Endocrine Hypertensive Emergencies

Caitlin Egan, Jacques Greenberg, and Thomas J. Fahey III

Contents

Caitlin Egan and Jacques Greenberg contributed equally to the preparation of this chapter.

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Case Presentation

Patient is a 55-year-old male presenting with intermittent headaches, palpitations, and sweating. He often notes these symptoms after exercise. He has no other complaints. Past medical history was unremarkable. He recalls an issue with sedation during his screening colonoscopy where his blood pressure was very high. He has no family history of cancer or endocrine tumors. He is on baby aspirin for "heart health." He has no previous abdominal imaging or surgeries. On physical exam, vital signs are within normal range; no other abnormalities are detected. Basic chemistries were within normal limits. Plasma fractionated metanephrines were significantly elevated.

Questions

1. What are criteria to establish the diagnosis of pheochromocytoma?
   (a) Elevated 24-h urine metanephrines and catecholamines
   (b) Elevated plasma fractionated metanephrines
   (c) MRI or CT scan with adrenal mass
   (d) (a) or (b) and (c)
   (e) (a) and (c)
2. What medications need to be started prior to surgical resection of pheochromocytoma?
   (a) Alpha-blockade for at least 7 days
   (b) Beta-blockade if tachycardic
   (c) (b) and then (a)
   (d) (a) and (b)
   (e) (a) and then (b)
3. Which of the following are causes of primary hyperaldosteronism?
   (a) Aldosterone-secreting adenoma
   (b) Adrenocortical carcinoma
   (c) Adrenal hyperplasia
   (d) (a) and (b)
   (e) (a) and (c)
   (f) All of the above
4. What are common lab findings in primary hyperaldosteronism?
   (a) Hypokalemia
   (b) Normokalemia
   (c) Alkalosis
   (d) Hypernatremia
   (e) (a), (c), (d)
   (f) (b), (c), (d)
   (g) All of the above

5. Which endocrine disorder is the most common cause of secondary hypertension?
   (a) Pheochromocytoma
   (b) Primary hyperaldosteronism
   (c) Cushing's syndrome
   (d) Thyroid storm
6. A 63-year-old woman presents with new-onset adiposity confined to her neck and trunk, intermittent low back aches, and fatigability, with new-onset systolic hypertension with SBP 172 mmHg. She was hitherto healthy but does carry a 15-pack-year smoking history. Her last colonoscopy was 3 years ago without diagnostic abnormality. She is ultimately diagnosed with Cushing's syndrome based on a two late-night salivary cortisol levels. Which of the following represents the most likely cause of the patient's Cushing's syndrome?
   (a) Functioning adrenal adenoma
   (b) Adrenal carcinoma
   (c) Colonic neuroendocrine tumor
   (d) Pancreatic neuroendocrine tumor
7. Which of the following is true with respect to diagnostic considerations in Cushing's disease or syndrome?
   (a) Obese patients have a preponderance to hypertension independent of circulating cortisol levels and therefore cannot be diagnosed with Cushing's syndrome based on a late-night salivary cortisol test.
   (b) While the most accurate method of diagnosing Cushing's disease involves measuring a central-to-peripheral ACTH gradient, patients may be spared this procedure if an MRI identifies a tumor exceeding 6 mm in size.
   (c) Octreotide scintigraphy has a >85% sensitivity in identifying occult ACTH-secreting tumors that are unable to be identified by CT or MRI.
   (d) Radiocholesterol scintigraphy remains the most commonly employed imaging modality in diagnosing a functional adrenal adenoma in the United States.
8. Which of the following is true with respect to the development of hypertension in Cushing's disease or syndrome?
   (a) Transsphenoidal resection of an ACTH-pituitary tumor achieves long-term resolution of hypertension in all patients with Cushing's disease and causes normalization of blood pressure with respect to sex and age-matched cohorts.
   (b) Hepatic synthesis of angiotensinogen typically increases in patients with Cushing's syndrome, while renin levels are either downregulated or remain normal.
   (c) Hypertension secondary to Cushing's syndrome is typically resistant treatment with an ACEi or ARBs.
   (d) Catecholamine receptor density is dramatically decreased in patients with Cushing's syndrome.

9. Which of the following features of thyroid-related hypertension is true?
   (a) The primary driver of hypertension in hypothyroidism is an increase in diastolic blood pressure due to an increase in systemic vascular resistance.
   (b) Esmolol is the preferred beta-blocker used during thyroid storm as it blocks the peripheral conversion of T4 to T3.
   (c) Hyperthyroidism is typically associated with systolic hypertension and a widened pulse pressure.
   (d) Diagnosis of thyroid storm mandates the presence of T4 twice the upper limit of normal and at least one of the following: sustained SBP > 150 mmHg, hyperpyrexia >39°, altered mental status, or cardiac dysfunction.

10. Which of the following is false with respect to the contribution of cortisol to hypertension in Cushing's disease and syndrome?
   (a) Mineralocorticoid receptors within the cell nucleus typically bind aldosterone with higher affinity than cortisol.
   (b) Functional mineralocorticoid excess is typically prevented by the presence of 11 beta-hydroxysteroid dehydrogenase type 2, which converts excess cortisol to cortisone.
   (c) Mifepristone, a selective glucocorticoid receptor blocker, lowers blood pressure to a greater extent than either spironolactone or eplerenone in patients with Cushing's syndrome.
   (d) An enhanced pressor response is often observed in patients with Cushing's disease.

42.1 Introduction

The American Heart Association (AHA) defines high blood pressure as sustained systolic or diastolic blood pressure greater than or equal to 130 or 80 mmHg, respectively. A hypertensive crisis is defined by the AHA as blood pressure of 180/120 mmHg or greater [1]. Hypertensive crisis with signs of end organ damage—including vision changes, chest pain, stroke symptoms, and shortness of breath—is defined as a hypertensive emergency.

Hypertensive emergencies require initial blood pressure control and potentially further treatment depending on the cause of the hypertension. Endocrine sources of high blood pressure, including pheochromocytomas and thyrotoxicosis, are considered secondary hypertension and can result in hypertensive emergencies. A thorough history and physical exam can often differentiate secondary hypertension from essential hypertension. Secondary endocrine sources of hypertension often have

abrupt onset, no family history, no age criterion, and increased severity [2]. Moreover, hypertension can be the presenting sign for 15 different endocrine disorders [3]. Endocrine hypertensive emergencies, once diagnosed, can be cured or prevented with surgery or medication or a combination of the two. Endocrine disorders associated with hypertension and hypertensive emergencies include pheochromocytomas and paragangliomas, primary hyperaldosteronism, Cushing's disease and syndrome, and disorders of the thyroid.

42.2 Pheochromocytoma

Pheochromocytomas are tumors of neuroectodermal origin, arising from the chromaffin cells of the adrenal medulla, that produce catecholamines. If the tumor is extra-adrenal, it is a considered a paraganglioma and may or may not produce functional catecholamines [4]. The elevated level of catecholamines secreted by pheochromocytomas and functional paragangliomas increases blood pressure and causes other signs and symptoms seen with pheochromocytomas [5]. Pheochromocytomas are a rare cause of hypertension, causing less than 1% of cases [2]. They can be sporadic or hereditary and have been associated with neurofibromatosis type 1 (NF1), multiple endocrine neoplasia type 2 (MEN2) types A and B, von Hippel-Lindau (VHL) syndrome, and mutations in succinate dehydrogenase gene family, among others [6, 7].

42.2.1 Diagnosis

The classic triad presentation for pheochromocytoma includes headache, sweating, and palpitations. Weight loss and anxiety can also be seen. Blood pressure patterns vary in patients with pheochromocytomas and include sustained hypertension, hypertension with crisis level blood pressure spikes, or normotension with blood pressure spikes. Of patients with pheochromocytomas, 50% have been noted to have orthostatic hypotension [8].

Suspicion of an underlying pheochromocytoma is probably the most important step in making a diagnosis of a "pheo." Patients with paroxysmal signs and symptoms suggestive of pheochromocytoma—including volatile hypertension new in onset or discovered during surgery or anesthesia, genetic predisposition, and incidental adrenal nodule—should be evaluated for the presence of a pheo [7]. Biochemical evidence of excessive catecholamine production is the next step in confirming a diagnosis of pheochromocytoma. Plasma metanephrines should be the first test, followed by 24-h urinary metanephrines if the plasma metanephrines are indeter-

minate [9, 10]. Once blood or urine tests confirm excess catecholamines, magnetic resonance (MR), computerized tomography (CT), or 123-I-metaiodobenzyeguanidine (MIBG) imaging of the abdomen and pelvis is performed to localize the tumor [7, 11, 12].

42.2.2 Treatment

Today, surgical resection of pheochromocytoma is considered safe and usually curative [13]. Laparoscopic surgical resection of metabolically active pheochromocytomas or paragangliomas is the treatment of choice if the patient can tolerate surgery [14]. Open adrenalectomy for pheochromocytoma in a retrospective study was associated with increased vasopressor needs, longer length of stay, and increased complications compared to minimally invasive adrenalectomy [15]. Preoperative optimization including volume expansion and hypertension control with alpha-adrenergic blockade or the calcium channel blocker nicardipine is of great importance to prevent catecholamine-induced complications during surgery, with the goal of systolic blood pressure of 130 mmHg or lower [14, 16]. While the gold standard for preoperative preparation was phenoxybenzamine for many years, its limited availability and excessive cost have caused a search for alternatives. Nicardipine has been an excellent preoperative blocking agent and has as an advantage of a greater simplicity in dosing as compared to phenoxybenzamine [17]. For tachycardia, beta-blockade can be initiated after alpha-blockade to avoid precipitating a hypertensive crisis from an unopposed alpha-adrenergic response [16]. The current guidelines from the Society of Surgical Oncology (SSO) Endocrine and Head and Neck Disease Site Working Group recommend at least 7 days of pharmacological treatment preoperatively [16]. During laparoscopic resection, the abdominal cavity should be surveyed for metastatic disease. While many authors advocate for ligation of the adrenal vein as an early step in the procedure, this is sometimes impractical and furthermore can lead to venous congestion of the gland and the potential for a higher likelihood of capsular disruption and seeding of the tumor [14] (Fig. 42.1). We routinely choose to ligate the adrenal vein only after the arterial supply has been taken.

42.3 Primary Hyperaldosteronism

Primary hyperaldosteronism (PA) may be the underlying cause of hypertension in up to 10% of patients and is due to increased aldosterone secretion [2, 3]. It is the most common cause of secondary hypertension but less likely to be the cause of a

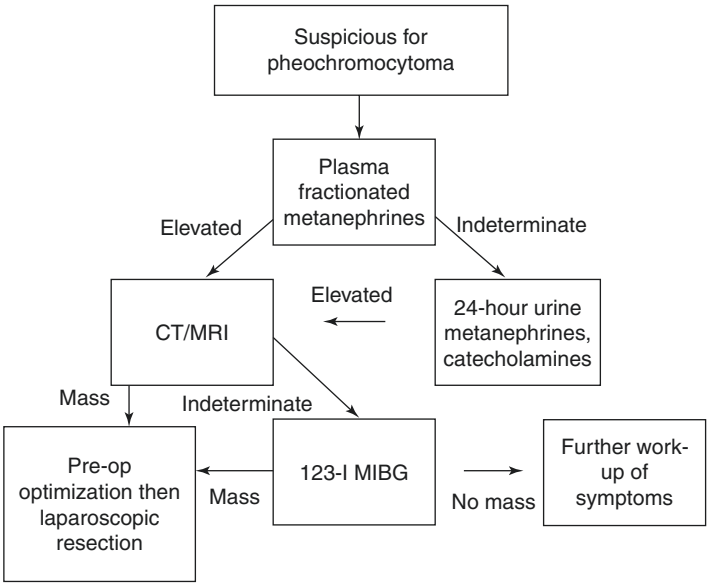

Fig. 42.1 Workup for pheochromocytoma

hypertensive crisis than a pheochromocytoma [18–20]. Elevated aldosterone levels cause increased sodium reabsorption with loss of potassium and hydrogen ions in the nephrons leading to hypertension, hypokalemia, and alkalosis and have been occasionally associated with hypertensive emergencies [21]. PA can be caused by unilateral aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia [22]. Aldosterone-producing adrenal cortical carcinoma is a rare cause of PA [23].

42.3.1 Diagnosis

PA classically presents with hypertension with hypokalemia but more often presents as normokalemic hypertension or resistant hypertension [20]. Resistant hypertension is defined as hypertension while taking three classes of properly dosed antihypertensives including a diuretic [24]. Patients with resistant hypertension or hypertension with hypokalemia should be screened for PA by calculating the aldosterone/renin ratio (ARR) [24]. The ARR is the ratio of the patient's plasma aldosterone concentration to the plasma renin activity and is elevated in patients with primary hyperaldosteronism [25]. In one prospective study using a cutoff of 32 ng/ng for the ARR, the sensitivity was 100% for patients for APA [26].

Confirmatory testing for PA can be done with oral or intravenous (IV) sodium load and measurement of aldosterone in the urine [24, 27]. Other confirmatory tests include the fludrocortisone suppression and captopril challenge tests [24]. However, confirmatory testing is not usually required for mak-

ing a diagnosis of primary hyperaldosteronism. Once a diagnosis of primary hyperaldosteronism is made, the subtype must be identified to guide treatment, as APA is typically treated by surgical resection, while bilateral hyperplasia is currently treated medically [28, 29]. Further workup includes CT imaging of the adrenal glands to assess for nodules and micronodular changes and possible adrenal vein sampling (AVS) to localize [24, 30]. CT localization alone has been found by some to be reliable for adenomas greater than 1 cm in young patients, while there is benefit to AVS when equivocal CT scan findings are present [31]. We recommend AVS in most patients, unless they are 35 years old or younger with an obvious unilateral adenoma greater than 1 cm.

For unilateral APA based on imaging and AVS, laparoscopic adrenalectomy is recommended and can cure primary hyperaldosteronism [24]. Laparoscopic transabdominal and retroperitoneal approaches are comparable for surgical resection and guided by surgeon preference and patient surgical history [32]. For bilateral adenomas, bilateral hyperplasia, or if a patient cannot tolerate surgery, treatment is medical with aldosterone antagonists—spironolactone or eplerenone—and continued antihypertensive medications [24] (Fig. 42.2).

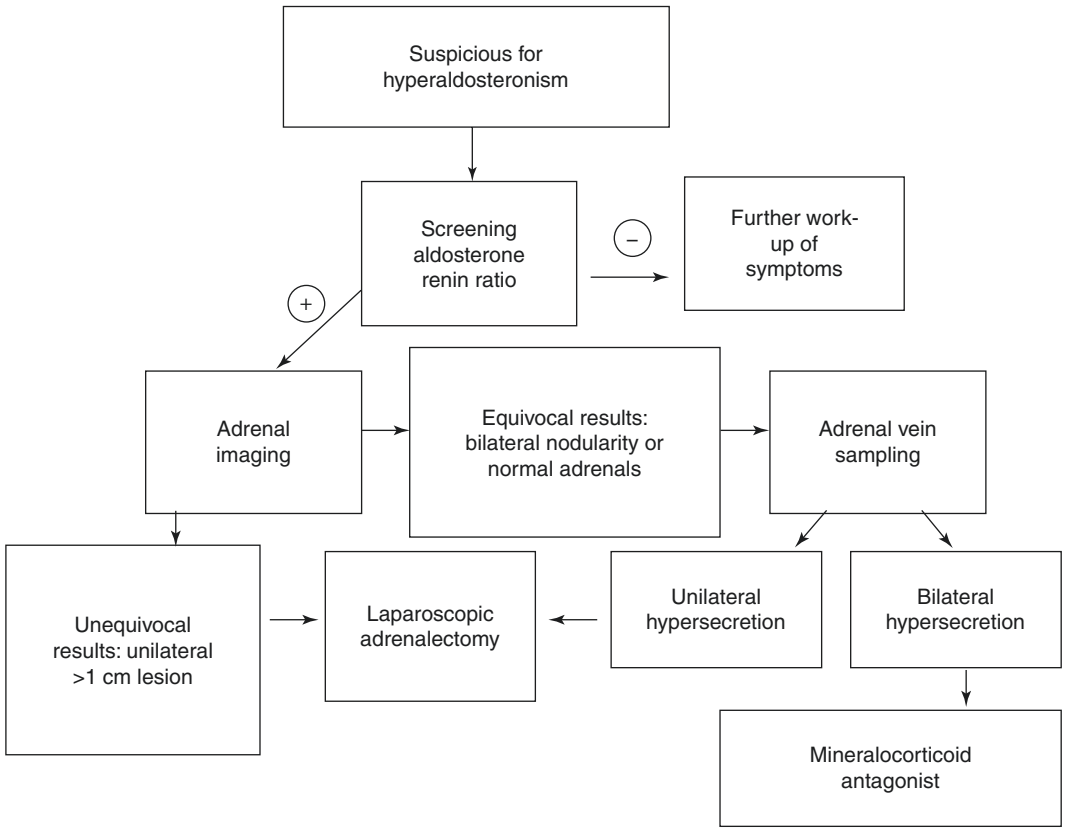

Fig. 42.2 Workup for primary hyperaldosteronism

42.4 Cushing's Disease and Syndrome

In 1932, Harvey Cushing, then at the Brigham Hospital in Boston, reported on 12 patients with the following characteristic features: "(a) a rapidly acquired, peculiarly disposed and usually painful *adiposity*…confined to face, neck and trunk, the extremities being spared; (b) a tendency to become round-shouldered (kyphotic)…; (c) a sexual dystrophy shown by early amenorrhea in the females and ultimate functional impotence in males; (d) An alteration in normal hirsuties shown by a tendency to hypertrichosis of face and trunk…; (e) a dusky or plethoric appearance of the skin with purplish lineae atrophicae; (f) Vascular hypertension…it varied from… 230/170 to …178/100; (g) a tendency to erythraemia…; (h) Variable backaches, abdominal pains, fatigability and ultimate extreme weakness" [33]. He ascribed many of these changes arising secondary to a "basophil adenoma" of the pituitary gland, and the clinical picture embodied by the aforementioned phenotypes rapidly became known as "Cushing's syndrome." By the 1940s, it had become clear that the syndromic characteristics ultimately arose secondary to excess circulating cortisol. Today, the majority of Cushing's syndrome arises due to exogenous sources of cortisol via the pharmacological administration of synthetic glucocorticoids (iatrogenic Cushing's syndrome). Cushing's syndrome arising from endogenous hypercortisolism is much rarer and is generally divided into corticotropin (ACTH)-dependent or corticotropin-independent hypercortisolism. While a detailed description will be reviewed elsewhere in this textbook, a focused overview will be provided here as it pertains to the profound hypertension occasionally observed in these patients, sometimes to the point of representing hypertensive emergencies.

ACTH-dependent Cushing's syndrome arises secondary to excessive stimulation of the adrenal cortex. The two sources of this excessive ACTH are (1) an ACTH-secreting pituitary adenoma (as initially described by Cushing, thus begetting the term Cushing's disease) or (2) an ectopic source of ACTH, typically from a neuroendocrine tumor—usually small-cell lung cancer, thymic malignancy, pancreatic endocrine tumors, or more rarely carcinoid tumors, medullary thyroid cancers, or pheochromocytomas [34–36].

ACTH-independent Cushing's syndrome arises from adrenal adenoma or carcinoma [36] or far more rarely from primary bilateral macronodular hyperplasia (BMAH) or primary pigmented nodular adrenocortical hyperplasia. While BMAH was initially thought to arise sporadically [37–40], several familial variants have been identified [41–47].

The overall incidence of Cushing's syndrome is very low, and thus its contribution to true hypertensive emergency is rare. In one Danish study analyzing all patients with Cushing's

disease and syndrome over an 11-year period, the incidence of Cushing's disease was 1.2–1.7 per million per year. Cushing's syndrome arises from adrenal adenoma (0.6 per million per year) or carcinoma (0.2 per million per year), with neuroendocrine tumors of the lung, thymus, colon, and appendix having an incidence of 0.1 per million per year [36].

As described by Cushing, hypertension is one of the key characteristics of the clinical picture, and it has maintained its syndromic prevalence at a rate of 25–93% [48–69]. Typically, both systolic and diastolic blood pressures are increased to a similar extent in patients with Cushing's syndrome [69, 70]. While hypertension is a common feature of Cushing's syndrome, only rarely does it drive elevations in blood pressure to acutely dangerous levels [71]. In a review of 14 studies identifying 842 patients with Cushing's disease and Cushing's syndrome due to an adrenal adenoma or due to ectopic ACTH production, mean SBP was only elevated to slightly above 140 mmHg [70]. This does stand in contrast to those patients described by Dr. Cushing himself, whose peak systolic blood pressures were noted to be as high as 230 mmHg—a true endocrine emergency.

42.4.1 Diagnosis

A patient presenting in true hypertensive emergency warrants a prompt and aggressive approach to obtaining a diagnosis with respect to the driving disease pathology. The diagnostic workup for Cushing's syndrome is principally based on the 2008 Endocrine Society guidelines [72]. Initial screening can proceed with one of the following tests: late-night salivary cortisol (two measurements), 24-h urinary free cortisol excretion (two measurements), or the overnight dexamethasone suppression test (classically 1 mg given at 11 PM). A number of conditions may lead to physiologic hypercortisolism which may resemble Cushing's syndrome and must be noted in the workup of the pathology. These include pregnancy, obesity, and physiologic stress states such as depression, illness, hospitalization, poorly controlled diabetes mellitus, alcoholism, and sleep apnea [73–76]. Of these, some have a preponderance toward hypertension independent of a patient's cortisol status—obesity and sleep apnea, for example.

Historically, a high-dose dexamethasone suppression test has been performed to determine whether Cushing's syndrome is ACTH-dependent (pituitary) or ACTH-independent (ectopic). Theoretically, the pituitary gland maintains responsiveness to the glucocorticoid negative feedback loop, and cortisol levels should be suppressed following high-dose dexamethasone administration [77]. In contrast, nonpituitary tumors excreting ACTH, such as a small-cell lung cancer, lack the neg-

ative feedback loop and will lack cortisol suppression following a high-dose dexamethasone suppression test. More recently, the CRH test has been used to better evaluate the etiology of a patient's hypercortisolism [78, 79]. Dehydroepiandrosterone sulfate (DHEA(S)), which is ACTH-dependent and the most common steroid in the body, has been shown to be highly correlated with circulating cortisol levels. Due to its long half-life, some authors have proposed that DHEA(S) best reflects ambient ACTH levels over a long period and may also serve to identify patients with subclinical Cushing's and adrenal incidentalomas [80–82]. Indeed, utilization of an age-adjusted DHEA(S) ratio has recently been proposed as a screening test for subclinical Cushing's following identification of adrenal incidentalomas and is being added to the armamentarium of tests in the workup of hypercortisolism [83].

The suspected pathological process driving a patient's Cushing's disease or syndrome helps guide further imaging or diagnostic abnormalities. In patients suspected of having Cushing's disease due to a pituitary tumor, the most direct way to measure ACTH hypersecretion is to measure a central-to-peripheral ACTH gradient via petrosal sinus sampling [84–86]. However, prior to performing this invasive procedure, MRI with and without gadolinium contrast should be obtained to exclude a tumor >6 mm in size as tumors of this magnitude obviate the need for petrosal sinus sampling. MRI is only able to localize 50% of tumors, with a positive predictive value of 86% but with an associated false-positive rate exceeding 18% [87–89].

Ectopic ACTH-secreting tumors may be found anywhere throughout the body, but focused imaging in the chest is likely the highest yield given the preponderance of small-cell lung cancer as a cause of the disease. CT and MRI appear to have largely similar sensitivities in identifying tumors [90]. Octreotide scintigraphy can detect occult tumors secreting ACTH with a sensitivity of 30–53% [90–93].

Imaging for primary adrenal disease usually starts with thin-section CT. MRI may be obtained when the unenhanced CT attenuation values are >10 Hounsfield units as this may provide extra information regarding the malignant potential of the neoplasm [94]. Radiocholesterol scintigraphy may also provide additional information, though this test is now largely unavailable [95]. When bilateral adrenal masses are identified and suspicion of Cushing's syndrome or subclinical Cushing's syndrome exists, adrenal venous sampling can be performed [96].

Not unexpectedly, few of these diagnostic modalities will provide the physician with an immediate answer regarding any level of contribution of Cushing's syndrome to a patient's hypertension, nor is a definitive diagnosis necessary to initiate treatment. As such, the aforementioned can be pursued in an appropriately timed fashion in conjunction with appropriate treatment.

42.4.2 Treatment

Hypertension is an independent predictor of mortality in patients with Cushing's disease [53, 54, 97]. The definitive therapeutic intervention of Cushing's syndrome -related hypertension involves surgical removal of the suspected neoplasm. When a pituitary tumor is the cause of a patient's Cushing's disease, transsphenoidal resection provides long-term cure in greater than 70% of cases, but there appear to be higher rates of hypertension 5 years after cortisol normalization in these patients when compared to sex and age-matched cohorts [51, 55, 59, 61, 98, 99]. In children with Cushing's syndrome, 93.5% had preoperative systolic hypertension, with a decrease to only 5.5% at 12-month follow-up [100] after surgical resection of the cortisol-secreting neoplasm. In cases of Cushing's syndrome due to an occult ACTH-secreting tumor, bilateral adrenalectomy can resolve hypertension in nearly two-thirds of patients [101].

A variety of mechanisms have been implicated in the development of hypertension in Cushing's syndrome. Principal among these are the renin-angiotensin system, mineralocorticoid activity, the sympathetic nervous system, and the vasoregulatory system [70]. The most extensively studied mechanism contributing to hypertension in Cushing's syndrome is the renin-angiotensin system. Hepatic synthesis of angiotensinogen increases [71], whereas renin may be either downregulated (as expected) [102] or more commonly normal [71]. Angiotensin II itself has also been reported to be normal [103], but the total number of angiotensin II receptors is increased, and an enhanced response to angiotensin II infusion is noted [104]. An acute decrease in blood pressure has been noted in patients with Cushing's syndrome following the oral administration of an angiotensin I-converting enzyme inhibitor (ACEi) [71, 105], which has become the first choice class of drugs along with angiotensin receptor blockers (ARBs) in patients with Cushing's syndrome [70].

While the renin-angiotensin system represents the primary mechanistic pathway involved in hypertension seen in Cushing's syndrome, the mineralocorticoid system is also extensively involved. The mineralocorticoid receptor is expressed on the cell nucleus and binds both aldosterone and cortisol with equal affinity [106]. 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2) typically protects against a functional mineralocorticoid excess by converting cortisol to cortisone [107]. However, in the setting of pathologically elevated cortisol in patients with Cushing's syndrome, 11beta-HSD2 becomes overwhelmed, and an effective hyperaldosteronism is observed with respect to the development of hypokalemia [108]. Paradoxically and somewhat counterintuitively, this hypertension appears sodium-independent, as chronically elevated cortisol has been associated with both normal circulating levels

and excretion of sodium [102, 109]. Perhaps this is best explained by the existence of another isoform of 11beta-HSD, the type 1 (11beta-HSD1) which reconverts cortisone into cortisol [107]. Indeed, there is suggestion that this reactivated cortisol itself is at least partially responsible for the hypertension observed in patients with Cushing's syndrome, as mifepristone, a selective glucocorticoid receptor blocker, lowers blood pressure more than spironolactone or eplerenone in these patients [110, 111].

Catecholaminergic receptor density is typically preserved in patients with Cushing's syndrome [103], and a hyperacute sympathetic response is controversially implicated in the development of hypertension in Cushing's syndrome. For example, an enhanced pressor response to norepinephrine (alpha 1, alpha 2, and beta 1 agonism) has been noted in patients with pituitary Cushing's disease, but this was not reproduced when individuals with Cushing's syndrome were treated with the selective alpha-1 agonist phenylephrine [112, 113].

A number of vasoregulatory substances have also been variably implicated in hypertension in the setting of Cushing's syndrome. Endothelin-1 (ET-1), erythropoietin (EPO), nitric oxide synthase (NOS), prostaglandins, prostacyclins, and compounds of the kallikrein-kinin system have all been reported to be deranged [71, 114–118].

There are numerous targets in the medical therapy of hypertension in Cushing's syndrome, although none necessarily in the emergent setting. An algorithm has been proposed by the "Altogether to Beat Cushing's" (ABC) [70]. ACEi or ARBs serve as first-line medications, with a goal of achieving normotension (Fig. 42.3). Further management is dependent on the presence or absence of hypokalemia. If hypokalemia is present, spironolactone or eplerenone may be added. If addition of either of these fails to properly control a patient's blood pressure, then addition of an alpha-blocker, nitric oxide donor, or calcium channel blocker can be considered. If blood pressure yet remains uncontrolled, then careful use of diuretics or beta-blockers should be added. Targeted therapy addressing the source of hypercortisolism should also be pursued. Modulation of pituitary and ectopic ACTH release can be achieved with somatostatin analogs and dopamine agonists. Drugs that inhibit steroidogenesis such as ketoconazole and metyrapone as well as those blocking the glucocorticoid receptor (mifepristone) also play a role [119–121]. Pasireotide, a somatostatin analog, and cabergoline, a dopamine agonist, have both demonstrated significant improvement in hypertension in patients with Cushing's disease [122, 123]. Synergistic effects have been demonstrated with the addition of ketoconazole [124]. While there are clearly a number of treatment modalities addressing Cushing's associated hypertension, the need for directed and immediate control of any hypertensive emergency takes precedence.

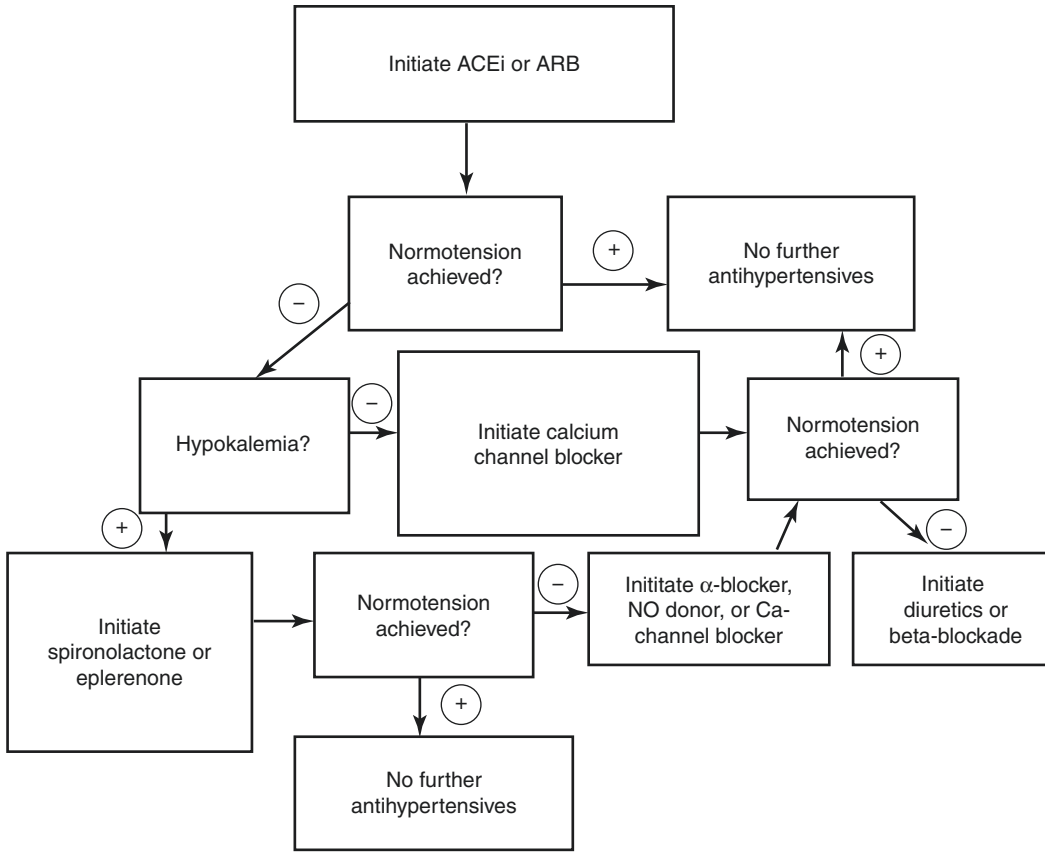

Fig. 42.3 Management of hypertension in Cushing's syndrome. While the management of hypercortisolemia is pursued, antihypertensive medications can be added in a targeted manner to control elevations in blood pressure. ACEi/ARB should be initiated first, followed by spironolactone or eplerenone if hypokalemia is present or calcium channel blockers if hypokalemia is absent. Following the addition of spironolactone or eplerenone, if blood pressure remains poorly controlled in patients with hypokalemia, then an alpha-blocker, nitric oxide donor, or calcium channel blocker can be added. Diuretics and beta-blockers are instituted as last line

42.5 Thyroid Disease

Diseases of the thyroid can often lead to disturbances in a patient's blood pressure, though these disturbances are rarely profound enough to lead to a hypertensive emergency. Nevertheless, both hypothyroidism and hyperthyroidism have been noted to lead to mild hypertension, and some cases of hypertensive emergencies have been reported [125].

Hypothyroidism primarily increases mean arterial pressure by increasing the diastolic blood pressure [126]. The catecholaminergic system has been implicated as the cause of hypertension in hypothyroidism. Higher levels of norepinephrine have been reported in hypothyroid patients when compared to normal controls [127, 128]. Furthermore, an increase in alpha-receptor responsiveness with an associated decrease in beta-adrenergic receptors has also been reported [129, 130], as has inappropriate secretion of antidiuretic hormone [130]. With

that said, there are reports of patients presenting with profound hypothyroidism with systolic blood pressure >220 mmHg and diastolic blood pressure >140 mmHg [125].

Hyperthyroidism is generally associated with systolic hypertension with a widened pulse pressure. This arises secondary to the physiologic changes associated with elevated thyroid hormones—including an increase in cardiac output by 50–300% via a decrease in systemic vascular resistance (thus accounting for the decrease in diastolic blood pressure), an increase in heart rate, an increase in left ventricular output, and an increase in circulating blood volume [131, 132]. However, the presentation of hypertensive emergency is rare, and in one study assessing the effects of treatment on patients with hyperthyroidism, the average pre-intervention systolic blood pressure was 132 +/− 2 mmHg, with no records of systolic blood pressure exceeding 150 mmHg [133]. These findings have been replicated in other studies of hypertension in hyperthyroidism [134].

Thyroid storm typically manifests as an exaggeration of hyperthyroid symptoms, and profound hypertension has historically been reported as a feature of this emergent disease pathology [135, 136]. However, as our understanding of emergent thyrotoxicosis has evolved, we've come to recognize a transient diastolic hypertension prior to the development of a supervening cardiogenic shock [135] rather than any overt hypertensive emergency.

42.5.1 Diagnosis

The diagnosis of hypothyroidism, hyperthyroidism, and thyroid storm will primarily be reviewed elsewhere within this book. Briefly, however, the diagnosis of thyroid storm will be reviewed here as it is the only thyroid emergency with respect to hypertension. Diagnosis is primarily clinical and based on the presence of severe, life-threatening symptoms including hyperpyrexia (generally greater than 39 °C), cardiac dysfunction, and altered mental status with biochemical evidence of hyperthyroidism. A number of scoring systems exist to aid in the diagnosis, including that proposed by Burch and Wartofsky in 1993 [137]. Thyroid function tests should also be ordered and assessed, although there exist no diagnostic criteria for the degree of hyperthyroidism during thyroid storm. The underlying etiology of the thyrotoxicosis should also be determined—often, Grave's disease or a toxic adenoma or multinodular goiter is implicated, as have checkpoint inhibitors utilized in cancer treatments [138]. A physiologic stress usually precedes the development of storm such as surgery, trauma, infection, or parturition [139–142]. Diagnoses of the underlying driver for the storm are essential as it helps guide management of the disease.

42.5.2 Treatment

The treatment of hypertension associated with thyroid storm focuses on the management of the storm rather than the hypertension itself. A beta-blocker, either propranolol or esmolol, may be used to blunt the sympathetic response related to excessive thyroid hormone [143]. Propranolol has the added benefit of inhibiting the conversion of T4 to T3. Antithyroid therapy is initiated to inhibit the production of new hormone—propylthiouracil is preferred over methimazole due to its peripheral inhibition of T4 to T3 conversion [143–145]. Glucocorticoids have also been employed, as has plasmapheresis/plasma exchange [146, 147]. Emergency thyroidectomy has also been employed, although it is imperative to note that these interventions are undertaken for the cardiovascular collapse that follows the progression of thyroid storm rather than the any features of the initial hypertension [148]. As the natural progression of thyroid storm continues, any hypertension will rapidly be replaced with profound hypotension as cardiovascular collapse develops.

Answers to the Questions

1. (d); 2. (e); 3. (f); 4. (g); 5. (b); 6. (a); 7. (b); 8. (b); 9. (c); 10. (a)

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