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Review

Secondary hypertension: Current diagnosis and treatment

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Abstract

Secondary hypertension affects a small but significant number of the hypertensive population and, unlike primary hypertension, is a potentially curable condition. The determinant for workup is dependent on the index of suspicion elicited during patient examination and treatment. Specific testing is available and must be balanced depending on the risk and cost of the workup and treatment with the benefits obtained if the secondary cause is eliminated. This article reviews common manifestations, workup, and the current treatments of the common causes of secondary hypertension.

Keywords: Hypertension; Secondary hypertension; Angiotensin; Kidneys; Endocrine; Hormones

Hypertension (HTN) is a major risk factor for the development of cardiovascular disease [1]. Primary HTN is the most frequent type of HTN. It has no identifiable cause but has been linked to family history of HTN and obesity. Increased awareness and focus on HTN has led to identification of modifiable risk factors (such as diet, physical activity, body weight, blood glucose) and non-modifiable variables (such as age, ethnicity, genetics and gender) in the adult population [2]. The incidence of secondary HTN is variably estimated between 5–10% and is linked to diseases of the kidneys, endocrine system, vascular system, lungs and central nervous system [2] (see Table 1). It has been reported to be higher in the specialty clinics compared to the primary care clinics [2]. The exact prevalence of secondary HTN is unknown and the diagnosis is probably missed in the majority of patients. Although patients with secondary HTN comprise only a small percentage of those with elevated BP, this subgroup should not be ignored. To this date, no consensus has been established as a parameter for the evaluation and treatment of secondary HTN.

Among the large number of people with HTN, it is helpful to know whether some secondary process may be present as these are potentially curable with specific therapies based on the underlying etiology or are more easily controlled by a specific drug. In many cases, correcting the cause of secondary HTN can lead to cure, avoiding the need for long-term medical therapy, with its attendant risks and economic toll. Because of the rarity of secondary HTN and the expense associated with its detection, it becomes very

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Table 1
Causes of secondary hypertension

Renal
Renal parenchymal disease
Renal vascular disease
Renin-producing tumors
Primary sodium retention (Liddle's syndrome)
Increased intravascular volume
Endocrine
Acromegaly
Hypothyroidism
Hyperthyroidism
Hyperparathyroidism
Adrenal cortical
Cushing syndrome
Primary aldosteronism
Apparent mineralocorticoid excess
Adrenal medulla
Pheochromocytoma
Carcinoid syndrome
Drugs and exogenous hormones
Neurological causes
Increase intracranial pressure
Quadriplegia
Guillain–Barre syndrome
Idiopathic, primary, or familial dysautonomia
Obstructive sleep apnea (OSA)
Acute stress related secondary HTN
Diseases of the aorta
Rigidity of the aorta
Coarctation of the aorta
Pregnancy induced HTN
Isolated systolic HTN due to an increased cardiac output

important to have a guide in deciding when to pursue these reversible causes. Studies on secondary HTN generally suffer from a small sample size and the absence of a control group. Because of the paucity of data on secondary HTN, clinicians rarely carry out specific test to uncover reversible causes. The objective of this review is to summarize the more common causes of secondary HTN, its diagnosis and recommended treatment.

1. Renal hypertension

1.1. Renal parenchymal disease

The association of renal parenchymal diseases (chronic kidney disease or CKD) and systemic HTN is well recognized as well as the need for aggressive management [1,11,12] The compelling evidence of CKD as an independent risk factor for cardiovascular disease, and cardiovascular related outcomes, especially when microalbuminuria or proteinuria are present, is now well established [13,14].

The incidence of acute and chronic glomerulonephritis of varying causes, autosomal dominant polycystic kidney disease, diabetic nephropathy and hydronephrosis secondary to obstructive uropathy have varied widely in the adult population [15]. The fastest rise and the two most significantly affected are the population with diabetics and hypertensive kidney disease. Chronic nephritis, polycystic kidney disease and other factors such as obstructive uropathy have remained fairly constant [15]. Overall, the NHANES III data reveals that 70% of the population with chronic renal disease has HTN [16]. It is well demonstrated that aggressive lowering of systolic BP slows the progression to end-stage renal disease [17].

Clinicians treating HTN in patients with a multitude of renal diseases would be advised that the goal should be to achieve JNC VII recommendations regarding desirable BP levels [1], but as noted, this attempt must balance against patient tolerance, as well as potential risks from drug side effects and the further possibility that diastolic BP <60 mmHg may put some patients at greater risk for a heart attack or stroke [18]. Yet, the vast literature suggests we are making substantial progress and the aggressive lowering of BP to goal levels in this high-risk population does benefit the patients and their outcomes. Definitive answers remain elusive as to what are the best therapeutic interventions to use. It may be a matter that we don't use a high enough dose of the antihypertensive agents [19]. The evaluation of systemic HTN presenting in conjunction with underlying renal diseases, should include, at the initial evaluation, a consideration for possible co-existence of contributing factors. Most are fairly evident or can be suspected by both the initial history and physical examination. A peri-umbilical bruit, other evidence of peripheral vascular disease, and known coronary artery disease) or certain laboratory values (low serum potassium), obesity may suggest the need to look further for contributory factors such as renal artery stenosis, hyperaldosteronism, and sleep apnea.

1.2. Renovascular disease

Renovascular HTN is a clinical consequence of excessive stimulation of the renin–angiotensin–aldosterone system. Renal artery stenosis is often caused by atherosclerosis leading to renal ischemia, which causes the release of renin from the juxtaglomerular cells of the kidneys and a secondary increase in BP [3]. The release of renin activates a cascade system in which renin promotes the conversion of angiotensin I to angiotensin II and increases aldosterone release from the adrenal gland. Angiotensin II causes severe vasoconstriction and aldosterone increases sodium and water retention, both causing an increase in BP [4].

The clinical signs that suggest renovascular disease include abdominal bruit, accelerated or difficult to control HTN, unexplained deterioration in renal function or electrolyte imbalance. Once renal artery obstruction is suspected, a screening test should be considered. Spiral computed tomography (CT), magnetic resonance imaging (MRI), captopril scintigraphy and Doppler ultrasound are noninvasive imaging techniques for detecting renal artery stenosis [5,6]. They all have high sensitivity and specificity

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but are highly dependent upon user expertise. The Doppler ultrasound and magnetic renal angiography have an additional advantage by being able to assess intrarenal hemodynamics noninvasively. These techniques are limited by their high cost and, in the case of spiral CT, the use of contrast agents [5,6]. Ultimately, renal angiogram is essential for the diagnosis and localization of lesions [7]. In patients with advanced renal insufficiency, a carbon dioxide angiogram is useful alternative to the renal angiogram with contrast agent.

True renovascular HTN is found in 1% to 5% of the hypertensive population, or 20 to 40% in those with severe, refractory HTN or those undergoing diagnostic coronary arteriography [6]. It is important to determine if the disease is significant, as unselective correction of renal artery stenosis has led to disappointing results [6,7]. Most studies that have compared conservative treatment with angioplasty have found only modest or no beneficial effects of angioplasty on renal function and BP. It is therefore mandatory to evaluate the functional significance of a stenosis such as renal resistance index before renal artery angioplasty [6,8].

Surgery has long been considered the standard for revascularization. Recent advances in endovascular technology have changed the options of clinical management of patients with renovascular disease [9]. Superiority trials have been conducted but the results are limited by study design flaws and small number of subjects. Nevertheless, percutaneous interventions have gained in popularity [10].

1.3. Intrarenal vasculitis

Vasculitides may also involve intrarenal vessels and may be associated with a variety of renal lesions. The kidneys are most often afflicted by small vessel vasculitides, such as microscopic polyangiitis, Wegener's granulomatosis, Henoch–Schonlein purpura, and cryoglobulinemic vasculitis. These vasculitides cause renal dysfunction predominantly by inducing glomerular inflammation with resultant nephritis and renal failure. Large vessel vasculitides, such as giant cell (temporal) arteritis and Takayasu's arteritis, rarely injure the kidneys. However, it causes ischemia secondary to vasculitic involvement of the renal arteries or abdominal aorta leading to a rise in BP.

Fever, malaise, weight loss and HTN are common presenting signs and symptoms. Renal biopsy is often necessary to identify the pathology. Prognosis is greatly dependent on early diagnosis, rapid initiation of accurate treatment and careful treatment monitoring [23]. A combination of oral corticosteroids and oral cyclophosphamide is effective in reversing or controlling disease in up to 90% of patients. New immunosuppressive drugs (mycophenolate), monoclonal antibody modulators of lymphocyte function (rituximab), and cytokine-directed therapies (infliximab and eternacept) are new therapeutic alternative, with better potential specificity for both the inflammation and immunologic causes of vasculitis [24].

1.4. Renin producing tumors

Another cause of secondary HTN with presentation similar to renovascular HTN is renin-secreting tumors. The tumor usually arises from the juxtaglomerular cells of the kidney. Patients manifest HTN and hypokalemia and like the other types of secondary aldosteronism, plasma renin activity (PRA) and plasma aldosterone concentration (PAC) are elevated with normal or reduced PAC/PRA ratio. This uncommon condition is often diagnosed after a renovascular source is ruled out. The diversity of histology and location creates difficulty in drawing conclusions regarding these patients. Extrarenal sites (adrenals, colon, lung, ovary and pancreas) have also been reported thus requiring imaging of both the abdomen and pelvis. Surgical excision is curative [20].

1.5. Primary sodium retention (Liddle's syndrome)

Liddle's syndrome is a familial disorder characterized by HTN, metabolic alkalosis, and urinary loss of potassium. HTN usually begins during the teenage years, but onset may occur even earlier. Hypokalemia, however, is not a common finding. Symptoms may include weakness, paresthesias, epigastric pain, polyuria, polydipsia, and acute paralysis. Plasma levels of renin and aldosterone are low [21]. Drugs that inhibit sodium reabsorption in the distal tubule (e.g. triamterene) may be effective [22]. Liddle's syndrome is curable by renal transplantation.

1.6. Increased intravascular volume

Volume overload has been associated with increased prevalence of uncontrolled HTN in end-stage renal disease patients. Hypervolemia as indicated by a higher inferior vena cava diameter is a risk factor for uncontrolled HTN and increased left ventricular mass index [25]. Dietary instructions to limit salt intake may prevent volume overload in peritoneal dialysis (PD) patients. Recent studies have also suggested that PD solutions with low sodium concentrations improve control of BP by removal of excess sodium without a change in body weight or ultrafiltration volume [25]. Furthermore, normalization of BP has also been reported in hypertensive PD patients by salt restriction and ultrafiltration with hypertonic solutions [26].

2. Endocrine hypertension

2.1. Acromegaly

Acromegaly usually results from Growth Hormone (GH) producing pituitary tumors, often manifest from third through fifth decades of life. Other causes are growth hormone secreting small cell lung cancer and pancreatic cancer. GH and insulin like growth factor-1 (IGF-1) oversecretion influence cardiovascular manifestations

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characterized by high cardiac output, low peripheral resistance followed by increase in myocardial mass and biventricular hypertrophy. This results in HTN, diastolic dysfunction, atherosclerotic disease and in extreme cases, dilated cardiomyopathy [27,28].

Serum IGF-1 is almost invariably elevated in acromegaly but not GH. GH suppression test after glucose loading should be performed and failure to suppress GH levels to <1 ng/ml 1 to 2 h after glucose load warrants a CT or an MRI of the pituitary gland with visual field examination by quantitative perimetry. If this fails to identify pituitary tumor, CT scan of the lungs and abdomen should be performed in search of GH releasing hormone secreting tumors [27,28].

The treatment includes surgery, radiation, medical therapy or combination of these modalities. Microsurgical transsphenoidal resection has a good success rate [29] with GH levels decreasing slowly up to 2 years. Adjunct treatment with radiation and/or medical treatments is required in some cases. Medical management includes use of somatostatin analogues (e.g. octreotide), dopamine agonist (e.g. bromocriptine, pergolide and carbergoline) and GH receptor antagonists (e.g. pegvisomant) [30].

2.2. Hyperthyroidism

The common causes of hyperthyroidism include Grave's disease, posttreatment of Grave's disease and overtreatment with thyroid hormone. The clinical presentation mimics hyperadrenergic state. Symptoms include palpitations, tremor, dyspnea, fatigue, angina, hyperactivity, insomnia, heat intolerance, weight loss even with increased appetite, nocturia, diarrhea, oligomenorrhea, and emotional lability. Physical examination may reveal tachycardia, HTN, hyperthermia, moist skin, lid lag, brisk reflexes and hyperdynamic precordium. A loud first heart sound with accentuated pulmonary component of the second heart sound, Third heart sound and midsystolic flow murmur can be heard. Increased cardiac output and myocardial contractility with decreased systemic vascular resistance and widened pulse pressure are other physical correlates. Patients may present with angina, myocardial infarction, high output congestive heart failure, atrial fibrillation, or supraventricular tachycardia secondary to atrioventricular nodal conduction abnormalities [31,32].

In some cases, clinical symptoms are absent making the diagnosis difficult. A low thyroid stimulating hormone (TSH) level is highly sensitive especially combined with elevated serum free T4 or free T4 index. Correction of thyroid functions and symptomatic management are the hallmarks of treatment strategies for hyperthyroidism. Beta-blockers are the drug of choice to control symptoms as well as the rapid rate of supraventricular tachyarrythmias, associated HTN and other hyperadrenergic symptoms. Diuretics, in addition, are useful in the presence of heart failure and HTN. Euvolemia has to be established in the presence of fluid retention before beta-blocker is initiated. Doses may need to be increased due to accelerated drug. Digoxin is also a good alternative [33]. Treatment of the underlying thyroid disorder remains the cornerstone of therapy in preventing complications. Methimazole or propylthiouracil followed by ablative therapy with radioactive iodine or surgical approach is indicated for a hyperthyroid state.

2.3. Hypothyroidism

Diastolic HTN occurs in 20% of hypothyroid patients, which can lead to coronary ischemia. Replacement of thyroid hormone usually normalizes the BP [34]. Electrocardiogram in these patients may vary from sinus bradycardia to low voltage QRS and nonspecific ST–T changes. Elevated TSH is a sensitive test that detects hypothyroidism. Free T4 and Free T4 index are decreased as well. Levothyroxine is the mainstay of hypothyroidism treatment. HTN usually is corrected with treatment of thyroid hormone supplementations. In those patients who continue to remain hypertensive, treatment with diuretic, dihydropyridine calcium channel blockers, ACE inhibitors or angiotensin receptor blockers work quite effectively [35].

2.4. Hyperparathyroidism

Primary hyperparathyroidism often manifest as hypercalcemia during routine biochemical testing. Nonspecific symptoms such as weakness, lethargy, abdominal discomfort and constipation are common. HTN is the principal manifestation on occasion. The underlying pathophysiology of HTN in hyperparathyroidism is unclear, but parathyroid hormone (PTH) plays a major role in vasoconstriction and nephrosclerosis.

Elevated calcium has a significant effect on vascular bed leading to HTN. Recently, a parathormone hypertensive factor has been identified in patients with HTN [36]. PTH induced calcium influx may lead to myocyte necrosis, deposition of calcium in coronary vascular bed and premature atherosclerosis. Hypercalcemia with serum calcium levels above 11 mg/dl associated with normal or elevated PTH levels is suggestive of hyperparathyroidism. In most cases of hypercalcemia, PTH level is suppressed. Thiazides may unmask a hyperparathyroid state. Surgical removal of parathyroid gland or adenoma is the definitive treatment for hyperparathyroidism. HTN usually improves with normalization of calcium and PTH levels. However, persistent HTN prior to surgery and postoperatively should be treated with agents other than thiazide diuretics.

2.5. Cushing's syndrome

Prevalence of Cushing's syndrome ranges from 1.4 to 10 per million populations. However, in subjects with obesity and uncontrolled diabetes, the range is up to 3 to 4%. In the setting of nonspecific symptoms, diagnosis is a challenge. The classic presentation of moon facies, purple striae and central obesity is rarely seen [37]. Cushing's syndrome must

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be considered as a diagnostic possibility if any of the following are present in decreasing order of specificity: unexplained osteoporosis, muscle weakness, ecchymosis, hypokalemia, central obesity, plethora, diastolic pressure >105 mmHg, red striae, acne, edema, hirsutism, oligomenorrhea and impaired glucose tolerance. 85% of the patients present with HTN and other risk factor for atherosclerosis such as hyperglycemia or frank diabetes and dyslipidemia are common [38]. In some cases, myocardial infarction, stroke and heart failure are present.

Left ventricular hypertrophy and diastolic dysfunction may result due to activations of renin angiotensin pathways. Other mechanisms in Cushing's syndrome that contribute to HTN include inhibition of prostacyclin, a powerful vasodilator, and bindings of cortisol to specific glucorticoid receptors which initiate the effect of hormone action in cardiac, renal and vascular tissues. Extracellular volume shifts and salt and water balance do not appear to be necessary for glucocorticoid HTN. Pseudo-Cushing state can occur from acute or chronic medical illness, psychiatric illness, or alcoholism. Preclinical Cushing's syndrome can occur in subjects with adrenal incidentalomas. Exogenous glucocorticoid use is an important differential diagnosis for Cushing's syndrome.

The first step in the diagnosis of Cushing's syndrome is to assess the clinical presentation. If hyperglycemia, HTN, physical habitus suggestive of Cushing's syndrome along with hypokalemia is present, one should initiate the first step in determining the cause. Overnight dexamethasone suppression test has 98 to 99% sensitivity and a false positive rate of 20 to 30%. Hence, a 24-hour urinary free cortisol measurement reduces the false positive rate and has 95–99% sensitivity and 98% specificity when performed in non-acutely ill outpatient. A cortisol level >5 μg/dl after dexamethasone suppression test and a 24-hour urinary cortisol level of >300 μg/day is diagnostic of Cushing's syndrome. Further delineation of adrenocorticotropic hormone (ACTH) dependent or independent etiology is determined by plasma ACTH levels, corticotropin releasing hormone stimulated ACTH, adrenal imaging, pituitary MRI and inferior petrosal sinus sampling. If ectopic ACTH syndrome is suspected, CT chest, abdomen may be required.

Treatment of Cushing's syndrome involves cause specific therapy, which may include surgical removal of adrenals, chemotherapy, or pituitary surgery. Medical therapy includes use of metyrapone, bromocyptine and ketoconazole. Treatment of HTN includes treatment of underlying cortisol excess, avoidance of diuretics that deplete potassium levels and use of agents that block renin angiotensin axis [39,40].

2.6. Primary hyperaldosteronism

A recent data demonstrated that primary aldosteronism is present in 9.1% of all HTN patients. The prevalence of primary aldosteronism is considerably higher than the previous data have suggested. Depending on the cutoff ratio of the SA/PRA testing, it is estimated that 1 in 10 patients in primary care clinics have primary aldosteronism. Using the serum aldosterone/plasma renin activity ratio, it ranged from 2.7% to 32% in selected normokalemic patients with arterial HTN [41].

Uncertainties in identifying the disease in hypertensives are due to the absence of the classic presentation of hypokalemia and metabolic alkalosis. BP is moderately elevated and headache secondary to uncontrolled BP or malignant HTN can occur. Symptoms of hypokalemia such as muscle weakness, paresthesia, tetany or paralysis may also be present. Screening for primary hyperaldosteronism is initiated if there is spontaneous hypokalemia or moderate to severe hypokalemia with difficulty maintaining a normal potassium level while receiving supplements. In adrenal incidentaloma, identification of primary aldosteronism in hypertensive patients is important, as specific therapeutic options are available. Surgery can provide definite cure in the case of a unilateral aldosterone producing adenoma, thereby obviating a lifetime dependency on costly and potentially harmful antihypertensive medications. In patients with idiopathic hyperaldosteronism, adding spironolactone to the antihypertensive regimen results in better control of HTN and therefore reduces target organ damage. BP completely normalized in 58 patients and improved in 18 of 77 who were treated surgically [42].

Mineralocorticoid excess is exhibited by many conditions. They include primary hyperaldosteronism secondary to adrenal adenoma, carcinoma, or bilateral hyperplasia, enzyme deficiencies such as 11-OH dehydrogenase deficiencies, 11-OH hydroxylase and 17-OH hydroxylase deficiencies, and chronic licorice ingestion. The more common form is the benign aldosterone producing adenoma. Less common varieties are bilateral hyperplasia, nodular hyperplasia, aldosterone producing renin responsive adenoma and glucorticoid suppressible hyperaldosteronism. The underlying pathology is secondary to the effects of autonomous secretion of aldosterone that produces a volume dependent HTN, although, there is a transient escape from sodium retention before edema gets noticeable.

The best screening test is plasma aldosterone to plasma renin activity ratio. It is best to stop antihypertensive agents for 2 weeks prior to the procedure as most agents can affect the levels of aldosterone or renin. Alpha-blockers and sympatholytic agents can be used to control BP in the meantime. Plasma renin activity ratio of >30 is suggestive of primary aldosteronism. This test has a sensitivity of 91%, positive predictive value of 69% and a negative predictive value of 98% [43,44]. Another test is oral sodium loading for 3 days and 24-hour urine collections of aldosterone. A 24-hour urine sodium must be >200 meq to document adequate sodium loading and a urinary aldosterone of >14 μg is suggestive of hyperaldosteronism [45]. Alternately, 2 l of isotonic saline is infused over 4 h to suppress aldosterone production and plasma aldosterone level >10 ng/dl is considered diagnostic of hyperaldosteronism.

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Following confirmation of aldosteronism, CT imaging of adrenals should be performed to differentiate aldosterone-producing adenoma from idiopathic hyperaldosteronism (bilateral hyperplasia). Radionuclide scanning with 131-iodocholesterol has also been used. However, it is cumbersome and has to be performed over 2 to 5 days and has only 72% accuracy. Differential adrenal venous sampling is quite useful in detecting unilateral disease. Complications of the procedure include adrenal infarction, technical limitation, and failure to cannulate the adrenal vein 25% of the time [46].

Removal of the adenoma decreases BP significantly. Spironolactone used preoperatively diminishes postoperative hypoaldosteronism and hypokalemia [47,48]. A success rate for surgery is around 70% and HTN may require treatment for 3 months postoperatively [49]. For all other conditions of mineralocorticoid excess, treatment is medical. Spironolactone is effective and doses from 25 to 400 mg. per day have been used. HTN may take about 2 months to normalize. Other antihypertensive agents may to be used concomitantly. Diuretics causing hypokalemia should be avoided.

2.7. Pheochromocytoma

Pheochromocytomas are neuroendocrine tumors developing from adrenal medulla on the sympathetic ganglionic neurons. Tumors arising from extra adrenal chromaffin tissue are referred to as paragangliomas or extraadrenal pheochromocytoma. These tumors produce catecholemines producing different symptoms and clinical responses. Prevalence of pheochromocytoma is about 0.1 to 6% in patients with HTN. Hereditary pheochromocytoma occurs in Von Hippel–Landau Syndrome, multiple endocrine neoplasia type 1, and familial paragangliomas. A family history of the tumor is associated with a 10% to15% risk of tumors in other members of the family. Less than 10% of all pheochromocytoma are malignant [50].

The symptoms vary mimicking multiple other conditions. In patients with HTN, symptoms such as headaches, panic attack, pallor, tachycardia and palpitations are the dominating clinical presentation. Other symptoms include tremor, nausea, abdominal or chest pain, orthostatic drop in BP, glucose intolerance, weight loss associated with fluctuating BP and on occasion, dramatic elevation in BP. Although less likely, clinically unresponsive BP with use of three or more agents should raise suspicion especially in those with paroxysmal HTN developing after clinical procedures or with use of tricyclics and phenothiazines.

Cardiovascular complications of pheochromocytoma include shock, arrhythmias, myocardial infarction, heart failure, hypertensive encephalopathy, stroke, or neurogenic pulmonary edema. Heart rate variability may be affected by increase in vagal tone [51]. Anesthesia and tumor manipulations may increase the catecholamine surge. Chemicals such as glucagon, radiological contrast agents, metoclopramide and tyramine may also stimulate release of catecholamines in the presence of such tumors [52].

Pheochromocytoma should be confirmed by biochemical testing in all patients suspected to have this tumor. First step is measurement of urinary and plasma catecholamines, urinary metanephrine and urinary vanillylmandelic acid. Measurements of plasma free metanephrine, a recently available test is the most sensitive and specific for diagnosis of pheochromocytoma.

A positive test for plasma or urinary catecholamines does not necessarily indicate pheochromocytoma. Many clinical conditions, use of medications, and physiological stimuli are confounding factors that contribute to this conundrum. The magnitude of increase above reference levels should be considered prior to making conclusive diagnosis. MRI or CT scan of the abdomen can detect nodules >1 cm in adrenal pheochromocytoma. 90% of these tumors are located in adrenal glands and 98% are in the abdomen. Nuclear imaging test using I [123] metaiodobenzylguanidine is useful to identify extraadrenal tumors [53].

BP control and volume expansion are two of the major factors that need to be addressed while awaiting diagnostic confirmative tests and surgery. Alpha-blockers such as phenoxybenzamine, terazosin, or doxazocin can be used to relieve chronic vascular constriction and allowing volume expansion. One needs to be careful about orthostatic hypotension and postoperative hypotension with these agents. Calcium channel blockers may also help in BP control and minimizing vasospasm. Beta-blockers are helpful, but only after adequate alpha blockade is established to avoid alpha-receptor mediated vasoconstriction and hypertensive crisis. Once detected, surgical resection is the treatment of choice. About a quarter of the patients who undergo surgery remains hypertensive postoperatively, related perhaps, to primary HTN or nephropathy [50].

2.8. Carcinoid syndrome

Carcinoid syndrome is a rare cause of secondary HTN. Carcinoid tumors are commonly present in small bowel and appendix in 60% of the cases and also occur in bronchi, testis, biliary tract, pancreas and ovaries. Metastatic tumors usually arise from the ilium and spread to the liver and lymph nodes. Clinical presentation includes weight loss, flushing sensation, diarrhea, HTN, bronchoconstriction and fibrous endocardial plaques in the heart. These manifestations are a result of carcinoid tumors secreting large amounts of serotonins, bradykinins and other neurohormones [54–56].

Carcinoid syndrome in heart disease is difficult to diagnose and suspicion should be raised when patients with right heart failure, jugular venous pressure elevations with large V waves and severe tricuspid regurgitations have no other etiology that explains the right heart failure. In addition to tricuspid regurgitations, tricuspid stenosis may be

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present, producing an early diastolic sound and a diastolic rumble above the left sternal border. Pulmonic stenosis and/or regurgitation may also be present giving rise to ejection systolic murmurs and/or early blowing diastolic rumble in pulmonic area [57]. Diagnostic tests include chest X-ray, Echocardiography, and urinary 5 hydroxyindole-acetic acid levels, the main metabolite of serotonin. Chest X-ray may show cardiomegaly with right-sided enlargement, normal dimensions of pulmonary trunk, pleural effusion and pulmonary nodules. Electrocardiogram is usually nonspecific and may show right atrial enlargement, right ventricular hypertrophy and nonspecific ST–T changes with tachycardia. Echocardiography is a sensitive test suggesting right-sided valvular involvement with right ventricular volume overload. Tricuspid valve is thickened, shortened and shows retraction and incomplete coaptation and decreased excursion due to tricuspid stenosis and regurgitation [58]. Pulmonic valve may show similar features if visualized. Transesophageal echocardiography may be useful in assessing the thickness of valve leaflets [55–58].

Carcinoid syndrome affecting the heart has poor prognosis with or without treatment. Treatment involves somatostatin analogues, serotonin antagonists and alpha-adrenergic blockers. Removal of the primary tumors is rarely indicated, although occasionally liver metastatic tumors are removed. While digoxin and diuretics are useful in right heart failure management, alpha-blockers are useful to treat secondary HTN. Balloon valvuloplasty of tricuspid stenosis and pulmonic stenosis can be performed for symptomatic relief. In advanced cases, tricuspid valve replacement and pulmonic valvotomy are recommended. Recurrence of carcinoid tumors is common in bioprosthetic valves. In spite of the poor prognosis and high surgical mortality, survivors can have significant symptomatic benefits [59,60].

3. Drug induced and toxin induced hypertension

Common, often remedial causes of secondary HTN are exogenous agents. Pharmaceuticals, nutriceutical and herbal preparations, and environmental toxins can either cause, or contribute to, chronic sustained HTN in a number of ways. Some facilitate arterial smooth muscle constriction by increasing cytosolic calcium (vitamin D [61], ergot alkaloids [62]), while others counteract the effect of endothelial-derived or circulating vasodilators (L-arginine analogs [63]). Many chemicals stimulate the sympathetic nervous system at postsynaptic (phenylephrine [64], phenylpropanolamine [65]), presynaptic (levodopa [66], yohimbine [67]), ganglionic (nicotine [68]), central (SSRI's [69], bromocryptine [70]), or multiple (cocaine [71], tricyclic antidepressants [72]) levels. Others (antiemetic phenothiazines [73]) have anticholinergic properties, which reduce parasympathetic vasodilatory influence on the vasculature. Chronic administration of sympathomimetics (fenfluramine [74], phencyclidine [75]) can have such pronounced effects on the systemic and pulmonary arterioles that HTN may become permanent even after drug discontinuation. Occasionally, exogenous hormones (e.g. growth and thyroid) can elevate BP through metabolic effects which increase heart rate and cardiac contractility, and have persisting effects through vascular remodeling. Both medications (glucocorticoids [76], mineralocorticoids [77], phenylbutazone [78]) and dietary substances (licorice [79]) can stimulate salt and water retention via aldosterone receptor agonism, or via renal effects simulating such agonists. Through altering glomerular filtration pressure via effects on afferent or efferent arteriolar tone, medications which inhibit angiotensin II action or inhibit prostaglandin production can promote volume retention and elevate BP, often with a pronounced reduction in renal function. Calcineurin inhibitors (cyclosporine [80]) can cause HTN by several mechanisms, including both vasoconstriction and volume retention, especially in patients with underlying renal insufficiency. Occasionally, sodium loading associated with bicarbonate antacids can produce HTN [81] in patients who are salt-sensitive.

Substances working by other mechanisms are less commonly identified. Volume contracted, high renin hypertensive patients may experience "paradoxic" BP elevation when diuretics or vasodilators (which further stimulate renin production) are added to their regimen [82]. Central alpha-2 agonists (clonidine) may cause peripheral vasoconstriction via cross-over stimulation of postsynaptic alpha-1 receptors [83], while other sympatholytics (methyldopa [84]) may cause transient hypertensive exacerbation before their hypotensive effects become manifest. Drugs which effect hepatic synthesis of hormonal precursors (androgens [85], estrogens [86], danazol [87]) can increase plasma concentrations of vasoconstrictor substrates (angiotensinogen), although their hypertensive actions involve other mechanisms as well. Reports have suggested that medications (ketoconazole) which inhibit metabolism of endogenous hormones (cortisol) can lead to persistant HTN during, and for some time after, co-administration [88]. Recurrent withdrawal of short-acting central nervous system depressants (GHB [89], ethanol [90]) or central antihypertensives (clonidine [91]) in chronic intermittent users can result in sustained HTN over time, although withdrawal syndromes are more often implicated in hypertensive emergencies [92]. Recombinant erythropoetin frequently precipitates HTN [93] (most likely as an oncotic/mass effect) which responds well to volume reduction or phlebotomy.

Some drugs require concurrent administration of other agents, or coexistence of another medical condition, to cause HTN. Although mono-amine oxidase inhibitors can themselves exacerbate HTN by increasing the half-life of norepinephrine at sympathetic nerve terminals [94], this effect is magnified many fold when amine precursors (dietary tyramine [95], L-dopa [96]) are present concurrently. Beta-blockers can lead to peripheral vasoconstriction and BP elevation when either endogenous (pheochromocytoma) or exogenous (cocaine) sympathomimetics are present [97],

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and occasionally when central alpha agonists are co-administered (clonidine, methyldopa) [98] via an "unopposed alpha" effect. Medications which inhibit hepatic pathways needed to convert prodrug forms of antihypertensive drugs (most oral ACE inhibitors) to their active moieties can produce resistance to antihypertensive therapy, though not causing HTN per se. Patients who consume ethanol while taking disulfiram are frequently hypertensive [99], but other symptoms (vomiting) usually inhibit combined ingestion on a recurring basis.

Chronic ingestion of heavy metals, specifically lead [100], thallium [101], cadmium [102], and arsenic [103], have been linked to human HTN, and environmental exposure (paint, pesticides) are potential sources. Ginseng [104] and Ma Huang (ephedra) [105] have all been linked to HTN, sometimes severe and/or acute, and occasionally associated with hypertensive emergencies (intracranial hemorrhage). Vitamins and their analogues (Vitamin A [106], tretinoin [107]) and mineral micronutrients (iron) [108] may exacerbate or cause HTN following overdose, or with regular use at supratherapeutic doses. Rare environmental exposures (organophosphates [109], scorpion and black widow venom [110]) and parenteral medications (ketamine [111], naloxone [112], thyrotropin-releasing hormone [113], others) have been linked to acute HTN, but do not appear to influence BP chronically.

A thorough history, addressing present and past medication use, over-the-counter (e.g. nonsteroidal antiinflammatory agents) and "natural" supplements, and where appropriate, environmental exposures, should be part of every evaluation of patients with marked, refractory, or atypical (by age and risk profile) HTN, usually prior to expensive/invasive testing for other etiologies is considered [114].

4. Neurological hypertension

4.1. Increase intracranial pressure

The central nervous system plays an integral role in the maintenance of systemic BP over a wide range of physiologic conditions as it controls peripheral autonomic nervous system activity and regulates the release of circulating hormonal factors. Increase in intracranial pressure can produce substantial elevations in systemic BP (Cushing response) [115]. It was thought to be a protective maneuver designed to preserve cerebral blood flow [116]. The mechanism appeared to be related to enhance sympathetic discharge as cervical cord dissection or the injection of local anesthetics blocks the reflex.

HTN following closed-head injury, subarachnoid hemorrhage, and acute stroke, is typically transient or episodic [117]. Sustained HTN may represent a preterminal event in which vasomotor circulatory collapse ensues [118]. Measures to reduce mortality in these settings are generally directed at reducing intracranial HTN. If treatment of systemic pressure is needed, a short-acting beta-adrenergic receptor antagonist would be preferred over a more potent vasodilator (i.e. hydralazine or nitroprusside) that may increase cerebral blood flow and intracranial pressure or result in systemic hypotension [119].

Brain tumors, especially those located in the supratentorial space or the posterior fossa or in the vasomotor area of the brain stem beneath the floor of the fourth ventricle may be associated with paroxysmal or labile HTN [120]. Sustained HTN associated with brain tumors is not common as the nuclei associated with vascular control, such as the nucleus tractus solitarius and the dorsal nucleus of the vagus, are protected from ischemia by multiple arterial sources [121].

A number of clinical features are common, but not universal, in patients with brain tumor who develop HTN and patients with pheochromocytoma [122]. Headache and symptoms of autonomic hyperactivity such as tachycardia, sweating, anxiety, tremor and nausea and vomiting occur frequently in both conditions. However, flushing was more common in patients with brain tumors. Intracranial pressure is elevated in the majority of patients with brain tumors in which it is measured. Increased catecholamine levels appear to be less common in patients with brain tumors (less than half) compared to patients with pheochromocytoma. In addition, increases in catecholamine levels with brain tumors appear to occur primarily during paroxysms of HTN and are normal at other times. Treatment of brain tumors with surgery or radiation resulted in normalization of BP in about two-thirds of patients [123].

4.2. Quadriplegia

Patients with cervical or high thoracic spinal cord injuries can develop a syndrome referred to as autonomic hyperreflexia [124]. Nerve stimulation below the spinal cord injury results in uncontrolled sympathetic discharge resulting in HTN, sweating, flushing, headache, and piloerection [125]. Nerve stimulation results from bladder or bowel distention, skeletal muscle spasm, or stimulation of the skin below the level of the cord injury [126]. HTN is usually transient and dissipates after the stimulus is removed. However, HTN can be sustained in situations where nerve stimulation persists as occurs with a blocked urinary catheter [121]. HTN can be associated with symptoms of headache, sweating, seizures, and neurologic deficits. The hemodynamic pattern in these patients includes a marked increase in vascular resistance, bradycardia, normal cardiac output, and volume contraction [124].

HTN in the setting of quadriplegia results from an increase in spinal cord sympathetic activity and an increase in sensitivity to alpha-adrenergic agonists [124]. Afferent baroreflex activity is largely intact as the heart rate slows appropriately during HTN. It appears that spinal cord transaction allows for unopposed adrenergic responses to viscerovascular, somtovascular, and cutaneovascular stim-

ulation that would normally be inhibited via centrally mediated negative feedback.

4.3. Guillain–Barre syndrome

Ascending polyneuritis of the afferent limb of the arterial and intrathoracic baroreflexes results in autonomic dysfunction in patients with Guillain–Barre syndrome [127]. The hemodynamic picture is defined by episodic HTN and tachycardia alternating with HTN and bradycardia [128]. Arrhythmias, both tachycardias and bradyarrhythmias (sinus arrest or complete heart block), are a significant cause of morbidity in these patients [129]. Management of hypertensive episodes is best accomplished with short acting parenteral agents that can be rapidly titrated.

4.4. Idiopathic, primary or familial dysautonomia

Autonomic failure is characterized by orthostatic hypotension, inadequate heart rate response, and bowel, bladder and erectile dysfunction [130]. In most cases, an etiology is unknown with classification based on clinical presentation. These include primary autonomic failure (Bradbury–Eggleston syndrome) [131], multiple system atrophy (Shy–Drager syndrome) [132], and familial dysautonomia (Riley–Day syndrome) [133]. Despite the fact that the most striking feature of primary dysautonomia is orthostatic hypotension, 50% of these patients are hypertensive when supine [134]. Supine HTN makes management of orthostatic hypotension more difficult by limiting its treatment options and by causing a pressure diuresis, which exacerbates the orthostasis. Dysautonomia may also occur secondary to neuropathies associated with systemic illness (diabetes mellitus [135] or amyloidosis [136]).

Patients with primary dysautonomia have been demonstrated to have residual sympathetic activity that appears to be responsible for the supine HTN observed in some of these patients [134]. Although there is a reluctance to treat supine HTN in these patients, there is some evidence that it is associated with end-organ damage [137]. Ganglionic blockade allowed patients to be differentiated into those with and without residual sympathetic function. In patients who have a depressor (vasodilatory) response to trimethaphan, indicating substantial residual sympathetic tone, orthostatic hypotension can be treated with drugs that raise sympathetic tone while supine HTN can be treated with drugs that either decrease sympathetic tone or block alpha-adrenergic receptors. In patients who do not demonstrate a depressor response to trimethaphan, orthostatic hypotension is best treated with direct vasodilators (transdermal nitroglycerin) [138].

5. Hypertension with obstructive sleep apnea

OSA is a common condition affecting 2–4% of the adult population and >50% of those with OSA have HTN [1]. Individuals with sleep disordered breathing or OSA have a 3-fold increased risk of HTN independent of other risk factors [139]. It is now recognized as a cardiovascular risk factor and is considered a real and significant problem in the general population [1,141] and is likely to increase given the increasing prevalence of obesity.

OSA is characterized by abnormal collapse of the pharyngeal airway during sleep is associated with daytime sleepiness and fatigue. Other more prominent symptoms include morning headache, disrupted sleep, feeling unrefreshed after awakening, memory loss, personality changes, decreased attention span, and poor judgment. Physical signs include loud snoring, witnessed apneic episodes, obesity, and increased neck size. The Wisconsin Sleep Cohort Study [139] provided evidence that OSA is causally related to HTN. Results indicated that worsening severity of OSA was independently associated with increasing risk for new HTN in normotensive patients followed for 4 years after an initial sleep study.

The pathophysiologic mechanisms involved in the OSA-systemic HTN relationship and the relationship of OSA with other cardiovascular risks are complex but are based primarily on sympathetic overactivity [142]. Catecholamine surges are generated during repeated episodes of apnea and hypopnea [143]. OSA may also act through other mechanisms including activation of inflammatory mechanisms [144], insulin resistance [145], and endothelial dysfunction [146].

The work up for OSA should begin with a complete medical history and physical examination. Questions pertaining to daytime sleepiness and quality of sleep should be asked. Because patients are often unaware of their behaviors during sleep, it is often necessary to elicit information about snoring and apneic episodes from the sleep partner. The physical examination should focus primarily on the nasopharynx and oropharynx to identify any abnormalities that may predispose the patient to OSA. Morphometric examination of the head and neck has been shown to be a reliable and accurate method of identifying patients with and without OSA [147].

Referral to a certified sleep disorders clinic is warranted to confirm the diagnosis and identify the degree of OSA present. The gold standard for diagnosing OSA is polysomnography. The treatment of OSA with concomitant systemic HTN is often aimed at both conditions with the anticipation that correcting the OSA will either reduce the systemic HTN or increase the efficacy of its treatment. A common treatment approach targets weight loss through diet change and exercise. A 10% reduction in body weight has been associated with clinically significant improvements in the apnea–hypopnea index [148].

Despite the promising results of weight loss, the most effective therapy for OSA is continuous positive airway pressure (CPAP) [149]. However, compliance with CPAP has been reported to be quite low (i.e., ranging from 65–80%), and alternative treatment strategies are often necessary [150].

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Other approaches include surgery [151], atrial overdrive pacing [152], and mandibular advancement devices [153].

A number of clinical trials have shown that CPAP effectively lowers systemic HTN [154]. Nasal CPAP alone resulted in decreased systemic BP comparable to decreases evidenced in patients with OSA receiving antihypertensive medications. High pretreatment heart rates and high mean pulse pressures could be used to predict a beneficial effect of CPAP on systemic HTN in patients with OSA. Oral appliance therapy has shown promising results in reducing systemic HTN. In fact, a 4-week trial of oral appliance therapy produced results similar to that of CPAP therapy in reducing systemic BP [155].

6. Acute stress related hypertension

The acute stress induces an abrupt catecholamine release resulting in an abrupt rise in BP even in normotensive individuals. HTN secondary to acute stress is seen with conditions such as surgery, trauma, hypoglycemia, alcohol withdrawal, and cardiopulmonary resuscitation. Acute postoperative HTN is defined as an acute rise in BP during the immediate postoperative period, usually observed within 2 h after surgery in most cases [156]. Postoperative HTN is usually of short duration, rarely persists beyond 24 h. It is most commonly associated with cardiothoracic, vascular, neurological, and head and neck surgeries [157]. Postoperative factors considered responsible for the development of acute postoperative HTN include pain, anxiety, shivering, hypoxia, hypercarbia, bladder distension, and use of vasopressor drugs or of beta-agonist bronchodilators [157,158]. The final common pathway leading to an acute rise in BP after surgery is by activation of sympathetic nervous system; postoperative plasma catecholamine concentrations are markedly higher in patients with acute postoperative HTN than normotensive postoperative patients [158–160].

Significant correlations have been reported between plasma catecholamine levels and mean arterial pressure in patients with acute postoperative HTN [159]. The predominant hemodynamic finding in patients with this condition is increased systemic vascular resistance, with or without tachycardia, indicating sympathetic mediated rise in BP predominately secondary to vasoconstriction. The stroke volume and cardiac index are usually not higher than in those with normal postoperative BP. Similarly, plasma rennin, angiotensin II, and aldosterone activity are not significantly different between patients with acute postoperative HTN and those with normal postoperative BP [159,160]. Although acute postoperative HTN is generally caused by excessive catecholamine release, part of it could be due to aggressive intravenous fluid therapy often instituted perioperatively.

Acute posttraumatic HTN is frequently seen during the first few days following severe multiple trauma, and is characterized by a hyperdynamic state, elevated BP, and tachycardia. Posttraumatic HTN can particularly develop after trauma to adrenal gland, kidney, and renal artery [161,162]. HTN after renal trauma occurs predominantly in young males following road traffic accidents or blunt abdominal trauma [161].

Insulin induced hypoglycemia results in an abrupt rise in systolic BP but the diastolic BP decrease or remains unchanged resulting in a widened pulse pressure [163–165]. Hypoglycemia powerfully stimulates sympathoadrenal system, and stimulation of adrenal medulla induces primarily epinephrine and, to minor extent, norepinephrine secretion [163]. Therefore, as a result, there is marked increase in serum concentration of circulating epinephrine, and a modest increase in circulating norepinephrine. Clinically, this translates into an increase in left ventricular stroke volume, ejection fraction, cardiac output, and heart rate but the systemic vascular resistance is decreased [164,165].

Acute HTN after alcohol withdrawal is from autonomic hyperactivity, and usually develops two to three days after the last drink. HTN is usually associated with tachycardia, sweating, tremors, and insomnia [166]. Postresuscitation BP rise is secondary to release of catecholamines, administration of inotropic and vasopressor drugs, and aggressive fluid therapy during resuscitation [167]. Postresuscitation HTN usually becomes normal in a short period.

The diagnosis of acute stress related secondary HTN is clear from the clinical scenario. However, it should be confirmed that patient was normotensive before the onset of acute stressful condition and that the BP returns to baseline after alleviation of such condition. These patients do not require any diagnostic workup for HTN. Nevertheless, a possibility of underlying undiagnosed chronic HTN should be considered if BP remains elevated after the acute stressful condition if well over.

7. Hypertension from aortic diseases

7.1. Aortic rigidity

Smooth muscle hypertrophy, increased matrix collagen deposition, reduction in the elastin/collagen ratio and especially, alteration in the glycosaminoglycan contents are interrelated and play a role in the aortic wall rigidity. A reduction in capacitance function of the arterial circulation augment systolic BP during left ventricular ejection and is believe to be the cause of isolated systolic HTN which is common among the elderly population. Isolated systolic HTN is defined by the presence of elevated systolic BP with a diastolic BP <90 mmHg. Increase aortic rigidity is also documented in diabetics, congestive heart failure and most importantly, chronic uremic patients on hemodialysis [168].

Pulse wave velocity is a noninvasive way to evaluate large artery rigidity. It is noninvasive and has been carefully evaluated and validated. In addition, it is also useful in subjects suffering from systemic vascular disorder and to evaluate the quality of pharmacological therapy [169]. The

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Systolic HTN in the Elderly Program demonstrated that antihypertensive therapy in this population could reduce morbidity and mortality [170].

7.2. Coarctation of aorta

Coarctation of the aorta is a constriction, which can occur anywhere along the course of the aorta, but is most commonly found just distal to the take-off of the left subclavian artery, where the Ductus Botalli enters into the aorta. Coarctation constitutes about 7% of all congenital cardiovascular disease; its incidence is slightly higher in patients with congenital bicuspid aortic valve. Because of its clinical findings, the disease is usually detected in childhood during routine clinical exams, only rarely does it escape diagnosis into adulthood.

The most common clinical presentation in adulthood are unexplained headaches, particularly with strenuous exercise in an otherwise healthy adult, symptoms can also include cold feet and/or claudication. The classical feature in the physical examination are high upper extremity BPs that contrast with low or nearly undetectable pressures in the lower extremities (weak femoral pulses or a delay during simultaneous palpation of the upper and lower extremity pulse [171]. Auscultatory findings include bruits in the front and back of the chest, particularly in the periscapular area due to turbulent flow in adjacent collateral vessels or due to flow acceleration at the site of constriction. In cases with severe stenosis, pulsations in the neck or chest wall may be visible, but physical findings may be subtle. If one presumes the diagnosis of coarctation, screening tests should include transthoracic echocardiography. Without optimal visualization of the proximal descending aorta, a transesophageal echocardiogram, or a contrast CT/MRI should be considered [172]. Three-dimensional reconstruction of the CT/MRI images may be helpful in planning of the surgical intervention, with is the treatment of choice in most cases with clinical presentation [172,173].

8. Pregnancy induced hypertension

Hypertensive disorders are the leading cause of maternal and perinatal morbidity and mortality. It occurs in 5.9% of all pregnancies [174] and is classified into 4 types: Preeclampsia–eclampsia, Preeclampsia superimposed on chronic HTN, chronic HTN and gestational HTN. Gestational HTN is characterized by HTN after 20 weeks gestation. Preeclampsia is when one or more of the following present: proteinuria, renal insufficiency, impaired liver function, neurological problems, (conculsions, hyperreflexia with clonus, severe headaches with hyperreflexia and persistent visual disturbances; hematologic abnormalities such as thrombocytopenia, hemolysis, disseminated intravascular coagulation), and fetal growth restriction [174,175].

The cause and pathogenesis remains unclear. The ultimate goal of treatment of HTN in pregnancy is delivery of a healthy newborn without compromising maternal health. Early diagnosis and subsequent close monitoring of both mother and fetus are crucial. High-risk patients should be evaluated and monitored for disease severity, progression and abnormalities in other organs. The choice of antihypertensive medication in pregnancy is limited by concerns for fetal safety. Methyldopa is the only antihypertensive agent with a proven record of safety in pregnancy, established by follow-up studies of children exposed to the drug in utero. Because of its long history of efficacy and acceptable side-effect profile, intravenous hydralazine is recommended for the treatment of severe HTN in women who are near term. Other antihypertensive medications are now being used more often, particularly if BP control cannot be achieved with first-line agents or in the presence of intolerable adverse effects.

Beta-blockers like labetalol have demonstrated effective BP control and a satisfactory safety profile when administered in the third trimester. The main concern about the use of beta-blockers is intrauterine growth retardation and low placental weight documented when atenolol was used in the second trimester. Beta-blockers can potentially cause additional adverse effects, such as fetal bradycardia, impaired fetal compensatory response to hypoxia, and neonatal hypoglycemia. Data on the safety and efficacy of calcium channel blockers, especially early in pregnancy, are limited. Calcium channel blockers are potent tocolytics and can affect the progression of labor. Nifedipine has been studied most extensively and has been shown to decrease BP and improve renal function without affecting blood flow in the umbilical artery. The availability of long-acting preparations has mitigated the risk of precipitous BP decreases that can potentially compromise uteroplacental blood flow and fetal well-being. Diuretics can be continued during pregnancy if initiated before conception, especially in women with salt-sensitive chronic HTN. However, diuretics can aggravate volume depletion and promote reactive vasoconstriction and should be avoided in women with preeclampsia. ACE inhibitors are contraindicated in pregnancy. They adversely affect the fetal renal system, causing anuria and oligohydramnios. Angiotensin II receptor blockers exert a similar hemodynamic effect on fetal renal circulation and women exposed to such agents during this time do not need to terminate their pregnancy. Nonpharmacological treatment consists mainly of bed rest, which has been shown not only to lower BP but also to promote diuresis and reduce premature labor. However, pregnant women with sodium-sensitive chronic HTN should continue salt restriction during pregnancy [175].

9. Isolated systolic hypertension from hyperdynamic circulation

The most common cause of isolated systolic HTN is increased vascular stiffness with reduced arterial compliance,

and has been discussed earlier in this paper. Other forms of secondary isolated systolic HTN are seen in patients with an increased cardiac output such as those with aortic valvular regurgitation, arteriovenous fistula, patent ductus arteriosis, thyrodoxicosis, Paget disease of the bone, beriberi, and a hyperkinetic circulation [176–179].

These high cardiac output states are associated with a reduction in systemic vascular resistance, an increase in stroke volume and in cardiac output, a widened pulse pressure with an increase in systolic BP and a decrease in diastolic BP, and bounding peripheral arterial pulses. These patients have a prominent apical impulse, an increase in intensity of the first heart sound and of the pulmonic component of the second heart sound, and a third heart sound heard at the apex. An early systolic or midsystolic ejection murmur is commonly heard at the base or along the left sternal border and is due to increased flow across the aortic and pulmonic valves.

Patients with aortic regurgitation will have a high-pitched blowing diastolic murmur that begins immediately after A_2. The diastolic murmur is best heard along the left sternal border in the third and fourth intercostals when aortic regurgitation is due to valvular disease. The murmur is best heard along the right sternal border when aortic regurgitation is due to dilatation of the ascending aorta. Aortic regurgitation is best diagnosed by Doppler echocardiography.

The physical findings of congenital or acquired systemic arteriovenous fistulas depend on the underlying disease and the location and size of the shunt. Most patients will have a Branham sign which is slowing of the heart rate with manual compression of the fistula [177]. Patients with a patent ductus arteriosis will have an infraclavicular and interscapular systolic murmur and occasionally a continuous murmur. Diagnosis is made by Doppler echocardiography.

Patients with thyrotoxicosis will have clinical manifestations of thyrotoxicosis unless they have apathetic hyperthyroidism. Usually levels of both T_3 and of T_4 are elevated in patients with thyrotoxicosis. However, thyrotoxicosis may be associated with elevated T_3 levels and normal T_4 levels or with high T_4 levels and normal T_3 levels [178].

The two main clinical manifestations of Paget's disease are pain and skeletal deformities most commonly affecting the skull, pelvis, spine, and long bones. A high alkaline phosphatase is present and diagnosis is confirmed X-ray of the bone affected. Beriberi heart disease is due to severe thiamine deficiency for at least 3 months. Clinical manifestations of the high output state, severe generalized malnutrition, and vitamin deficiency are present. Evidence of peripheral polyneuropathy with sensory and motor deficits is common.

A hyperkinetic circulation caused by increased sympathetic tone and decreased parasympathetic tone will cause isolated systolic HTN with a reduction in systemic vascular resistance, an increase in stroke volume and in cardiac output, an increase in heart rate, an increase in systolic BP, a decrease in diastolic BP, and bounding arterial pulses. Beta-blockers are the drugs of choice in treating isolated systolic HTN due to a hyperkinetic circulation [179].

10. Current perspectives

Secondary HTN is linked to diseases of the kidneys, endocrine system, vascular system, lungs and central nervous system. It is common to have both primary and secondary causes occurring simultaneously. This perhaps explains why HTN is not entirely reversed after the culprit lesion is removed. Therefore, it is important to determine whether the disease is present and if it is the cause of HTN. The primary determinant for the workup of secondary HTN is the index of suspicion. A skillful physician may illicit clinical clues during history taking and physical examination which heightens suspicion to most secondary forms of HTN; presence of abdominal bruit (renal artery stenosis), reduced or delayed femoral pulses (coarctation of aorta), abdominal masses (polycystic kidney), abdominal striae (Cushing disease), paroxysmal headaches, pallor and palpitations (pheochromocytoma); and the use of contraceptive medications or illicit drug use (drug induced HTN). Difficult to control HTN requiring multiple agents remains the most common reason for initiating secondary HTN workup. As the goal for BP control is lowered based on the results recent outcomes trials and practice guidelines, this definition covers many hypertensive patients.

Patient's initial response to antihypertensive therapy is another helpful screening technique. Pronounced hypokalemia due to low dose diuretic therapy (e.g. primary aldosteronism), acute renal failure or hypokalemia after initiation of ACE inhibitors or ARB (e.g. renal artery stenosis), paradoxical increases in BP with the use of beta-blockers (e.g. pheochromocytoma) are good reasons to initiate workup. Battery of test are available as part of the screening. Screening all hypertensives for secondary causes is not appropriate. Sensitivity and specificity of these test varies greatly. The decision to recommend secondary HTN workup depends on a balance between the risk and cost of the workup and treatment as well as the local expertise and benefits obtained if the secondary cause is successfully eliminated. Validation of the impact of antihypertensive therapy on screening parameter for secondary hypertension is crucial for the clinical practice. Although there is the danger of discontinuing antihypertensive treatment for the differential diagnosis of hypertensive patients, in some cases it is important to discontinue medications for a few days for adequate washout before stating diagnostic work-up.

Before choosing any therapy for secondary hypertension, the potential consequences must be carefully considered since currently available data on this subject come from relatively short term, often-uncontrolled studies in small numbers of highly selected patients.

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