# 46-Year-Old Man With Treatment-Resistant Hypertension

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A 46-year-old man presented for evaluation of treatment-resistant hypertension (HTN). He recalled being told that his systolic blood pressure was high when he was in high school; however, he did not begin taking antihypertensive medications until age 42 years. Despite multiple antihypertensive regimens, his HTN has been difficult to control and is consistently above his blood pressure target (<140/90 mm Hg) in multiple settings, including the physician's office and at home. His current regimen consists of 320 mg of valsartan, 200 mg/d of extended-release metoprolol, and 10 mg/d of amlodipine, which were his only medications. He had previously taken 25 mg/d of hydrochlorothiazide (in combination with valsartan and metoprolol); however, this was discontinued because of the inability to reach his blood pressure target and the development of hypokalemia (potassium level, 2.8 mmol/L). The patient reported that he adhered strictly to a low-sodium diet, rarely drank alcohol, never smoked, and rode a stationary bicycle for 60 minutes every day. He had intentionally lost about 11.4 kg (25 lbs) in the past 4 years. His medical history included obesity, hyperlipidemia, impaired fasting glucose levels, hypothyroidism treated with thyroid hormone replacement therapy, gout, and obstructive sleep apnea treated with continuous positive airway pressure (CPAP). He was recently evaluated in the sleep clinic, and his obstructive sleep apnea was being adequately treated with his current CPAP settings. The patient reported adherence to his antihypertensive medication regimen and CPAP use. He denied using nonsteroidal anti-inflammatory drugs or stimulant medications. He also denied headaches, palpitations, and diaphoresis.

Findings on physical examination were as follows: blood pressure, 158/88 mm Hg (average of 6 readings in the left arm sitting); pulse, 51 beats/min and regular; and body mass index (calculated as the weight in kilograms divided by height in meters squared), 47. Other than an obese appearance, his physical examination was unremarkable.

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See end of article for correct answers to questions.

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Laboratory testing yielded the following results (reference ranges provided parenthetically): sodium level, 140 mEq/L (135-145 mEq/L); potassium level, 4.0 mmol/L (3.6-5.2 mmol/L); and creatinine level, 1.0 mg/dL (0.8-1.3 mg/dL). Electrocardiography revealed sinus bradycardia with borderline left ventricular hypertrophy. Renal ultrasonography revealed normal kidney size with no evidence of renal artery stenosis. Echocardiography revealed a mild increase in left ventricular thickness, normal function, and no valvular abnormalities.

***1. In addition to advising continued efforts toward weight loss, which <u>one</u> of the following is the <u>most appropriate</u> next step in the management of this patient's HTN?***

***a.*** *Advise follow-up blood pressure check in 3 months*
***b.*** *Increase extended-release metoprolol to 300 mg/d*
***c.*** *Evaluate for identifiable (secondary) causes of HTN*
***d.*** *Refer the patient to an HTN specialist*
***e.*** *Add clonidine*

This patient has medically complicated obesity as evidenced by his body weight and multiple weight-related comorbid conditions (HTN, hyperlipidemia, impaired fasting glucose level, and obstructive sleep apnea). Additional weight loss, including consideration of bariatric surgery, will be paramount to improving blood pressure control and lowering his overall cardiovascular risk. However, in the meantime maintaining his current drug regimen is not appropriate. Further titration of his β-blocker dose is unlikely to provide additional blood pressure lowering and would likely induce symptomatic bradycardia given his current resting heart rate. His HTN was considered to be resistant because he had been unable to reach his blood pressure goal despite taking 3 appropriate medications. After completing a thorough review of adherence to lifestyle decisions and medications, the most appropriate next step in management would be to evaluate for identifiable secondary causes of HTN, such as sleep apnea, renovascular disease, primary aldosteronism, Cushing syndrome, pheochromocytoma, and thyroid disease. This patient's history of developing HTN at a young age (<20 years) and hypokalemia with diuretic use are additional factors that suggest the need to evaluate for other contributors to his HTN. Referral to a specialist in HTN is sometimes necessary in patients with treatment-resistant HTN. However, at this point further investigation is within the realm of the general practitioner. Clonidine can be

used as therapy for essential HTN and would be a reasonable agent to add; however, as already discussed, it is important to pursue other etiologies at this time.

This patient's TSH level was 3.14 mIU/mL (0.30-5.0 mIU/mL); 24-hour urinary free cortisol level, 17 µg (3.5-45 µg/24 h); plasma free metanephrine level, <0.20 nmol/L (<0.50 nmol/L); plasma free normetanephrine level, 0.24 nmol/L (<0.90 nmol/L); plasma aldosterone concentration (PAC), 16 ng/dL (1-21 ng/dL); plasma renin activity (PRA) level, <0.6 ng/mL/h (0.6-3.0 ng/mL/h); and PAC:PRA ratio, 27 (<20).

***2. Which one of the following best explains this patient's very low PRA level?***

***a.*** *Primary adrenal insufficiency*
***b.*** *Primary aldosteronism*
***c.*** *Valsartan use*
***d.*** *Sodium-restricted diet*
***e.*** *Pheochromocytoma*

In the setting of a normally responsive renin-angiotensin-aldosterone (RAA) axis, hypoaldosteronism (eg, primary adrenal insufficiency) would cause an elevated PRA, not a suppressed one as in this patient. In contrast, primary aldosteronism promotes negative feedback on the RAA axis, resulting in a low PRA level, making this the correct answer. Concomitant antihypertensive drug therapy is important to consider when interpreting the results of renin and aldosterone levels. Angiotensin-converting enzyme inhibitors (ACEIs) block conversion of angiotensin I to angiotensin II, which in turn decreases aldosterone levels. This inhibition actually causes elevated renin secretion through the RAA axis feedback. As a result, a low PRA level in a patient taking an ACEI or angiotensin II receptor blocker should increase clinical suspicion for primary aldosteronism, as in this case.[1] Restriction of dietary sodium results in increased aldosterone production via increased renin secretion. In pheochromocytoma, catecholamines are released that increase sympathetic neural tone and increase renin levels.

***3. Which one of the following is the most appropriate next test to confirm the diagnosis?***

***a.*** *Sodium-loading test with measurement of 24-hour urine aldosterone excretion*
***b.*** *Computed tomography (CT) of the adrenal glands*
***c.*** *Adrenal venous sampling (AVS)*
***d.*** *Blood pressure response to a trial of a mineralocorticoid antagonist*
***e.*** *Fine needle aspiration biopsy of the adrenal glands*

An increased PAC:PRA ratio alone is not diagnostic for primary aldosteronism. Primary aldosteronism must be confirmed by demonstrating inappropriate aldosterone secretion.[1] Confirmatory testing can be done by evaluating 24-hour urine aldosterone levels after a sodium load, making this the correct answer. This functions to maximally suppress intrinsic aldosterone secretion. Computed tomography of the adrenal glands is not a good confirmatory study because it does not provide information regarding the functional status of any potentially visualized abnormalities. Surgical removal of an adenoma, which has not been proven to be functional, would be premature, so this would not contribute to the patient's current management. Adrenal venous sampling is useful to distinguish between subtypes of primary aldosteronism but is only indicated after confirmatory blood testing is complete. Empirical treatment with a mineralocorticoid antagonist would be premature because some patients may benefit from surgical intervention. Fine needle aspiration biopsy of the adrenal glands has no role in the work-up of primary aldosteronism. Occasionally, fine needle aspiration biopsy is useful in the investigation of an adrenal mass suspected to be metastatic disease in the setting of a known malignancy. However, it has no role in an isolated adrenal mass work-up because cytology cannot distinguish a benign adrenal mass from adrenal carcinoma.

The patient was referred for a sodium-loading test with measurement of 24-hour urine aldosterone excretion. The patient consumed a 6000-mg sodium diet for 3 days. His 24-hour urine collection revealed the following results: urine volume, 3008 mL; creatinine concentration, 0.8 mg/dL (0.8-1.3 mg/dL); 24-hour urine sodium level, 343 mmol/24h (40-217 mmol/24h); sodium concentration, 114 mmol/L (135-145 mmol/L); and aldosterone, 17 µg/24h (<12 µg/24h if 24-hour urine sodium level is >200 mmol).

Because the urine aldosterone level was well above the 12 µg/24h cutoff, the diagnosis of primary aldosteronism, due to either adrenal adenoma or idiopathic adrenal hyperplasia, was entertained. Computed tomography of the abdomen with 3-mm cuts through the adrenal glands did not demonstrate adrenal masses.

***4. Which one of the following is the most appropriate next step in management?***

***a.*** *Radionuclide scintigraphy of the adrenal glands*
***b.*** *Magnetic resonance imaging (MRI) of the adrenal glands*
***c.*** *Follow-up CT of the adrenal glands in 6 months*
***d.*** *AVS*
***e.*** *Proceed directly to surgery*

Radionuclide scintigraphy with [$^{131}$I] iodocholesterol was formerly used to correlate adrenal function with visualized anatomic lesions to help clarify a target for possible surgical resection. However, this patient has no clear radiographic evidence of an adrenal adenoma. An MRI of the adrenal glands cannot rule out unilateral aldosterone-

producing disease and would not contribute any additional information for this patient. Although serial CT imaging, like MRI, may reveal a new adrenal lesion, nonfunctioning adrenal incidentalomas are relatively common in patients older than 40 years, and this would not provide any information regarding whether the lesion was hormonally functional. Moreover, aldosterone-producing adenomas can be very small, so CT imaging may not universally exclude this disorder. Adrenal venous sampling performed by an experienced interventional radiologist is the only means of detecting laterality of disease. Even though AVS is not available at all medical centers, it should be considered in all patients willing to pursue surgical management. If not initially pursued, it should be reconsidered in patients who either do not tolerate or do not benefit from medical management. Proceeding directly to adrenalectomy without prior AVS in this case would not be indicated because the disease could be bilateral.

Adrenal venous sampling was offered, but the patient did not wish to pursue surgical treatment. In the absence of an obvious adrenal carcinoma or adrenal adenoma, he was thought most likely to have the idiopathic bilateral hyperplasia subtype of primary aldosteronism.

***5. Which one of the following is the most appropriate empirical treatment option for this patient?***

***a.*** *Low-dose glucocorticoid*
***b.*** *Mineralocorticoid antagonist*
***c.*** *Triamterene*
***d.*** *More aggressive salt restriction*
***e.*** *Percutaneous radiofrequency ablation*

Low-dose glucocorticoid is only used as first-line therapy in the subtype of primary aldosteronism known as *glucocorticoid-remediable aldosteronism*, which is a very rare genetic condition that needs to be confirmed with specific genetic testing before initiating treatment. The best treatment option for this patient with bilateral disease is medical treatment with a mineralocorticoid receptor antagonist such as spironolactone or eplerenone. Triamterene is a potassium-sparing diuretic agent that also targets the distal renal tubule; however, unlike spironolactone and eplerenone, it is not an aldosterone antagonist and is therefore not the preferred agent. A low-salt diet is a reasonable recommendation for all patients with HTN but would not be sufficient for this patient. Percutaneous radiofrequency ablation is occasionally used to treat unilateral adrenal lesions but would clearly not be useful in this scenario.

The patient began a therapeutic trial of an aldosterone antagonist, eplerenone, at a dose of 50 mg by mouth twice daily. After 2 months of therapy, his valsartan and metoprolol doses were decreased by 50%, with systolic blood pressures maintained in the range of 135 to 145 mm Hg.

## DISCUSSION

Treatment-resistant HTN is defined as blood pressure that remains above goal despite the concurrent use of 3 antihypertensive agents of different classes. Ideally, 1 of the 3 agents should be a diuretic agent, and all agents should be prescribed at optimal doses.[2] The etiology of treatment-resistant HTN is often multifactorial. Successful treatment requires identification and reversal of lifestyle factors contributing to treatment resistance (ie, obesity, dietary salt intake, physical inactivity, lack of adherence to medication regimen) and use of effective multidrug regimens.

Once confounding factors have been ruled out, evaluation for potentially treatable secondary causes of HTN should be considered. Primary aldosteronism is considered the most common cause of secondary HTN and should be considered in patients with any of the following: (1) HTN and spontaneous hypokalemia (although most are normokalemic), (2) excessive hypokalemia with diuretic therapy, (3) young age of HTN onset (<20 years), (4) an adrenal incidentaloma with HTN, (5) treatment-resistant HTN, or (6) severe HTN (>160 mm Hg systolic or >100 mm Hg diastolic).[1,3] Evidence suggests that up to 13% of all patients with essential HTN have an element of primary aldosteronism, with a greater prevalence in those with more severe HTN.[1,3,4] This is an important condition to consider because patients with primary aldosteronism have been shown to have an increased risk of end-organ damage compared with those with HTN from other etiologies.[5]

As already discussed, the preliminary screening test for primary aldosteronism is an elevated PAC:PRA ratio (>20:1).[6] The PAC:PRA ratio is most sensitive when used in patients from whom samples are collected in the morning after they have been out of bed for at least 2 hours, usually after they have been seated for 5 to 15 minutes. Ideally, patients should have unrestricted dietary salt intake before testing. Agents that markedly affect the PAC:PRA ratio should be withdrawn for at least 4 weeks before testing and include the following: (1) spironolactone, eplerenone, amiloride, and triamterene; (2) potassium-wasting diuretic agents; and (3) products derived from licorice root.[6] Because ACEIs and angiotensin II receptor blockers may falsely elevate the PRA level through negative feedback of the RAA system, low or undetectable PRA levels in patients using these medications, as was seen in this case, should raise suspicion for primary aldosteronism. A diagnosis of primary aldosteronism is likely if the PAC:PRA ratio is 20 or greater and the PAC is greater than 15 ng/dL. Confirmatory testing is accomplished by 24-hour urine aldosterone excretion after a 3-day sodium load. It is important to ensure that patients successfully achieve a high-sodium diet (5000-6000 mg/d) and are not volume depleted

to ensure that their endogenous aldosterone production is maximally suppressed. The 24-hour urine collection should be performed from the morning of day 3 to the morning of day 4, and an aldosterone level greater than 12 μg makes primary aldosteronism highly likely.[6]

Although primary aldosteronism has many subtypes, the vast majority of cases are due to either bilateral idiopathic hyperplasia or an aldosterone-producing adenoma, which was the original syndrome reported by Conn.[7] Other causes of primary aldosteronism are quite rare. Treatment for primary aldosteronism hinges on whether the disease is unilateral (generally surgical) or bilateral (medical). As a result, in clinical practice the next investigation is often dedicated CT of the adrenal glands with and without contrast medium. However, a recent review demonstrated that the adrenal morphologic appearance on CT or MRI did not accurately identify the source of aldosterone excess in more than one-third of cases compared with AVS.[8] Therefore, in patients with a high probability of aldosterone-producing adenomas (more severe HTN, spontaneous or more severe hypokalemia, and high aldosterone levels) who are healthy enough for and would consider surgical treatment, AVS should be offered.

Laparoscopic adrenalectomy is the procedure of choice for unilateral adrenal disease, and in patients with aldosterone-producing adenoma, surgery almost universally results in improvement in blood pressure and normalization of potassium levels. About one-third of these patients can have normal blood pressures without additional antihypertensive therapy postoperatively.[9] The treatment for aldosterone-producing adrenocortical carcinoma is more extensive and is beyond the scope of this article. The first-line treatment for bilateral idiopathic hyperplasia is therapy with a mineralocorticoid receptor antagonist. Spironolactone has traditionally been the agent of choice and has the most evidence supporting its role in blood pressure control. However, because of its nonspecific binding to various steroid receptors, spironolactone has progesterone-like and antiandrogenic adverse effects that can cause gynecomastia, erectile dysfunction, and decreased libido in men and menstrual irregularity in women. Eplerenone, a newer, more selective mineralocorticoid antagonist, has significantly fewer interactions with both testosterone and progesterone receptors, resulting in an improved adverse effect profile compared with spironolactone.[10] A small prospective, randomized study that compared treatment with eplerenone vs spironolactone in patients with bilateral idiopathic hyperplasia concluded that eplerenone was as effective as spironolactone in reducing blood pressure and that the risk of mild hyperkalemia was similar with both medications.[11] Although better tolerated due to its more selective mineralocorticoid antagonism, eplerenone is more expensive, and no data are available on the long-term effects in patients with primary aldosteronism. Nonetheless, spironolactone is still considered the first-line agent for bilateral idiopathic hyperplasia. However, eplerenone can be considered, particularly in men, because of its limited adverse effects.[6]

In conclusion, primary aldosteronism is a common cause of secondary HTN. When the diagnosis is suspected, a screening PAC:PRA ratio should be obtained. If the PAC:PRA ratio is increased and the PAC is appropriately elevated, then confirmatory testing (24-hour urine aldosterone measurement after sodium loading) should be performed. Once the diagnosis of primary aldosteronism has been confirmed, CT imaging of the adrenal glands and possibly AVS are used to determine the subtype of primary aldosteronism. In general, unilateral disease is treated surgically, and bilateral disease is treated with mineralocorticoid receptor antagonists. Appropriate treatment typically results in improvement or resolution of hypertension.

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**Correct answers: 1. *c*, 2. *b*, 3. *a*, 4. *d*, 5. *b***