CME

Understanding resistant hypertension

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ABSTRACT

Resistant hypertension affects about 17% of the US population. However, it is difficult to diagnose because of multiple factors that influence adequate treatment of BP, including patient lifestyle and comorbidities, improper therapeutic regimens, and secondary mechanisms. Possible causes of resistant hypertension include nonmodulator hypertension, which affects patients who have an inappropriate response to elevated sodium through the renin-angiotensin-aldosterone system. Early identification and frequent follow-up can help patients achieve BP goals more rapidly and may reduce morbidity and mortality associated with complications of hypertension, including cerebrovascular accident, cardiovascular disease, and kidney disease.

Keywords: resistant hypertension, BP, risk factors, nonmodulators, cardiovascular disease, secondary hypertension

Learning objectives

- Define resistant hypertension and list its major risk factors and common secondary causes.
- Describe barriers to treatment, such as clinician resistance and patient resistance.
- Identify common and novel treatment options
- Understand the role of PAs in diagnosing and treating patients with resistant hypertension.

A 62-year-old obese White man with a longstanding history of hypertension, obstructive sleep apnea (OSA), and chronic low back pain presents with complaints of high home BP readings.

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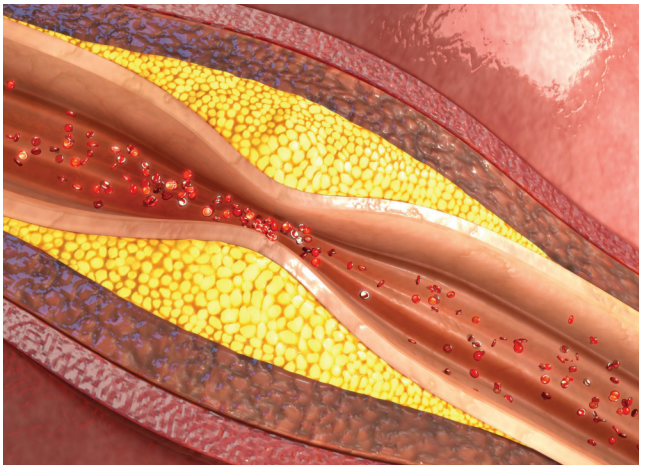

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The patient is on maximum tolerated doses of amlodipine, nebivolol, and hydrochlorothiazide. He states his systolic BP measured at home has been 160 to 170 mm Hg despite adhering to his medical regimen for the past 3 months. On presentation, his BP is 190/95 mm Hg in the right arm and 195/95 mm Hg in the left arm. His physical examination is benign and he has no evidence of end-organ damage. Ambulatory BP monitoring showed a mean reading of 175/90 mm Hg over 24 hours.

The patient was diagnosed with hypertension 20 years ago and has been on many medications for it over the years. He states that while on these medications, his BP was never well-controlled and his systolic BP remained above 150 mm Hg. The patient has attempted lifestyle modifications but he has not been able to remain consistent. He does not adhere to a low-sodium diet. He denies use of alcohol or illicit drugs. He has no significant cardiac family history. He has been evaluated by another clinician for secondary causes of hypertension and was found to have OSA and remains compliant with his continuous positive airway pressure therapy.

The patient was diagnosed with resistant hypertension and started on spironolactone. He was encouraged to comply with lifestyle modifications, including a low-sodium antihypertensive diet and incorporating physical activity into his routine. The patient was referred to a hypertension specialist and will have continued close follow-up to measure adherence to lifestyle modifications and effectiveness of medical therapy.

Key points

- Resistant hypertension is defined as hypertension above 130/80 mm Hg despite the use of three antihypertensive medications of different classes (one of which is a diuretic), or controlled hypertension with the use of four or more antihypertensive medications.
- Risk factors include nonmodulating hypertension, tobacco use, diabetes, physical inactivity, poor diet, hyperlipidemia, older age, and Black ethnicity.
- Secondary causes include obstructive sleep apnea, renal parenchymal disease, coarctation of the aorta, pheochromocytoma, primary aldosteronism, Cushing disease, thyroid disorder, and drugs.
- Treatment includes nonpharmacologic and pharmacologic options and renal denervation.

DEFINING RESISTANT HYPERTENSION

Guidelines from the American College of Cardiology (ACC) define resistant hypertension as BP above 130/80 mm Hg despite the use of three antihypertensive medications of different classes (one of which is a diuretic), or controlled hypertension with the use of four or more antihypertensive medications.[1] The American Heart Association (AHA) provides a similar definition that does not require the use of a diuretic.[2] This definition is new with stricter guidelines, because before 2017 most sources cited BP goals of below 140/90 mm Hg.[1,3] Based on previous goals, an estimated 13% of the adult US population and 10% of the global population had resistant hypertension.[1,4] Given new guidelines and the BP goal change to less than 130/80 mm Hg, new estimates are higher, estimating that 17% of the US population have resistant hypertension.[1]

Risk factors for hypertension and resistant hypertension include older age, male sex, diabetes, obesity, sedentary lifestyle, and Black ethnicity.[2] Additionally, to classify a patient as having resistant hypertension, clinicians should rule out patient resistance to therapy, pseudoresistance, clinician resistance to appropriate medication regimens, and secondary causes.[1,3] Previous data from the National Health and Nutrition Examination Survey (NHANES) demonstrate that over time, unlike hypertension, the prevalence of resistant hypertension has increased.[5] Patients with resistant hypertension tend to have poorer prognoses in terms of end-organ damage, including retinopathy, left ventricular (LV) hypertrophy, heart failure, myocardial infarction (MI), cerebrovascular accident (CVA), chronic kidney disease (CKD), and death.[3,4]

PATHOPHYSIOLOGY OF BP CONTROL

Long-term BP control is mainly a function of balancing oral fluid and electrolyte intake with urinary output in the kidneys. A key modulator of this balance is the renin-angiotensin-aldosterone system (RAAS), which when activated reduces urinary output so that blood volume and BP rise. Renin is synthesized by juxtaglomerular cells of the afferent arterioles and is triggered by four independent mechanisms:

- renal baroreceptors in the afferent arterioles that sense changes in renal perfusion pressure
- changes in delivery of sodium chloride to the distal tubules
- sympathetic nerve stimulation via beta$_1$ adrenergic receptors
- negative feedback by angiotensin II on juxtaglomerular cells.[6]

Renin then activates angiotensinogen into angiotensin I, an inactive peptide that is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is the major hormone involved and is a potent vasoconstrictor that can increase BP directly. Additionally, angiotensin II acts on the renal tubule to increase sodium and water reabsorption. Finally, angiotensin II acts on the adrenal cortex to stimulate aldosterone synthesis, which regulates sodium and potassium balance, resulting in sodium and water reabsorption in exchange for potassium excretion.[6] Increased sodium and water reabsorption is a major mechanism behind elevated BP, making angiotensin II's role in the RAAS system very important (**Figure 1**).

POTENTIAL PATHOPHYSIOLOGY

Reduced sodium delivery to the kidneys results in elevated BP via activation of the RAAS. Increased serum sodium is renally excreted with water, lowering blood volume and arterial pressure. The above mechanism is achieved by downregulating the RAAS system. However, there is evidence that a high-sodium diet is associated with elevated BP.[7] Patients with hypertension who are nonmodulators have an impaired ability to downregulate RAAS signaling in response to hypernatremia, rendering the kidneys unable to regulate against hypervolemia and hypertension. These patients accumulate twice as much sodium compared with patients with hypertension and the ability to modulate.[8] Nonmodulation is a nonmodifiable risk factor for resistant hypertension and is determined by multiple factors including race, genetics, age, and comorbidities such as obesity and diabetes.[7]

SIGNS AND SYMPTOMS

Not every patient is easily identified as having resistant hypertension and many may present as asymptomatic. However, even with an asymptomatic presentation, patients with resistant hypertension are at risk for developing hypertensive crises.[9]

Hypertensive urgency is a systolic BP greater than 180 mm Hg or a diastolic BP greater than 120 mm Hg without signs and symptoms of end-organ damage.[1] A *hypertensive emergency* meets this same criteria, but additionally, patients present with signs and symptoms of end-organ damage, such as severe retinopathy, acute kidney injury, acute coronary syndrome, or seizure.[1] The severity of the condi-

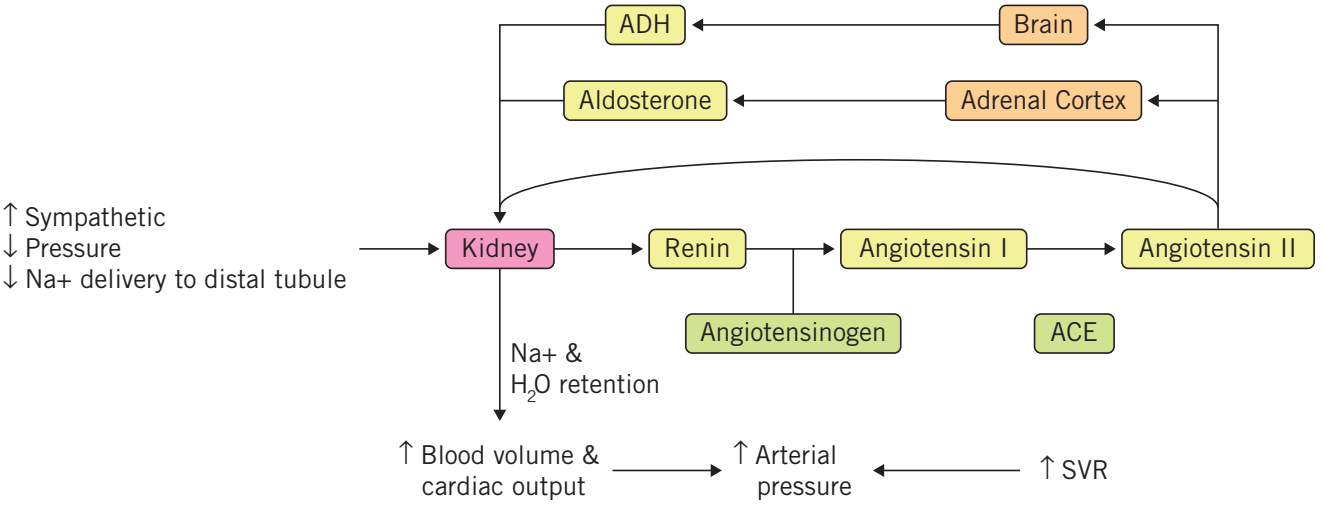

FIGURE 1. Normal BP regulation via the RAAS[6,7]

tions and the potentially life-threatening consequences support the need to properly identify resistant hypertension to prevent hypertensive crises.[10] Patients with resistant hypertension are 47% more likely than patients with hypertension to experience adverse clinical outcomes including CKD, CVA, heart disease, and death.[2,9]

DIAGNOSIS

The first step in diagnosing resistant hypertension is to accurately measure the patient's BP in a clinical setting. An estimated 33% of patients inappropriately referred for resistant hypertension had an inaccurate BP reading.[2] Recent guidelines from the AHA recommend use of automated oscillatory BP over manual auscultation for standardized measurements.[1] Standardized conditions should be implemented, including having the patient relaxed, seated in a chair with uncrossed legs and an empty urinary bladder; patients also should avoid caffeine, exercise, and smoking for 30 minutes before a BP measurement.[2] Measure BP in both arms unless contraindicated, and use the arm that yields the higher measurement for later readings. The patient should have at least two BP recordings on two separate occasions to confirm the level of hypertension. Ambulatory BP monitoring is considered the gold standard and may be used to assess patients with masked or white-coat hypertension; ambulatory monitoring also can determine the extent of nocturnal dippings, identify early morning surges, and estimate a patient's variability in BP.[3,10]

Aside from accurately determining a patient's BP, obtain baseline tests to assess the presence of end-organ disease, possible causes of secondary hypertension, cardiovascular risk factors, and baseline values to measure the effects of treatment. Tests include urinalysis; fasting blood glucose; A1C; lipid profile; complete blood cell count; serum electrolytes including sodium, potassium, and calcium; estimated glomerular filtration rate (GFR); thyroid-stimulating hormone; ECG; and optional echocardiogram.[1,11] Additionally, the AHA recommends performing a physical examination and assessment specific to target organ damage and secondary causes in patients with resistant hypertension.[2] Examples of examinations assessing end-organ damage include a fundoscopic examination, auscultating for bruits, and measuring BP in both arms.[2]

PATIENT AND PROVIDER RESISTANCE

The patient population that meets criteria for resistant hypertension is influenced by multiple factors. In the initial evaluation, consider factors such as diet and activity level, as well as other behaviors that affect BP. Excess dietary sodium or alcohol intake can contribute to a patient's resistance.[12,13] Patients who are non-modulators are unable to process increased sodium the same as normotensive or modulating patients, so increased dietary sodium contributes to their hypertension instead of achieving sodium and fluid balance through RAAS downregulation.[7,14] In addition, clinicians should explain patient factors that could influence pseudoresistance. Pseudoresistance is affected by how the BP is measured, white-coat hypertension, as well as medication adherence.[1] Pseudoresistant hypertension is defined as hypertension that is affected by how the patient's BP is measured, in addition to other factors interfering with the necessary treatment, such as white-coat hypertension and the patient's ability to adhere to prescribed medication.[1] Although pseudoresistance cannot be prevented, clinicians must be aware of potential factors that could contribute to resistance.

Also assess pharmacologic resistance. Many patients who require a multidrug regimen may have poor adherence.[13,15] They may fail to take all their medications because of adverse reactions, cost, or frequency of doses, thereby reducing the efficacy of the medications.[2] An indicator that may suggest nonadherence, and that may be beneficial to

assess during evaluation, is a resting heart rate greater than 80 beats/minute in a patient taking a beta-blocker or non-dihydropyridine calcium channel blocker.[1] Multiple tools can be used to assess medication adherence, including the Morisky Medication Adherence Scale and the Hill-Bone Compliance Scale.[2]

True drug resistance occurs when the patient is on the maximum tolerated doses of medication but does not meet the BP goal. Take BP measurements and assess for drug interactions with the patient's current medications.[2,13]

Another component to consider is clinician resistance: prescribing insufficient dosages, poor education in regard to medication adherence or lifestyle modifications, and inappropriate BP medication combinations.[1,13]

When considering an all-encompassing treatment approach for patients, remember the effects of patient adherence, optimal medications and/or dosages, as well as the white-coat effect and how this affects the diagnosis.[15]

SECONDARY HYPERTENSION

Secondary hypertension accounts for 5% to 10% of cases of resistant hypertension.[3,11] OSA, a common cause of secondary hypertension, is found in up to 70% of patients with resistant hypertension.[1-3,11] Other common causes of secondary hypertension include renal parenchymal disease, primary aldosteronism, and renal artery stenosis. In renal parenchymal disease, elevated serum creatinine and GFR are the best indicators for disease progression.[11,12] Primary aldosteronism causes an inappropriate aldosterone production in relation to serum sodium status, occurring in up to 20% of patients with resistant hypertension.[1,11] Renal artery stenosis is associated most commonly with atherosclerosis but also can present in younger patients with fibromuscular dysplasia.[11] Causes and diagnostics of secondary hypertension are summarized in **Table 1**.

Other factors that can cause resistant hypertension, and are pertinent to consider when obtaining a patient history, include general use of nonsteroidal anti-inflammatory drugs, oral contraceptives, corticosteroids, tricyclic antidepressants, monoamine oxidase inhibitors, and other substances such as caffeine, cocaine, amphetamines, and alcohol.[10,11,16] Psychosocial stressors, poor sleep quality or duration, loud noises such as traffic, cold temperatures, air pollutants, and high altitudes also can be linked to resistant hypertension.[2]

TREATMENT

Controlling resistant hypertension incorporates nonpharmacologic and pharmacologic therapy. A healthful diet, such as the Dietary Approaches to Stop Hypertension (DASH) diet, can reduce systolic BP up to 11 mm Hg.[1,3,10] The DASH diet includes foods low in saturated and trans fats; rich in potassium, calcium, magnesium, fiber, and protein; and low in sodium (**Table 2**).[17] DASH has been shown to have a synergistic effect with ACE inhibitors in lowering systolic BP.[18] Other lifestyle modifications include sodium restriction to less than 1,500 mg per day, increased dietary potassium of 3,500 to 5,000 mg per day (if not contraindicated by serum potassium levels), increased physical activity of 90 to 150 minutes per week, and reduction in alcohol consumption.[1,2,10] Weight loss of 1 kg can correlate to reducing systolic BP by 1 mm Hg.[1,2]

Low sodium intake is particularly important for patients who are nonmodulators.[7,14] A patient's daily sodium intake can be measured with 24-hour urine collection. Recommending a 25% decrease in sodium intake may result in lower BP and also enhance the efficacy of all antihypertensive medications.[1] Patients who drink alcohol are recommended to reduce intake to fewer than two drinks per day for men and less than one drink per day for women.[1,10] Referral to a registered dietitian/nutritionist as well as frequent follow-up with primary care providers can help patients achieve better adherence to these nonpharmacologic therapies.

Patients with resistant hypertension are on a combination of three or more antihypertensives at maximum tolerated doses. This should include an ACE inhibitor or angiotensin receptor blocker, a calcium channel blocker,

TABLE 1. Common secondary causes of hypertension, clinical findings, and appropriate diagnostics[1,10-12,16]

Secondary cause	Clinical presentations	Diagnostic testing
Coarctation of the aorta	Differing BPs in upper and lower extremities	CT angiogram
Cushing syndrome	Purple striae, buffalo hump, moon face, central adiposity	Dexamethasone suppression test
Pheochromocytoma	Headache, episodic palpitations, diaphoresis	24-hour urine metanephrine and normetanephrine test
Primary aldosteronism	Incidental finding	Plasma aldosterone: renin activity
Renovascular hypertension	Fibromuscular dysplasia, renal bruit	Doppler ultrasonography, MRI, CT angiogram
OSA	Increased neck circumference, obesity	Polysomnography
Hyperthyroidism	Heat intolerance, goiter, unintentional weight loss, diarrhea	Thyroid-stimulating hormone
Hyperparathyroidism	Abdominal pain, recurrent kidney stones, bone pain	Serum parathyroid hormone, serum calcium

and a long-acting thiazide diuretic.[1,3,12,16] Prescribe long-acting combination formulations when possible to reduce the number and frequency of medications. Data show a greater benefit with chlorthalidone compared with hydrochlorothiazide in patients with resistant hypertension.[1,12] Prescribe loop diuretics instead of thiazide diuretics in patients with GFR less than 30 mL/min, and especially in patients with fluid volume excess.[1,2] Monitor patients for potential adverse reactions to these medications, including hepatotoxicity, renal impairment, neutropenia, and hyperkalemia.

If a patient is at maximum tolerated doses of three or more medications, add a mineralocorticoid receptor antagonist such as spironolactone or eplerenone for increased antihypertensive benefit.[12,19] Counsel patients on adverse reactions to spironolactone that could cause medication nonadherence, such as gynecomastia, erectile dysfunction, and breast tenderness.[19]

If appropriate BP control is still not achieved, additional medications can be added to the regimen. Consider vasodilating beta-receptor antagonists such as labetalol, carvedilol, and nebivolol; centrally acting agents such as clonidine or guanfacine; and direct vasodilators, such as hydralazine or minoxidil.[1,12] Refer patients to a hypertension specialist or clinic, if available.[1,2,15] Close follow-up is important to ensure adherence and effectiveness of therapy.

Although lifestyle modifications and a strict medication regimen are the mainstays of treatment for patients with resistant hypertension, a novel approach—renal denervation—has been studied as an additional therapy and is pending FDA approval. Renal sympathetic nerves are denervated using catheter-based radiofrequency ablation or ultrasound ablation.[3,12,20] A recent meta-analysis reviewed data from six renal denervation clinical trials, which assessed the reduction in 24-hour ambulatory systolic and diastolic BP with renal denervation therapy versus sham therapy.[4,20] The studies took into account patients with essential hypertension as well as resistant hypertension. The research found a statistically significant reduction in ambulatory BP when patients were treated with renal denervation.[12] Because the study did not specifically focus on patients with resistant hypertension, denervation should not be offered as a sole therapy in achieving BP goals. However, it offers a potential new therapy with further data from clinical trials that may be used in future treatments for hypertension.

PHYSICIAN ASSISTANT ROLE

Physician assistants (PAs) can serve a vital role in identifying and treating patients with resistant hypertension. Clinics with a large number of patients who have resistant hypertension may benefit by adding a specialty clinic with a dedicated clinician.[2,21] These clinics use a team-based approach that emphasizes thorough and comprehensive management of hypertension and ensures that current treatment guidelines are met. A designated hypertension specialist can ensure close follow-up with optimal medical management, which may offer a solution in adequately managing resistant hypertension. In addition, PAs who see a high volume of patients with hypertension or resistant hypertension can obtain certification offered by the American Hypertension Specialist Certification Program (AHSCP).[2,21]

TABLE 2. DASH diet recommended daily servings based on a 2,000 daily calorie intake

Food group	Daily servings
Grains	6-8
Lean meats, poultry, fish	6 or fewer 1-oz servings
Vegetables	4-5
Fruits	4-5
Low-fat or fat-free dairy products	2-3
Fats and oils	2-3
Sodium	2,300 mg*
Nuts, seeds, dry beans, and peas	1 or fewer (4-5 servings per week)
Sweets	1 or fewer (5 or less servings per week)

*Daily intake of 1,500 mg of sodium or less lowers BP further than 2,300 mg[17]

CONCLUSION

Identifying patients with resistant hypertension requires a thorough investigation into secondary features including underlying pathologies, lifestyle management, and medication review. Early identification and proper treatment are critical to preventing secondary and often permanent damage due to uncontrolled hypertension. Clinical trials of renal denervation are in progress and the procedure is awaiting FDA approval as an adjunct treatment for resistant hypertension. A potential new area of research may involve the ability to identify patients who are nonmodulators and target therapies to them directly.[14] Improving access to healthcare, minimizing patient education gaps, referrals to hypertension specialists, and providing close follow-up will help ensure patients are well managed and may minimize the morbidity and mortality associated with resistant hypertension. PAs are uniquely positioned to step into these vital roles in our healthcare system. **JAAPA**

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