Evaluation of secondary hypertension

Author: Stephen Textor, MD
Section Editors: George L Bakris, MD, William J Elliott, MD, PhD
Deputy Editor: John P Forman, MD, MSc

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2021. | **This topic last updated:** Mar 19, 2020.

INTRODUCTION

The evaluation of a patient with hypertension depends upon the likely cause and the degree of difficulty in achieving acceptable blood pressure control since many forms of secondary hypertension lead to "treatment-resistant" hypertension [1]. Patients likely to have primary (idiopathic or "essential") hypertension undergo a relatively limited evaluation because extensive laboratory testing is usually of little value. (See "Initial evaluation of the hypertensive adult".)

By contrast, patients who have clinical clues suggesting the possible presence of secondary hypertension should undergo a more extensive evaluation. If secondary hypertension is present, the most effective treatment strategy often is one that is focused upon the specific mechanism underlying the hypertension. In addition, some of these disorders can be cured, leading to partial or complete normalization of the blood pressure.

Because it is not cost effective to perform a complete evaluation for secondary hypertension in every hypertensive patient, it is important to be aware of the clinical clues that suggest secondary hypertension. The identification of patients who should undergo an evaluation for secondary hypertension will be reviewed here. Testing methods for renovascular hypertension and treatment of unilateral and bilateral atherosclerotic renal artery stenosis are discussed separately:

- (See "Establishing the diagnosis of renovascular hypertension".)
- (See "Treatment of unilateral atherosclerotic renal artery stenosis".)

- (See "Treatment of bilateral atherosclerotic renal artery stenosis or stenosis to a solitary functioning kidney".)

GENERAL CLINICAL CLUES

There are a number of general clinical clues that, in isolation or in combination, are suggestive of secondary hypertension (table 1):

- Severe or resistant hypertension. Resistant hypertension is defined as the persistence of hypertension despite concurrent use of adequate doses of three antihypertensive agents from different classes, including a diuretic. (See "Definition, risk factors, and evaluation of resistant hypertension", section on 'Definitions'.)
- An acute rise or increased lability in blood pressure developing in a patient with previously stable values.
- Age less than 30 years in nonobese patients with a negative family history of hypertension and no other risk factors (eg, obesity) for hypertension.
- Malignant or accelerated hypertension (eg, patients with severe hypertension and signs of end-organ damage such as retinal hemorrhages or papilledema, heart failure, neurologic disturbance, or acute kidney injury). (See "Moderate to severe hypertensive retinopathy and hypertensive encephalopathy in adults".)
- Hypertension associated with electrolyte disorders including hypokalemia and metabolic alkalosis.
- Proven age of onset before puberty.

In addition to these clues, there are other findings that specifically suggest renovascular or other forms of secondary hypertension, as described in the following sections.

CLINICAL CLUES FOR RENOVASCULAR HYPERTENSION

Renovascular hypertension is among the most common potentially correctable causes of secondary hypertension. The incidence varies with the clinical setting. It probably occurs in less than 1 percent of patients with mild hypertension [2]. By comparison, a substantial proportion of patients with moderate to severe hypertensive retinopathy and/or other hypertensive target organ injury have renal artery stenosis. Renal artery stenosis can be detected in many

individuals with other manifestations of atherosclerosis, such as coronary artery disease (10 to 14 percent) and peripheral arterial and aortic disease (24 to 35 percent) [3].

For reasons that are not well understood, renovascular disease is less commonly identified in black patients [4,5]. As an example, the prevalence of renal artery stenosis in high-risk patients with severe or refractory hypertension was 27 to 45 percent in white patients, compared with 8 to 19 percent in black patients [4]. A more extreme disparity was found in a retrospective review of all patients diagnosed with renal artery stenosis at a single center, 95 percent of whom were white [5]. However, two studies that prospectively screened individuals with or without clinical clues for renovascular hypertension found similar rates of renal artery stenosis in black and white patients [6,7]. Referral bias is a possible explanation for this discrepancy, given that black patients diagnosed with renal artery stenosis were more likely than white patients to have severe or refractory hypertension and a history of stroke or myocardial infarction [5].

There are a variety of findings associated with a higher likelihood of hypertension being secondary to renovascular disease. The 2011 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on peripheral artery disease and the 2014 consensus statement from the Society for Cardiovascular Angiography and Interventions propose that diagnostic testing for renal artery stenosis could be performed in the following settings, assuming that a corrective procedure would be considered if renovascular disease were detected [8,9]. As with other vascular diseases, long-term management of these patients can be affected by the potential for progressive vascular occlusion. Recommendations for selecting patients for renal artery revascularization are presented elsewhere. (See "Treatment of unilateral atherosclerotic renal artery stenosis", section on 'General approach to therapy' and "Treatment of bilateral atherosclerotic renal artery stenosis or stenosis to a solitary functioning kidney", section on 'General approach to therapy'.)

- The general, clinical clues for any cause of secondary hypertension, as cited in the preceding section. (See 'General clinical clues' above.)
- Onset of severe hypertension (blood pressure ≥180 mmHg systolic and/or 120 mmHg diastolic) after the age of 55 years.
- Unexplained deterioration of kidney function during antihypertensive therapy, especially an acute and sustained elevation in the serum creatinine concentration by more than 50 percent that occurs within one week of instituting therapy with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), or direct renin inhibitor. (See "Renal effects of ACE inhibitors in hypertension".)

- Severe hypertension in patients with diffuse atherosclerosis, particularly those over age 50. The relationship between atherosclerotic renal artery stenosis and atherosclerosis at other sites (eg, coronary, peripheral arterial) is discussed separately. (See "Clinical manifestations and diagnosis of chronic kidney disease resulting from atherosclerotic renal artery stenosis".)

- Severe hypertension in a patient with an unexplained atrophic kidney or asymmetry in kidney sizes of >1.5 cm. A unilateral small kidney (≤9 cm) has a 75 percent association with the presence of large vessel occlusive disease.

- Severe hypertension in patients with recurrent episodes of acute (flash) pulmonary edema or refractory heart failure with impaired kidney function [10]. In a series of 55 patients with renovascular hypertension, for example, 23 percent had recurrent episodes of pulmonary edema requiring hospitalization. Flash pulmonary edema was more common in patients with bilateral compared with unilateral renal artery stenosis. The factors that contribute to acute decompensation include a hypertension-induced increase in afterload, inability of a hypertrophied left ventricle to relax in diastole (ie, diastolic with or without systolic dysfunction), sodium retention due to activation of the renin-angiotensin-aldosterone system, and associated kidney dysfunction [11,12]. Registry data from the United Kingdom indicate that patients with episodes of pulmonary edema and renal artery stenosis have reduced mortality after successful renal revascularization [13]. (See "Approach to diagnosis and evaluation of acute decompensated heart failure in adults".)

- A systolic-diastolic abdominal bruit that lateralizes to one side. This finding has a sensitivity of approximately 40 percent (and is therefore absent in many patients) but has a specificity as high as 99 percent [14]. Systolic bruits alone are more sensitive but less specific [14]. The patient should be supine, moderate pressure should be placed, using the diaphragm of the stethoscope, and auscultation should be performed in the epigastrium and all four abdominal quadrants.

In summary, radiologic testing to confirm the presence of renal artery stenosis **may** be indicated in patients for whom the history is suggestive (based upon a general assessment of clinical risk factors) **and** in whom a corrective procedure will be performed if renovascular disease is detected or progresses. There is little value and potential harm from radiologic testing if the patient is not a candidate for a corrective procedure. Imaging methods for renovascular hypertension, and how one makes the choice between medical and interventional therapy in such patients over time, are discussed elsewhere:

- (See "Establishing the diagnosis of renovascular hypertension".)

- (See "Treatment of unilateral atherosclerotic renal artery stenosis".)
- (See "Treatment of bilateral atherosclerotic renal artery stenosis or stenosis to a solitary functioning kidney".)
- (See "Treatment of fibromuscular dysplasia of the renal arteries".)

CLUES FOR OTHER MAJOR FORMS OF SECONDARY HYPERTENSION

Other causes of secondary hypertension also must be excluded in the appropriate settings (table 1).

Primary kidney disease — The presence of primary kidney disease is suggested by an elevated serum creatinine concentration and/or an abnormal urinalysis. (See "Overview of hypertension in acute and chronic kidney disease".)

Primary aldosteronism — The main clinical clue suggestive of primary aldosteronism is otherwise unexplained or easily provoked hypokalemia due to urinary potassium wasting. However, more than one-half of patients have a normal serum potassium concentration at detection, and, therefore, nearly all patients with suspected secondary hypertension should be evaluated for primary aldosteronism. Primary aldosteronism should also be suspected in the presence of slight hypernatremia, drug-resistant hypertension, and/or hypertension with an adrenal incidentaloma. Measurement of the ratio of the plasma aldosterone concentration to plasma renin activity can help identify such patients [15], although inappropriate elevation of aldosterone is also a common feature in obese patients [16]. (See "Diagnosis of primary aldosteronism" and "Evaluation and management of the adrenal incidentaloma", section on 'Aldosteronomas'.)

Sleep apnea syndrome — The sleep apnea syndrome is most commonly identified in obese men who snore loudly while asleep. These patients have repeated apneic episodes at night due to passive collapse of the pharyngeal muscles during inspiration, such that the airway becomes temporarily occluded from the apposition of the tongue and soft palate against the posterior oropharynx. A variety of other symptoms may be seen, including headache, daytime somnolence and fatigue, morning confusion with difficulty in concentration, personality changes, depression, persistent systemic hypertension, and potentially life-threatening cardiac arrhythmias. (See "Clinical presentation and diagnosis of obstructive sleep apnea in adults".)

Patients with obstructive sleep apnea often retain sodium and fail to respond optimally to antihypertensive drug therapy [17]. Correction of the sleep apnea may improve blood pressure

control and improve the response to antihypertensive drug therapy [18]. (See "Obstructive sleep apnea and cardiovascular disease in adults", section on 'Hypertension'.)

LESS COMMON FORMS OF SECONDARY HYPERTENSION

Oral contraceptives — Oral contraceptives often raise the blood pressure within the normal range but can induce overt hypertension. (See "Effect of hormonal contraceptives and postmenopausal hormone therapy on blood pressure".)

Pheochromocytoma — Pheochromocytoma should be suspected if there are paroxysmal elevations in blood pressure (which may be superimposed upon stable chronic hypertension), particularly if associated with the triad of headache (usually pounding), palpitations, and sweating. Patients identified with pheochromocytoma are rarely asymptomatic. In addition, patients with drug-resistant hypertension and those with an adrenal incidentaloma should be evaluated for pheochromocytoma. Other patients with suspected secondary hypertension who do not have these symptoms or an adrenal incidentaloma should not be evaluated for this rare cause of hypertension. (See "Clinical presentation and diagnosis of pheochromocytoma" and "Evaluation and management of the adrenal incidentaloma", section on 'Pheochromocytoma'.)

Cushing's syndrome — Cushing's syndrome (including that due to glucocorticoid administration) is usually suggested by the classic physical findings of Cushingoid facies, central obesity, proximal muscle weakness, and ecchymoses. However, Cushing's or subclinical Cushing's syndrome should also be suspected in patients with drug-resistant hypertension who have an adrenal incidentaloma. In the absence of such clues, patients with suspected secondary hypertension do not require evaluation for Cushing's syndrome. (See "Epidemiology and clinical manifestations of Cushing's syndrome" and "Evaluation and management of the adrenal incidentaloma", section on 'Subclinical Cushing's syndrome'.)

Coarctation of the aorta — Coarctation of the aorta is one of the major causes of secondary hypertension in young children but may first be detected in adulthood (image 1A-B). The classic findings are hypertension in the upper extremities, diminished or delayed femoral pulses ("brachial-femoral delay"), and low or unobtainable arterial blood pressure in the lower extremities. In addition, a prominent "to-and-fro machinery murmur" from the aorta may be heard over the posterior chest.

Patient age, the site of origin of the left subclavian artery, and the severity of the coarctation affect the pattern of blood pressure findings. As an example, the origin of the left subclavian artery is just distal to the coarctation in some patients; in this setting, the left brachial pulse is

diminished compared with the right and equal to the femoral pulse. (See "Clinical manifestations and diagnosis of coarctation of the aorta".)

Based upon the 2013 European Societies of Hypertension and Cardiology (ESH/ESC) report on hypertension and the 2008 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for adults with congenital heart disease, patients with hypertension should be evaluated for possible coarctation of the aorta [19,20]. This involves palpating the brachial and femoral pulses simultaneously to assess amplitude and timing, looking for diminished arterial pulses and brachial-femoral delay. In addition, the ACC/AHA guidelines recommended measurement of supine bilateral arm (brachial artery) blood pressures and prone right or left supine leg (popliteal artery) blood pressures to search for differential pressures. (See "Examination of the arterial pulse", section on 'Unequal or delayed pulses'.)

Other endocrine disorders — Hypertension may be associated with hypothyroidism, which may be suspected because of suggestive symptoms or an elevated serum thyroid-stimulating hormone level (measured as part of the evaluation of resistant hypertension), or primary hyperparathyroidism. The latter is most often suspected because of otherwise unexplained hypercalcemia, which may affect vascular reactivity, day-night blood pressure regulation, and kidney function [21-23]. (See "Diagnosis of and screening for hypothyroidism in nonpregnant adults" and "Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation" and "Clinical manifestations of hypercalcemia".)

Chemotherapeutic agents — A number of chemotherapeutic agents result in secondary hypertension and kidney injury. Problematic agents include those associated with microvascular injury (such as thrombotic microangiopathy from gemcitabine). The newer classes of antiangiogenic agents that inhibit vascular endothelial growth factor (VEGF) signaling pathways regularly produce a rise in arterial pressure, often associated with proteinuria and kidney dysfunction [24,25]. (See "Drug-induced thrombotic microangiopathy" and "Chemotherapy nephrotoxicity and dose modification in patients with kidney impairment: Molecularly targeted agents and immunotherapies" and "Chemotherapy nephrotoxicity and dose modification in patients with kidney impairment: Conventional cytotoxic agents".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hypertension in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Renovascular hypertension (The Basics)")
- Beyond the Basics topics (see "Patient education: High blood pressure in adults (Beyond the Basics)" and "Patient education: High blood pressure treatment in adults (Beyond the Basics)" and "Patient education: High blood pressure, diet, and weight (Beyond the Basics)").

SUMMARY AND RECOMMENDATIONS

- It is not cost effective to perform a complete evaluation for secondary hypertension in every hypertensive patient. Thus, it is important to be aware of the clinical clues that suggest secondary hypertension. (See 'Introduction' above.)
- There are a number of general, clinical clues that are suggestive of secondary hypertension (table 1) (see 'General clinical clues' above):
  - Severe or resistant hypertension. Resistant hypertension is defined as the persistence of hypertension despite concurrent use of adequate doses of three antihypertensive agents from different classes, including a diuretic.
  - An acute rise in blood pressure developing in a patient with previously stable values.
  - Age less than 30 years in nonobese patients with a negative family history of hypertension and no other risk factors (eg, obesity) for hypertension.

- Malignant or accelerated hypertension (eg, patients with severe hypertension and signs of end-organ damage such as retinal hemorrhages or papilledema, heart failure, neurologic disturbance, or acute kidney injury).
- Proven age of onset before puberty.

- In addition to these clues, there are other findings that specifically suggest renovascular hypertension, such as an acute sustained elevation in the serum creatinine by more than 50 percent within a week of instituting therapy with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), or direct renin inhibitor, severe hypertension in a patient with an unexplained atrophic kidney or asymmetry in kidney sizes, severe hypertension in a patient with recurrent episodes of acute (flash) pulmonary edema or refractory heart failure with impaired kidney function, and severe hypertension in conjunction with a systolic-diastolic abdominal bruit that lateralizes to one side. (See 'Clinical clues for renovascular hypertension' above.)
- Other causes of secondary hypertension, including primary kidney disease, primary aldosteronism, use of oral contraceptives, pheochromocytoma, Cushing's syndrome, sleep apnea syndrome, and coarctation of the aorta, must also be excluded in the appropriate settings (table 1). (See 'Clues for other major forms of secondary hypertension' above.)

Topic 3862 Version 25.0

GRAPHICS

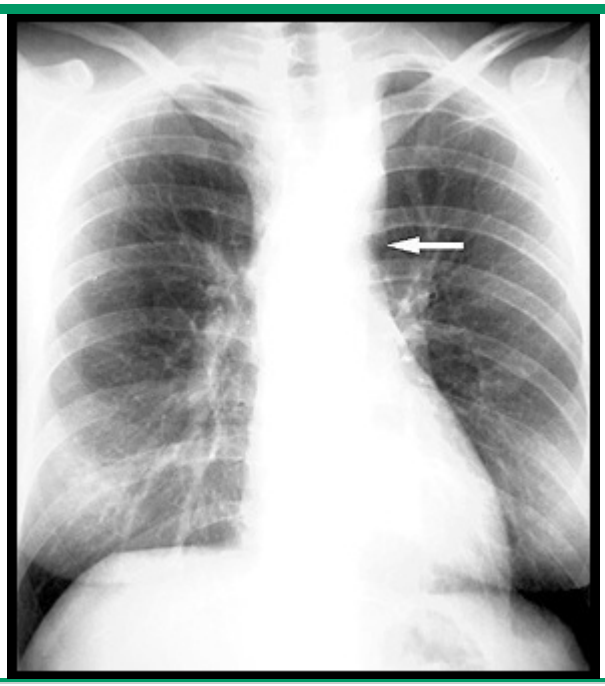
Clinical features of several causes of secondary hypertension

Disorder	Suggestive clinical features
General	▪ Severe or resistant hypertension ▪ An acute rise in blood pressure over a previously stable value ▪ Proven age of onset before puberty ▪ Age less than 30 years with no family history of hypertension and no obesity
Renovascular disease	▪ Unexplained creatinine elevation and/or acute and persistent elevation in serum creatinine of at least 50% after administration of ACE inhibitor, ARB, or renin inhibitor ▪ Moderate to severe hypertension in a patient with diffuse atherosclerosis, a unilateral small kidney, or asymmetry in kidney size of more than 1.5 cm that cannot be explained by another reason ▪ Moderate to severe hypertension in patients with recurrent episodes of flash pulmonary edema ▪ Onset of hypertension with blood pressure >160/100 mmHg after age 55 years ▪ Systolic or diastolic abdominal bruit (not very sensitive)
Primary kidney disease	▪ Elevated serum creatinine concentration ▪ Abnormal urinalysis
Drug-induced hypertension: ▪ Oral contraceptives ▪ Anabolic steroids ▪ NSAIDs ▪ Chemotherapeutic agents (eg, tyrosine kinase inhibitors/VEGF blockade) ▪ Stimulants (eg, cocaine, methylphenidate) ▪ Calcineurin inhibitors (eg, cyclosporine) ▪ Antidepressants (eg, venlafaxine)	▪ New elevation or progression in blood pressure temporally related to exposure
Pheochromocytoma	▪ Paroxysmal elevations in blood pressure ▪ Triad of headache (usually pounding), palpitations, and sweating
Primary aldosteronism	▪ Unexplained hypokalemia with urinary potassium wasting; however, more than one-half of patients are normokalemic
Cushing's syndrome	▪ Cushingoid facies, central obesity, proximal muscle weakness, and ecchymoses ▪ May have a history of glucocorticoid use
Sleep apnea syndrome	▪ Common in patients with resistant hypertension, particularly if overweight or obese ▪ Loud snoring or witnessed apneic episodes ▪ Daytime somnolence, fatigue, and morning confusion
Coarctation of the aorta	▪ Hypertension in the arms with diminished or delayed femoral pulses and low or unobtainable blood pressures in the legs ▪ Left brachial pulse is diminished and equal to the femoral pulse if origin of the left subclavian artery is distal to the coarct
Hypothyroidism	▪ Symptoms of hypothyroidism ▪ Elevated serum thyroid stimulating hormone
Primary hyperparathyroidism	▪ Elevated serum calcium

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; NSAID: nonsteroidal antiinflammatory drug; VEGF: vascular endothelial growth factor.

Graphic 56130 Version 13.0

Plain radiograph showing coarctation of the aorta

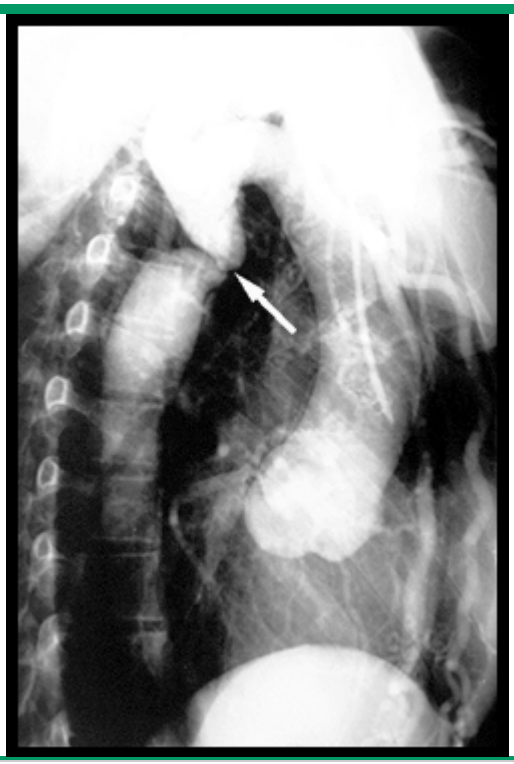


Plain frontal chest radiograph from a patient with known coarctation of the aorta demonstrates an absence of the proximal descending aortic arch shadow in the expected location (arrow), immediately superior to the left main pulmonary artery. Another plain radiographic finding, not seen in this example, includes notching of the posterior thoracic ribs.

Courtesy of Jonathan Kruskal, MD.

Graphic 70656 Version 4.0

Aortogram showing coarctation of the aorta



Aortogram, obtained after injection of contrast material into the root of the aorta in a patient with coarctation of the aorta, demonstrates marked focal narrowing of the proximal descending thoracic aorta (arrow).

Courtesy of Jonathan Kruskal, MD.

Graphic 79548 Version 3.0