT) angiography are equally accurate. If MRI and CT angiography are contraindicated, renal Doppler can be used.

Thyroid dysfunction

Hypothyroidism can cause an elevation in diastolic blood pressure, whereas hyperthyroidism can cause an isolated elevation of systolic blood pressure, leading to a widened pulse pressure. Although hypothyroidism is one of the more common secondary causes of hypertension in young adults, there is actually an increased incidence of hypothyroidism with age, peaking in a patient's 60s. In

contrast, hyperthyroidism is significantly associated with elevated blood pressures in 20- to 50-year-olds. Thyroid-stimulating hormone is a sensitive marker used for initial diagnosis of either condition.

MIDDLE-AGED ADULTS (40 TO 64 YEARS OF AGE)**Aldosteronism**

Non-medication-induced hypokalemia should lead the physician to suspect aldosteronism, although this abnormality occurs in only 30 percent of patients. Aldosteronism affects 10 to 20 percent of patients with resistant hypertension, making it the most common cause of secondary hypertension in this subgroup. The best initial test for aldosteronism is measurement of the aldosterone/renin ratio. Ideally, aldosterone and renin levels should be measured in the morning at least two hours after waking and in the upright position. If the aldosterone/renin ratio is above 20 (when plasma aldosterone is reported in ng/dL and plasma renin activity in ng/mL/hour), and is accompanied by an aldosterone level above 15 ng/dL (416.10 pmol/L), the patient should undergo salt suppression tests.

Obstructive sleep apnea

Obstructive sleep apnea is a notable cause of secondary hypertension, particularly in 40- to 59-year-olds. The standard diagnostic test is polysomnography, but clinical assessment tools (e.g., Epworth Sleepiness Scale, Sleep Apnea Clinical Score) with night-time pulse oximetry may be sufficient for the diagnosis of moderate to severe obstructive sleep apnea. In patients with obstructive sleep apnea, the normal variation in blood pressure over 24 hours is impaired and it may be beneficial to perform ambulatory blood pressure monitoring on these patients to fully evaluate their circadian pressures.

Pheochromocytoma

Pheochromocytomas are rare tumors responsible for approximately 0.5 percent of cases of secondary hypertension. Patients typically present between 30 and 60 years of age. Diagnosis is important because of the cardiovascular sequelae and because the hypertension is largely reversible with surgery. Testing can be done by measuring metanephrines in a 24-hour urine sample, but measurement of plasma free metanephrines is easier for the patient and has a negative likelihood ratio close to zero, making it a good test to rule out the disorder.

Cushing syndrome

Most presentations of Cushing syndrome (hypercortisolism) are iatrogenic from prescribed corticosteroids. Options for

Table 1: Clinical features of secondary hypertension

Signs/symptoms	Possible secondary hypertension cause	Diagnostic test options
<ul style="list-style-type: none"> • Arm to leg systolic blood pressure difference > 20 mm Hg • Delayed or absent femoral pulses • Murmur 	Coarctation of the aorta	<ul style="list-style-type: none"> • Magnetic resonance imaging (adults)
<ul style="list-style-type: none"> • Increase in serum creatinine concentration (≥ 0.5 to 1 mg per dL after starting angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) • Renal bruit 	Renal artery stenosis	<ul style="list-style-type: none"> • Computed tomography angiography • Doppler ultrasonography of renal arteries • Magnetic resonance imaging with gadolinium contrast media
<ul style="list-style-type: none"> • Bradycardia/tachycardia • Cold/heat intolerance • Constipation/diarrhea • Irregular, heavy or absent menstrual cycle 	Thyroid disorders	<ul style="list-style-type: none"> • Thyroid-stimulating hormone
<ul style="list-style-type: none"> • Hypokalemia 	Aldosteronism	<ul style="list-style-type: none"> • Renin and aldosterone levels to calculate aldosterone/renin ratio
<ul style="list-style-type: none"> • Apneic events during sleep • Daytime sleepiness • Snoring 	Obstructive sleep apnea	<ul style="list-style-type: none"> • Polysomnography (sleep study) • Sleep Apnea Clinical Score with nighttime pulse oximetry
<ul style="list-style-type: none"> • Flushing • Headaches • Labile blood pressures • Orthostatic hypotension • Palpitations • Sweating • Syncope 	Pheochromocytoma	<ul style="list-style-type: none"> • 24-hour urinary fractionated metanephrines • Plasma free metanephrines
<ul style="list-style-type: none"> • Buffalo hump • Central obesity • Moon facies • Striae 	Cushing syndrome	<ul style="list-style-type: none"> • 24-hour urinary cortisol • Late-night salivary cortisol • Low-dose dexamethasone suppression

initial testing include 24-hour urinary free cortisol, low-dose dexamethasone suppression or late-night salivary cortisol tests.

OLDER ADULTS (65 YEARS AND OLDER)

Renal artery stenosis caused by atherosclerosis

It should be suspected in those who develop hypertension after 50 years of age, have known atherosclerosis elsewhere, have unexplained renal insufficiency or have a rapid deterioration in kidney function when started on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

Renal failure

Hypertension can be a major cause of renal parenchymal damage, particularly in older adults, which in turn leads to worsening hypertension. Alternatively, renal damage from another process, such as diabetes mellitus, can

Table 2: Select drugs that may elevate BP

Drug class	Common examples
Estrogen	Oral contraceptives
Herbal	Ephedra, ginseng, ma huang
Illicit drugs	Amphetamines, cocaine
Nonsteroidal anti-inflammatory	Cyclooxygenase-2 inhibitors, ibuprofen, naproxen
Psychiatric medicines	Buspirone, carbamazepine, clozapine, fluoxetine, lithium, tricyclic antidepressants
Steroids	Methylprednisolone, prednisone
Sympathomimetic drugs	Decongestants, diet pills

result in hypertension. Evaluation for possible chronic renal failure should include calculating the estimated

Table 3: Most common causes of secondary hypertension by age

Age groups	Percentage of hypertension with an underlying cause	Most common etiologies
Adolescents (12 to 18 years)	10 to 15	Renal parenchymal disease
Young adults (19 to 39 years)	5	Coarctation of the aorta Thyroid dysfunction Fibromuscular dysplasia Renal parenchymal disease
Middle-aged adults (40 to 64 years)	8 to 12	Aldosteronism Thyroid dysfunction Obstructive sleep apnea Cushing syndrome Pheochromocytoma
Older adults (65 years and older)	17	Atherosclerotic renal artery stenosis Renal failure Hypothyroidism

glomerular filtration rate and obtaining a urinalysis to assess for albuminuria.

REFERENCES

1. U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Revised May 2005. NIH Publication No. 05-5267. http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf. Accessed July 16, 2014.
2. Elliott WJ. Renovascular hypertension: an update. *J Clin Hypertens (Greenwich)* 2012; 10:522-533.
3. Zhang HL, Sos TA, Winchester PA, Gao J, Prince MR. Renal artery stenosis: imaging options, pitfalls, and concerns. *Prog Cardiovasc Dis* 2010; 52:209-219.
4. Rountas C, Vlychou M, Vassiou K, et al. Imaging modalities for renal artery stenosis in suspected renovascular hypertension: prospective intraindividual comparison of color Doppler US, CT angiography, GD-enhanced MR angiography, and digital subtraction angiography. *Ren Fail* 2010; 29:295-302.
5. Elamin MB, Murad MH, Mullan R, et al. Accuracy of diagnostic tests for Cushing's syndrome: a systematic review and metaanalyses. *J Clin Endocrinol Metab* 2011; 93:1553-1562.
6. Klein I, Danzi S. Thyroid disease and the heart [published correction appears in *Circulation*. 2011;117(3):e18]. *Circulation* 2007; 116:1725-1735
7. Myint KS, Watts M, Appleton DS, et al. Primary hyperaldosteronism due to adrenal microadenoma: a curable cause of refractory hypertension. *J Renin Angiotensin Aldosterone Syst* 2012; 9:103-106.
8. Viera AJ, Hinderliter AL. Evaluation and management of the patient with difficult-to-control or resistant hypertension. *Am Fam Physician* 2009; 79:863-869.
9. Funder JW, Carey RM, Fardella C, et al.; Endocrine Society. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2013; 93:3266-3281.
10. Grossman E, Messerli FH. Secondary hypertension: interfering substances. *J Clin Hypertens (Greenwich)* 2009; 10:556-566.