

CLINICAL MEDICINE

Corridor Consult

Evaluation of Hypertension with Hypokalemia

Antoine C Abcar, MD
Dean A Kujubu, MD**Vignette**

Your colleague asks for your suggestions on the evaluation and treatment of a woman age 70 years with a five-year history of hypertension who has required progressively more medication because of persistent high blood pressure. She is taking five medications, including a diuretic, but still has a blood pressure of 165/95 mm Hg (well above the current standard definition of hypertension of 140/90 mm Hg). He says that the patient is asymptomatic and that her physical examination was normal. The patient's serum potassium levels have ranged from 3.2 to 3.5 mEq/L for many years despite potassium supplementation, which had been attributed to her diuretic use. Her renal function is normal.

Discussion**Common Causes of Poorly Controlled Hypertension**

Hypertension that remains in poor control despite the use of many medications is a difficult problem that every primary care physician has faced.¹ Common causes of uncontrolled hypertension include *white coat hypertension*, nonadherence to a salt-restricted diet or to a medication regimen, failure to include a diuretic in the antihypertensive regimen, use of concurrent medications such as nonsteroidal anti-inflammatory agents or oral contraceptives, obe-

sity, obstructive sleep apnea, and parenchymal renal disease. Home blood pressure measurements or 24-hour ambulatory blood pressure monitoring are useful in the evaluation for *white coat hypertension*. Obtaining a 24-hour urine collection for sodium and creatinine to assess dietary sodium intake is frequently helpful. An otherwise healthy patient ingesting a diet limited to 2000 mg of sodium should excrete no more than 87 mEq of sodium in a 24-hour urine sample; higher amounts of sodium excretion suggest dietary nonadherence. Symptoms such as daytime somnolence, not feeling rested after a full night of sleep, mood disturbances, and a lack of concentration suggest that obstructive sleep apnea should be considered and a sleep study ordered. A frank discussion with the patient about the importance of blood pressure control on cardiovascular health, the adherence to medication regimens despite potential side effects, and the benefits of exercise, weight loss, smoking cessation, and reduction of alcohol intake are essential.

Any efforts to simplify the medical regimen will help with patient adherence.

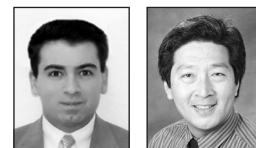
Less Common Causes of Poorly Controlled Hypertension

Although the majority of hypertension in the adult population is

essential hypertension, in selected cases it is reasonable to evaluate for possible secondary causes of hypertension. Hypertension of new onset in patients younger than age 30 years or of sudden onset in those older than age 50 years; hypertension in the absence of obesity; the lack of a strong family history of hypertension; the requirement for three or more medications, one of which is a diuretic, with suboptimal control; the acute deterioration of renal function with the initiation of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs); paroxysmal symptoms of anxiety, diaphoresis, or palpitations; Cushingoid features; renal dysfunction; and the presence of hypokalemia and metabolic alkalosis are all findings suggestive of secondary hypertension. Because this patient has a relatively late onset of worsening hypertension, persistent hypokalemia despite potassium supplementation, and resistant hypertension, it is reasonable to evaluate her for underlying causes of hypertension.

The most common cause of hypokalemia in a hypertensive patient is diuretic use. By enhancing urinary flow and sodium delivery through the collecting tubule, both thiazide and loop diuretics promote renal potassium secretion. Potassium secretion is further enhanced in the setting of diuretic-induced

Antoine C Abcar, MD, (left) is Assistant Program Director of the Nephrology Fellowship, in the Department of Nephrology, at the Los Angeles Medical Center, in Los Angeles, CA. E-mail: antoine.c.abcar@kp.org.
Dean A Kujubu, MD, (right) is Program Director of the Nephrology Fellowship, in the Department of Nephrology, at the Los Angeles Medical Center, in Los Angeles, CA. E-mail: dean.a.kujubu@kp.org.



intravascular volume depletion and secondary aldosterone stimulation. Hypokalemia may also result from gastrointestinal problems, such as diarrhea or vomiting, though these patients would generally not be hypertensive. Magnesium deficiency due to malabsorption, poor dietary intake, or exposure to medications such as aminoglycosides is another cause of persistent hypokalemia. Spontaneous hypokalemia, in the absence of diuretic use, deserves further evaluation.

The most common causes of hypertension with hypokalemia are presented in Table 1. Primary aldosteronism, or Conn's syndrome, previously thought to be an uncommon condition, in some studies is now seen to account for between 5% and 13% of all hypertension; the increase in diagnoses is due to the advent of more widespread screening.² Although hypokalemia and metabolic alkalosis are classic findings of primary aldosteronism, hypokalemia is seen in only 20% to 50% of documented cases. The ratio of plasma aldosterone concentration to plasma renin activity (PAC:PRA) is widely used as a first step in evaluating patients with both hypertension and hypokalemia. If the morning PAC:PRA is >30, with PRA expressed as ng/mL per hour, and the PAC is >15 ng/dL, the results are highly suggestive of primary aldosteronism. Relying solely on an elevated PAC:PRA without attention to the level of PAC may yield false positive results because patients with low-renin essential hypertension will be included. Aside from stopping aldosterone-receptor an-

tagonists, such as spironolactone or eplerenone, for six weeks, there is no need initially to stop other antihypertensive medications before obtaining a PAC:PRA. Of course, a more representative PAC:PRA is obtained if other antihypertensive medications that may affect the ratio are likewise withheld; however, this is rarely practical. Diuretics, ACEIs, and ARBs increase renin levels, which may lead to a low PAC:PRA; in contrast, β -blockers and clonidine reduce renin secretion, resulting in a higher PAC:PRA than would be seen in their absence. Since hypokalemia itself inhibits aldosterone secretion, potassium depletion should be corrected before the PAC:PRA is obtained. PAC and PRA values are highly laboratory dependent, and the calculated ratio depends on the units used to express concentration or activity. Moreover, since aldosterone is secreted in bursts, the PAC:PRA could change within minutes. Early morning levels are most representative. The decision about whom to evaluate further for primary aldosteronism should not be dependent on only one determination of PAC:PRA. If repeated determinations demonstrate a PAC:PRA >30 and a PAC >15 ng/dL, confirmatory biochemical testing, such as measuring PAC before and after 2 L of normal saline administration or a 24-hour urinary aldosterone excretion after three days of oral salt loading (six g sodium chloride) with careful blood pressure monitoring is indicated to diagnose primary aldosteronism. Neither oral salt loading nor saline infusion should suppress the autonomously secreted hormone from an adenoma. The clinical response to a trial of aldosterone-receptor antagonists is not in itself diagnostic of primary aldoster-

Table 1. Common causes of hypertension with hypokalemia

Essential hypertension with diuretic use
Primary aldosteronism
Cushing's syndrome
Pheochromocytoma
Renal vascular disease
Malignant hypertension

onism, because many patients with resistant essential hypertension have a favorable response to these medications. Consultation with a nephrologist or endocrinologist may be helpful for advice on conducting these tests correctly.

Another cause of hypertension with hypokalemia is Cushing's syndrome. Cushing's syndrome, a result of excess endogenous glucocorticoid secretion, presents with hypertension, central obesity, abdominal striae, glucose intolerance, depression, weakness, and characteristic moon facies. Hypokalemia is most noted in the ectopic adrenocorticotrophic hormone syndrome.³ It is thought that high levels of endogenously produced cortisol, corticosterone, and deoxycorticosterone simulate the mineralocorticoid receptor, resulting in hypertension and hypokalemia. The use of aldosterone-receptor antagonists does not completely ameliorate the hypertension, suggesting that other reasons exist for hypertension in Cushing's syndrome, aside from excessive mineralocorticoid effect. The initial screening involves collecting a 24-hour urine for free cortisol. Values that are more than three to four times normal are diagnostic for Cushing's syndrome.⁴ Owing to the difficulty in correctly collecting a 24-hour urine sample, however, some physicians prefer performing a low-

... the majority of hypertension in the adult population is essential hypertension ... the benefits of exercise, weight loss, smoking cessation, and reduction of alcohol intake are essential.

dose dexamethasone-suppression test by obtaining an 8 AM cortisol level after the administration of 1 mg of dexamethasone at bedtime (11–12 PM). A level of <5 $\mu\text{g/dL}$ indicates appropriate suppression. Morning cortisol levels >5 $\mu\text{g/dL}$ after low-dose dexamethasone suppression warrant further evaluation. Endocrinology consultation would be helpful.

Pheochromocytoma is classically described as presenting with paroxysms of adrenergic symptoms, such as palpitations, headaches, anxiety, and sweating, associated with labile hypertension.⁵ Most pheochromocytomas, however, present with persistent hypertension. The clinical manifestations of a pheochromocytoma depend on the predominant catecholamine that the tumor produces and whether the secretory pattern is continuous or paroxysmal. Although pheochromocytomas are rare, autopsy studies suggest that they are present more often than they are diagnosed. These patients tend to have a decreased intravascular volume status, and thus both PRA and PAC levels are elevated. The preferred test for diagnosing pheochromocytoma is under debate. Twenty-four-hour urinary fractionated metanephrines and catecholamines may be the preferred diagnostic test, but some advocate the use of plasma-fractionated free metanephrine because of its ease of collection and high sensitivity.⁶ Negative findings on a plasma test essentially rule out pheochromocytoma as a diagnostic possibility. Medications such as levodopa, tricyclic antidepressants, buspirone, adrenergic decongestants, and amphetamines may interfere with the analytic assay. Ideally, these medications should be tapered and stopped two weeks before testing, if possible.

Renovascular hypertension, though relatively uncommon in the general hypertensive population, is increased in prevalence in both the younger (<30 years of age) and in the older (>50 years of age) patient with new-onset hypertension.¹ Fibromuscular dysplasia is the most common cause of renovascular hypertension in the younger patient, whereas atherosclerotic vascular disease is the most common in the older patient. Both may manifest as resistant hypertension. Acute renal deterioration after administration of ACEI or ARB and recurrent episodes of flash pulmonary edema suggest either bilateral renal vascular disease or disease in a patient with a solitary kidney. The presence of a systolic–diastolic abdominal or flank bruit or a renal sonogram demonstrating marked differences in kidney sizes suggest renal vascular disease. Although renal arteriography remains the diagnostic gold standard for renovascular disease, magnetic resonance angiography techniques and computed tomography (CT) angiography have shown promise in visualizing the renal arteries without arterial cannulation. The use of gadolinium and iodinated contrast agents, however, is not without risk in patients with chronic renal impairment. Both gadolinium and iodinated contrast agents have nephrotoxic potential. Moreover, gadolinium use in patients with an estimated glomerular filtration rate of <30 mL/min has on rare occasions been associated with nephrogenic fibrosing dermopathy, a progressive sclerodermatous condition for which there is no defined treatment. For this reason, nonenhanced magnetic resonance imaging (MRI) or carbon dioxide angiography to avoid the use of iodinated contrast agents has been tried with some success. Duplex ultrasonography

has been used in some institutions in selected patients to visualize the renal arteries and measure hemodynamic changes within them. The latter is technically demanding, and its success depends on the skill of the operator and on the patient's body habitus. Captopril-enhanced nuclear medicine renal scanning, which images the differential perfusion of the kidneys, may fail to detect bilateral renal artery disease. If findings suggestive of hemodynamically important stenosis are discovered, renal arteriography may be indicated, particularly if the patient is a candidate for either surgical revascularization, angioplasty, stent deployment, or all of these procedures. Whereas revascularization is often successful in alleviating hypertension in patients with fibromuscular dysplasia, the long-term results with atherosclerotic renal artery disease are less promising. The optimal treatment for atherosclerotic renal vascular disease remains primarily medical.

Finally, hypertension from any cause, if unmanaged, may enter into an accelerated phase, resulting in a hypertensive emergency. Manifestations include encephalopathy, retinopathy, pulmonary edema, acute renal failure, and microangiopathic hemolytic anemia. Hypertensive crisis is a state of intense vasoconstriction; PRA and PAC levels are generally markedly elevated.⁷ Catecholamine levels may also be elevated. Hypokalemia is frequently found on presentation. Evaluation for secondary causes of hypertension should be postponed until after hypertension is better controlled and the vasoconstricted state is corrected.

Conclusion

The patient whose case is described here deserves evaluation

for an underlying cause of her resistant hypertension. An initial approach would include correction of hypokalemia with potassium supplementation, and then obtaining a random PAC:PRA, assuming that she is not taking an aldosterone-receptor antagonist. A ratio of >30, with a PAC of >15 ng/dL on repeated determinations, is highly suggestive of primary aldosteronism. Biochemical confirmation would then be indicated. If the PAC:PRA is not elevated and plasma renin activity is high, evaluation for renal vascular disease with MRI or CT angiography is reasonable because her renal function is not compromised. A 24-hour urinary fractionated metanephrines or plasma fractionated free metanephrines and a 24-hour urinary free cortisol or an overnight low-dose dexamethasone-suppression test,

screening tests for pheochromocytoma and Cushing's syndrome, respectively, may also be performed if there is clinical suspicion for these conditions. Obtaining a nephrology or endocrinology consultation to assist with the evaluation and interpretation of results should be considered. ♦

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgment

Katharine O'Moore-Klopf, ELS, of KOK Edit provided editorial assistance.

References

- Hall WD. Resistant hypertension, secondary hypertension, and hypertensive crisis. *Cardiol Clin* 2002 May;20(2):281-9.
- Young WF. Primary aldosteronism: renaissance of a syndrome. *Clin Endocrinol (Oxf)* 2007 May;66(5):607-18.
- Torpy DJ, Mullen N, Ilias I, Nieman LK. Association of hypertension and hypokalemia with Cushing's syndrome caused by ectopic ACTH secretion: a series of 58 cases. *Ann N Y Acad Sci* 2002 Sep;970:134-44.
- Meier CA, Biller BM. Clinical and biochemical evaluation of Cushing's syndrome. *Endocrinol Metab Clin North Am* 1997 Dec;26(4):741-62.
- Failor RA, Capell PT. Hyperaldosteronism and pheochromocytoma: new tricks and tests. *Prim Care* 2003 Dec;30(4):801-20, viii.
- Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab* 2003 Feb;88(2):553-8.
- McAllister RG Jr, Van Way CW 3rd, Dayani K, et al. Malignant hypertension: effects of therapy on renin and aldosterone. *Circ Res* 1971 May;28(5):Suppl 2:160-74.

The Ischemic Kidney

These experiments indicate that, in dogs at least, ischemia localized to the kidneys is a sufficient condition for the production of persistently elevated systolic pressure. When the constriction of both main renal arteries is made only modestly severe ... the elevation of systolic blood pressure is unaccompanied by signs of materially decreased renal function Almost complete constriction of both main renal arteries ... results in great elevation of systolic blood pressure, which is accompanied by ... uremia.

—Goldblatt H, Lynch J, Hanzal R, Summerville W. *Journal of Experimental Medicine*. 1934