CHAPTER

76

Young Hypertensive : How and How much to Investigate?

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Introduction

Majority of young (< 40 years) patients with high blood pressure have essential hypertension. But many also have secondary hypertension, which can be cured. Hence it is very important to diagnose these conditions and reverse the high blood pressure in order to avert target organ damage. Many of the investigations for secondary hypertension are time-consuming, tedious and expensive. Then why perform them when it has been shown that in most situations a final diagnosis of essential hypertensive will be arrived at. The following article gives us an insight into who should be investigated and to what extent.

Causes of Hypertension in the Young

Essential Hypertension

Secondary Hypertension

- Renal Parenchymal Hypertension
- Drugs
- Obstructive Sleep Apnea Syndrome
- COPD
- Lifestyle – Diet / Nutrition
- Hypothyroidism
- Hyperthyroidism
- Renovascular Hypertension
- Coarctation of the Aorta
- Cushing's Syndrome
- Aldosteronism
- Pheochromocytoma

Practical points

Accurate measurement of blood pressure is very important. Thorough medical history and physical examination is very valuable, and will help to arrive at conclusion very often and eliminate many unnecessary investigations that may be time-consuming, expensive, and ultimately lead nowhere.

Why should hypertension be investigated?

- Detection of target organ disease (e.g., renal damage, congestive heart failure)
- Identification of other risk factors for cardiovascular disorders (e.g., diabetes mellitus, hyperlipidemia); and
- Detection of secondary causes of hypertension

The routine investigations to be done in any patient with hypertension are shown in Table 1.

Table I : Routine Screening Laboratory Tests for Hypertension

- Urinalysis
- Complete blood count
- Blood chemistries (potassium, sodium, creatinine, fasting glucose)
- Fasting lipid profile (LDL, HDL, triglycerides, total cholesterol)
- 12-lead electrocardiogram
- Ultrasonography of the abdomen for the kidneys

Who should be investigated and how far?

We have a battery of investigations for the hypertensive patient. But all need not be done in every patient. Before we proceed to the actual investigations, there are clinical symptoms and signs that will point out and assist us to determine the investigations that should be done and how far should we proceed. These are elaborated in Table 2. A more aggressive approach should be taken in these situations.

In addition any patient who does not have predisposing factors for essential hypertension (Table 3) should be investigated for secondary hypertension.

Findings on history, physical examination, or laboratory testing that suggest a secondary cause (Table 2).

Secondary causes of hypertension can be determined by the mnemonic "ABCDE"

A. Obstructive Sleep Apnea (OSA)

Obstructive sleep apnea is an independent risk factor for hypertension[1]. At least one half of patients with OSA have hypertension[2]. Features that suggest OSA are daytime somnolence, obesity, snoring, lower-extremity edema (secondary to the right-sided congestive heart failure), morning headaches, and nocturia. A sleep study usually is needed for diagnosis of OSA and determination of corrective interventions. Treatment of OSA consists of nasal continuous positive airway pressure (CPAP). Surgery may be considered in some patients. Treatment reduces hypertension in these patients.[3,4] There is a high incidence of OSA in patients with chronic obstructive pulmonary disease (COPD).

Aldosteronism (Mineralocorticoid Excess Syndrome)

Increased urinary excretion of potassium signals hyperaldosteronism. This should be suspected in all hypertensive patients with hypokalemia who are not on potassium-wasting diuretics (frusemide, ethacrynic acid, thiazides). If hypokalemia occurs in a hypertensive patient taking a potassium-wasting diuretic, the diuretic should be discontinued and the patient should be given potassium supplements. After 1-2 weeks, the potassium level should be remeasured. If hypokalemia persists, the patient should be evaluated for a mineralocorticoid excess syndrome.

The criteria for the diagnosis of primary aldosteronism are:

1. diastolic hypertension without edema
2. low plasma renin that fails to increase appropriately during volume depletion (upright posture, sodium depletion)
3. hypersecretion of aldosterone that does not suppress appropriately in response to volume excretion. It should be remembered that approximately 25% patients with essential hypertension have suppressed renin activity.
4. The diagnostic test should be demonstration of an elevated ratio of plasma aldosterone level to plasma renin activity[5].

B. Bruits (Renal Artery Stenosis - RAS)

Younger hypertensives (< 40 years of age) or those seen after 60 years, especially those patients at risk for arterial compromise (e.g., smokers, diabetics, or those with known atherosclerotic

Table 2

Clinical features	Preliminary Tests	Disease suspected	Additional Diagnostic Studies
• Edema, sallow skin, breathlessness Oliguria +	elevated BUN and creatinine levels, proteinuria	Renal parenchymal disease	Creatinine clearance, renal ultrasonography kidney biopsy
• Systolic/diastolic abdominal bruit		Renovascular hypertension	Magnetic resonance angiography, Captopril-augmented radioisotopic renography, Renal arteriography
• Inequality of pulsations in both upper extremities		Aorto-arteritis	Aortogram with angiogram of upper extremity
Decreased or delayed femoral pulses, abnormal chest radiograph		Coarctation of aorta	Doppler or CT imaging of aorta
• Use of sympathomimetics, Perioperative setting, Acute stress, Tachycardia		Excessive catecholamines	Confirm patient is normotensive in absence of catecholamine excess
• Snoring, Daytime somnolence, Obesity (esp truncal)		OSA	Sleep study
• Diet: high salt, excessive alcohol,		Diet side effects	Lifestyle modifications
• Central obesity	Hyperglycemia, hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia	Dysmetabolic syndrome, insulin resistance	Lifestyle modifications
• Use of drug in Table 4		Drug side effect	Take off drug
• Weight gain, fatigue, weakness, hirsutism, amenorrhea, moon facies, dorsal hump, purple striae, truncal obesity, hypokalemia		Cushing's Syndrome	8 AM serum cortisol, Dexamethasone suppression Test
• Paroxysmal hypertension, headaches, diaphoresis, palpitations, tachycardia		Pheochromocytoma	Urinary catecholamine metabolites (VMA, metanephrines, normetanephrines) Plasma free metanephrines MIBG scan
• Fatigue, weight loss, hair loss, diastolic hypertension, muscle weakness		Hypothyroidiosm	Thyroid function tests
• Heat intolerance, weight loss, palpitations, systolic hypertension, exophthalmos tremor, tachycardia		Hyperthyroidism	Thyroid function tests
• Kidney stones, osteoporosis, depression, lethargy, muscle weakness		Hyperparathyroidism	Serum calcium, parathyroid hormone levels
• Headaches, fatigue, visual problems, enlargement of hands, feet, tongue		Acromegaly	X-ray skull, hands, CT brain/ MRI Growth hormone levels

Table 3 : Risk Factors for Secondary Hypertension

- Poor response to therapy (resistant hypertension)
- Worsening of control in previously stable hypertensive patient
- Stage 3 hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure >110 mm Hg)
- Onset of hypertension in persons younger than age 20 or older than age 50
- Significant hypertensive target organ damage
- Lack of family history of hypertension

disease) should be auscultated for a renal bruit. About one half of patients with renovascular hypertension will have an abdominal bruit identifiable on physical examination. Bruits heard in both systole and diastole are more suggestive of renovascular hypertension than systolic bruits alone[6]. Hypertensive patients with the above characteristics should be subjected to a renal artery doppler.

Renal artery stenosis can be due to atherosclerosis (65%) or fibromuscular dysplasia. The incidence of renovascular hypertension is less than 1%. It is important to identify RAS because surgery or angioplasty can reverse the hypertension, especially if performed early enough to prevent permanent renal damage.

If RAS is suspected, the patient should be subjected to one of the three noninvasive techniques: captopril-augmented radioisotopic renogram (the preferred choice), magnetic resonance angiography (MRA), or duplex Doppler flow study of the renal arteries. Captopril-augmented radioisotopic renogram is based on the fact that a kidney that is receiving an inadequate blood supply will activate the renin-angiotensin system. Therefore, a single dose of the angiotensin-converting enzyme (ACE) inhibitor captopril will abruptly reduce renal function in the ischemic kidney. A scan is considered positive if there is delayed or decreased uptake of the radioisotope in the stenotic kidney compared with the nonstenotic one, so this test is not as useful if stenosis is present bilaterally. MRA is a noninvasive imaging modality with a sensitivity of 100 per cent and a specificity of 70 to 90 per cent compared with renal arteriography for detection of renal artery stenosis. MRA best delineates the proximal renal vasculature and is therefore useful as an initial diagnostic tool for patients suspected of having atherosclerotic renal artery stenosis, which usually involves the proximal renal artery. Patients suspected of having FMD, which tends to involve the distal renal artery, should undergo conventional angiography or computed tomographic angiography.

Renal arteriography remains the gold standard for defining the vessel anatomy but does not always correlate with postprocedural outcomes (i.e. surgical correction of the renal artery stenosis often does not resolve the hypertension). Renal arteriogram establishes the presence of a renal arterial lesion and aids in determining whether the lesion is due to atherosclerosis or FMD. It does not however prove that the lesion is responsible for the hypertension. RAS is a frequent finding by angiography and at poatmortem in many normotensive individuals. Bilateral renal vein catheterization and estimation of plasma renin activity (PRA) will assess the functional significance of any lesion noted on arteriography and also whether surgical correction will be beneficial. The kidney on the side of RAS has PRA at least 1.5 times higher than the normal side. The renal vein renin level in the normal kidney is the same as that of the inferior vena cava.

Bad Kidneys

Renal function tests are routinely done in all hypertensive patients. Elevated BUN and serum creatinine levels and decreased creatinine clearance diagnose renal dysfunction, although it may be impossible to tell if the dysfunction is primary or secondary to the hypertension. Ultrasonography will show small size of the kidneys. Kidney biopsy may be required to

determine the cause of renal failure, and for further management.

C. Catecholamines, Coarctation, Cushing's Syndrome

Catecholamines

Patients having sweating, tachycardia, palpitations, and tremors in addition to a raised BP usually have elevated catecholamine levels. Elevated catecholamines play a role in causing white-coat hypertension and hypertension in pheochromocytoma, OSA, and other diseases discussed in this article. Acute stress induces catecholamine release and often contributes to preoperative or postoperative hypertension. Over-the-counter or prescription decongestants can have sympathomimetic effects, as do nonprescription weight-loss preparations containing ephedra (ma huang).[7,8] Cocaine and amphetamines also have hypertensive effects because of stimulation of the sympathetic nervous system. Hence the value of a thorough history and physical examination in a hypertensive patient should not be undermined.

Coarction of the Aorta

Coarctation of the aorta is a congenital narrowing of the aortic lumen, most often occurring just distal to the origin of the left subclavian artery. Patients with less severe forms of the disorder may not be diagnosed until young adulthood but have a high incidence of premature death.[9]

Decreased lower-extremity (femoral) pulses with upper-extremity hypertension suggest Coarctation of the Aorta. Hence it is very important to examine all the peripheral pulsations and take BP in all four extremities. Patient may have dyspnea on exertion. Chest radiographic findings of notched ribs (from dilated collateral vessels) and dilation of the aorta above and below the constriction (the "3" sign) are highly suggestive.[9]

Other diagnostic tests that should be done include ECG and Echocardiography for hypertrophy of the heart chambers and their function. CT / MRI of the chest and aortography may be useful to delineate anatomic narrowing. Doppler ultrasound and cardiac catheterization can be used to see if there are any differences in blood pressure in different areas of the aorta. This is very important prior to surgery and to determine post surgical prognosis.

Surgery is usually recommended. The narrowed part of the aorta will be removed. In some cases, balloon angioplasty may be done instead of surgery.

Cushing's Syndrome

Cushing's syndrome can cause hypertension via the mineralocorticoid effects of excess glucocorticoids. Weight gain, fatigue, weakness, hirsutism, amenorrhea, moon facies, buffalo hump, purple striae, truncal obesity suggest Cushing's syndrome. Serum potassium may be low.

For initial screening of Cushing's syndrome, 8.00 a.m. serum cortisol or the overnight dexamethasone suppression test is recommended. In difficult case (obese or patients with depression), measurement of a 24-hour urine free cortisol can also be good screening test. A level $>$ 140 nmol/d (50 µg is suggestive of Cushing's syndrome). The definitive diagnosis is then established by failure of urinary cortisol to fall to $<$ 25 nmol/d (10 µg/d) or plasma cortisol to fall to $<$ 140 nmol/L (5 µg/dL) after a standard low-dose dexamethasone suppression test (0.5 mg every 6 h for 48 hrs). Once the diagnosis is established further testing should be done to determine the etiology.[10]

D. Drugs, Diet

Drugs : Many prescription and nonprescription drugs can cause or exacerbate hypertension (Table 4).

Table 4 : Drugs That Can Raise Blood Pressure

Drug class	Drug examples
Immunosuppressive agents	Cyclosporine, Tacrolimus, corticosteroids
Nonsteroidal anti-inflammatory drugs	Ibuprofen, naproxen, piroxicam
COX-2 inhibitors	Celecoxib, rofecoxib, valdecoxib
Estrogens	30- to 35-mcg estrogen oral contraceptives
Weight-loss agents	Sibutramine, phentermine, ma huang
Stimulants	Nicotine, amphetamines
Mineralocorticoids	Fludrocortisone
Antiparkinsonian	Bromocriptine
Monoamine oxidase inhibitors	Phenelzine
Anabolic steroids	Testosterone
Sympathomimetics	Pseudoephedrine

Diet

Dietary factors that can cause hypertension are excess consumption of salt (sodium); while low intake of potassium, calcium, and magnesium can have a similar but less pronounced effect. The lower limit of "excess salt" has not been determined. An average typical Indian diet contains at least 17-20 g of salt. Blacks, elderly, patients, those with diabetes, and patients with essential hypertension appear to be particularly sensitive to dietary sodium intake. High calorie, low fiber diet and dietary patterns that cause obesity also can cause hypertension. Sustained weight reduction lowers blood pressure--often to normal levels--in at least one half of obese patients. A loss of 5 to 10 per cent of body weight can significantly reduce blood pressure.

E. Endocrine Disorders, Erythropoietin

Hypothyroidism causes decreased cardiac output with a compensatory increase in vascular tone, resulting in a more prominent rise in diastolic blood pressure than in systolic blood pressure. Features of hypothyroidism are fatigue, cold intolerance, weight gain, non-pitting edema, hair loss, diastolic hypertension, muscle weakness. Measurement of TSH is a screening test for hypothyroidism. If TSH is elevated, free T_4 level should be done to confirm the presence of clinical hypothyroidism. T_3 measurements are not indicated because free T_3 levels may be normal in about 25% of hypothyroid patients.

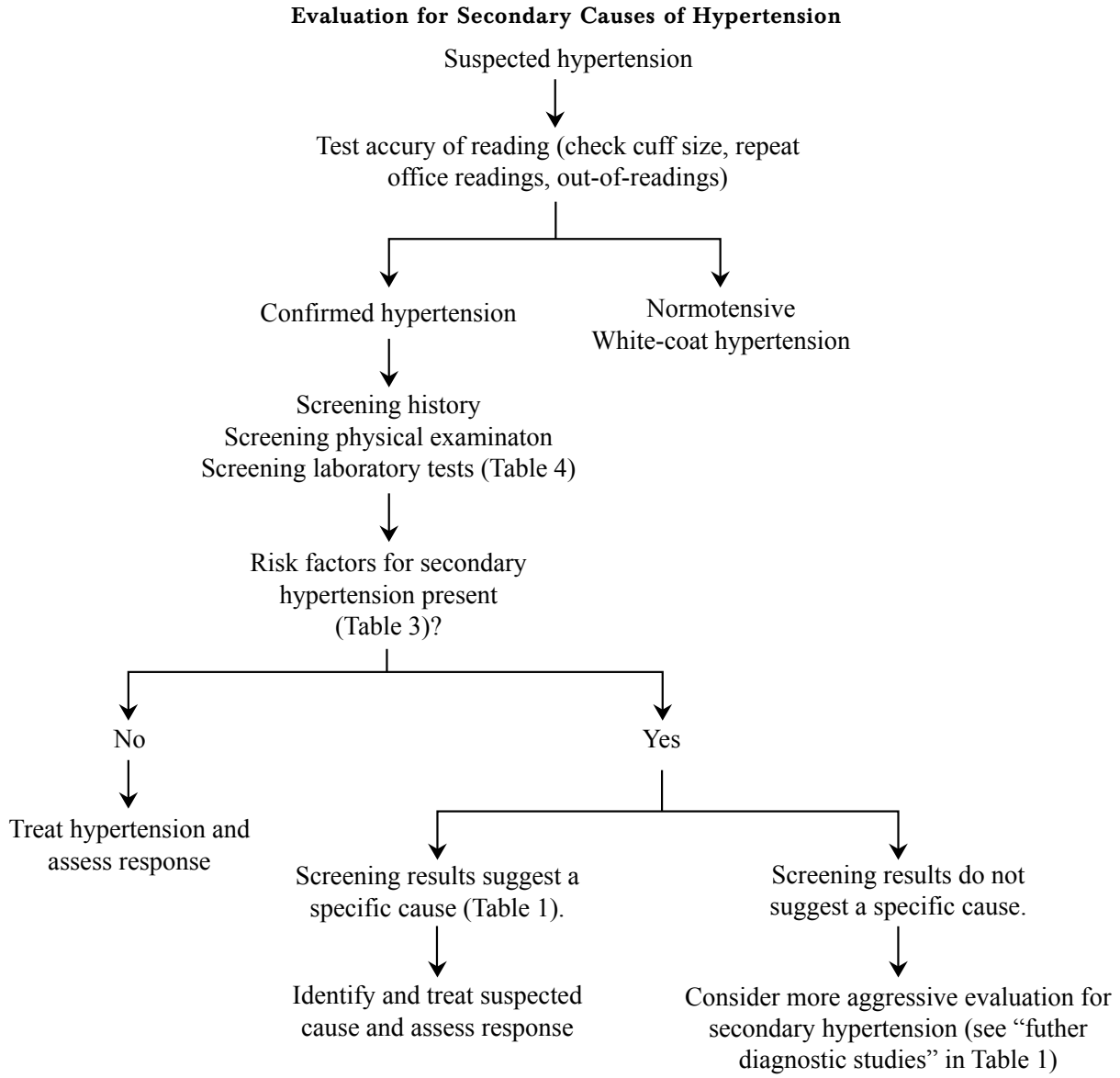
Hyperthyroidism induces increased cardiac output and compensatory decreased vascular tone, causing a greater increase in systolic blood pressure. Heat intolerance, weight loss, palpitations, systolic hypertension, exophthalmos, tremors, tachycardia suggest hyperthyroidism. The TSH level is suppressed, while total and free T_3 and T_4 levels are increased.

Hyperparathyroidism (primary or secondary to chronic renal insufficiency) is a potentially reversible cause of hypertension. Its incidence in hypertensive patients is about 1%, compared with a 0.1% incidence in the general population. However, only 30 to 40 per cent of patients with hyperparathyroidism have hypertension,

Kidney stones, osteoporosis, depression, lethargy, muscle weakness are features of hyperparathyroidism. Serum calcium and parathormone levels will determine the diagnosis. It is important to distinguish between primary hyperparathyroidism and secondary hyperparathyroidism due to renal failure. It should be remembered that in primary hyperparathyroidism, parathyroidectomy may not reliably resolve hypertension.

Pheochromocytoma is another endocrine cause of hypertension. The classic symptoms include headache, diaphoresis, palpitations, and paroxysmal hypertension. The syndrome can vary depending on the types of catecholamines being produced, the amount and frequency of their release into the circulation, and other factors. The usual screening test has been urinary measurement of catecholamine metabolites (vanillylmandelic acid, metanephrines,

Figure 1 : General strategy for diagnosing a secondary cause of hypertension.



normetanephrines).[11] Determination of plasma free metanephrines might be the test of first choice for diagnosis of this tumor, although availability of this test at hospital and reference laboratories is limited. Pheochromocytoma is very rare, and routine screening in hypertensive patients is not recommended. MIBG scan is one more useful diagnostic modality,

Acromegaly (elevated growth hormone -GH) is a rare endocrine cause of hypertension. There is coarsening of features, prognathism, diastema (widely spaced teeth), increased ring and shoe sizes; hands become enlarged, moist and soft with tufting of distal phalanges. Generalized thickening of the skin with increased sweating and oiliness, hypertrichosis, acanthosis nigricans and acne are also seen.

When acromegaly is clinically suspected, IGF-I estimation is a useful screening test and estimation of serum GH is confirmatory.

IGF-1 measurement (normal ranges vary in different laboratories) is an indirect measurement

of GH. Since IGF-1 levels are much more stable over a day, they are often more practical and reliable than the measurements of GH levels. Another advantage of this test is showing activity of the disease. IGF-I level is a useful laboratory screening measure when clinical features raise the possibility of acromegaly.

The normal level of serum GH is 3 to 5 ng/mL. GH level greater than 10 ng/mL is found in 90% of patients with acromegaly. A single measurement is not entirely reliable because GH is secreted by the pituitary in spurts and its concentration can vary widely. At a given moment, an acromegalic may have normal GH levels, whereas a GH level in a healthy person may be 5 times higher, especially in conditions such as stress, sleeping time, exercise. Because of this, more accurate diagnosis can be done when GH is measured under conditions in which GH secretion is normally suppressed. Oral Glucose Tolerance Test (OGTT) is often used for this. 100 g of Glucose is administered after an overnight fast. The results are interpreted as follows: Normal GH < is 2 µg/L. The diagnosis of acromegaly is confirmed by demonstrating the failure of GH suppression to < 1 µg/L within 1-2 hours of the oral glucose load. About 20% of patients exhibit high levels of GH (called "paradoxal increase").

Erythropoietin. High erythropoietin levels can elevate blood pressure either via a polycythemia/hyperviscosity mechanism or by direct pressor effects.[7] Elevated erythropoietin levels can be endogenous (as in response to the chronic hypoxia of COPD) or exogenous (administered to alleviate the anemia seen in chronic renal failure).

In conclusion, the value of accurate measurement of BP, thorough medical history and clinical examination should not be underestimated. Doing so would screen for most of the secondary causes of hypertension discussed in this article, along with signs of target organ disease and comorbid factors.

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