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Resistant hypertension: Diagnostic strategies and management

ABSTRACT

Blood pressure that remains above target levels despite drug therapy is an increasingly common problem. The evaluation of resistant hypertension includes confirming blood pressure measurements with an automated device that works without the clinician present and with 24-hour ambulatory monitoring; assessing for target-organ damage; and determining if kidney disease is present or if the hypertension is secondary to another condition. The goal of management should be to optimize drug therapy by using different classes of appropriate drugs.

KEY POINTS

Resistant hypertension is arbitrarily divided into two categories: apparent resistance (pseudoresistant hypertension) and true resistance. Apparent resistance is much more common.

Common causes of true resistant hypertension are volume overload, excessive alcohol use, some drugs (eg, nonsteroidal anti-inflammatory drugs), and some over-the-counter supplements.

Volume overload commonly results from excess sodium intake, kidney disease, or a counterregulatory response to arterial vasodilation.

To address volume overload, an appropriate diuretic at an adequate dosage is a cornerstone of therapy, along with potassium supplementation.

Hospitalization may be needed to monitor drug intake if poor compliance is suspected.

Medical Grand Rounds articles are based on edited transcripts from Medicine Grand Rounds presentations at Cleveland Clinic. They are approved by the author but are not peer-reviewed.

doi:10.3949/ccjm.80gr.12005

Poor control of blood pressure is one of the most common risk factors for death worldwide, responsible for 62% of cases of cerebral vascular disease and 49% of cases of ischemic heart disease as well as 7.1 million deaths annually. As our population ages and the prevalence of obesity, diabetes, and chronic kidney disease increases, resistant hypertension will be seen more often in general practice.

Using a case study, this article will provide a strategy for diagnosing and treating resistant hypertension.

CASE: A WOMAN WITH LONG-STANDING HIGH BLOOD PRESSURE

A 37-year-old woman was referred for help with managing difficult-to-control hypertension. She had been diagnosed with hypertension at age 32, and it was well controlled until about 2 years ago. Various combinations of antihypertensive drugs had been tried, and a search for a cause of secondary hypertension revealed no clues.

On examination, her blood pressure averaged 212/124 mm Hg, and her heart rate was 109 beats per minute. Her medications were:

- Amlodipine (Norvasc), a calcium channel blocker, 10 mg once daily
- Valsartan (Diovan), an angiotensin II receptor antagonist, 160 mg once daily
- Carvedilol (Coreg), a beta-blocker, 25 mg twice daily
- Labetalol (Normodyne), a beta-blocker, 400 mg three times daily
- Clonidine (Catapres), a sympatholytic agent, 0.05 mg three times daily
- Doxazosin (Cardura), a peripheral alpha-blocker, 16 mg once daily

- Xylometazoline (Xylomet), an alpha agonist nasal spray for nasal congestion.

She had previously been taking spironolactone (Aldactone), hydralazine (Apresoline), and hydrochlorothiazide, but they were discontinued because of adverse effects.

Does this patient have resistant hypertension? How should her condition be managed?

RESISTANT HYPERTENSION DEFINED

The seventh Joint National Committee and the American Heart Association define resistant hypertension as an office blood pressure above the appropriate goal of therapy (< 140/90 mm Hg for most patients, and < 130/80 mm Hg for those with ischemic heart disease, diabetes, or renal insufficiency) despite the use of three or more antihypertensive drugs from different classes at full dosages, one of which is a diuretic.[1,2]

In this definition, the number of antihypertensive drugs required is arbitrary. More importantly, the concept of resistant hypertension is focused on identifying patients who may have a reversible cause of hypertension, as well as those who could benefit from special diagnostic or therapeutic intervention because of persistently high blood pressure.

This definition does not apply to patients who have recently been diagnosed with hypertension.

Resistant hypertension is not synonymous with uncontrolled hypertension

Resistant hypertension is not synonymous with uncontrolled hypertension, which includes all cases of hypertension that is not optimally controlled despite treatment, including apparent resistance (ie, pseudoresistance) and true resistance (defined below).

COMMON, BUT ITS PREVALENCE IS HARD TO PINPOINT

The prevalence of resistant hypertension is unknown because of inadequate sample sizes in published studies. However, it is common and is likely to become more common with the aging of the population and with the increasing prevalence of obesity, diabetes mellitus, and chronic kidney disease.

In small studies, the prevalence of resistance in hypertensive patients ranged from 5% in general medical practice to more than 50% in nephrology clinics. In the National Health and Nutrition Examination Survey in 2003 to 2004, only 58% of people being treated for hypertension had achieved blood pressure levels lower than 140/90 mm Hg,[3] and the control rate in those with diabetes mellitus or chronic kidney disease was less than 40%.[4]

Isolated systolic hypertension—elevated systolic pressure with normal diastolic pressure—increases in prevalence with age in those with treated, uncontrolled hypertension. It accounted for 29.1% of cases of treated, uncontrolled hypertension in patients ages 25 to 44, 66.1% of cases in patients ages 45 to 64, and 87.6% of cases in patients age 65 and older.[5]

Even in clinical trials, in which one would expect excellent control of hypertension, rates of control ranged from 45% to 82%.[6–10]

APPARENT RESISTANCE VS TRUE RESISTANCE

Resistant hypertension can be divided arbitrarily into two broad categories: apparent resistance and true resistance, with the prevalence of apparent resistance being considerably higher. Each broad category has a long list of possible causes; most are readily identifiable in the course of a thorough history and physical examination and routine laboratory testing. If resistance to therapy persists, referral to a hypertension specialist is a logical next step.

Detecting pseudoresistance

Causes of apparent resistance include improper technique in measuring blood pressure, such as not having the patient rest before measurement, allowing the patient to have coffee or to smoke just before measurement, or not positioning the patient's arm at the level of the heart during measurement.

Many elderly patients have calcified arteries that are hard to compress, leading to erroneously high systolic blood pressure measurements, a situation called pseudohypertension and a cause of pseudoresistance. The only way to measure blood pressure accurately in such cases is intra-arterially. These patients often do not have target-organ disease, which would be expected with high systolic pressure.

The white-coat phenomenon is another

common cause of apparent resistance. It is defined as persistently elevated clinic or office blood pressure (> 140/90 mm Hg), together with normal daytime ambulatory blood pressure (the "white-coat effect" is the difference between those blood pressures).

Finally, poor patient adherence to treatment is estimated to account for 40% of cases of resistant hypertension.[4,5,11] Poor adherence is difficult to prove because patients often claim they are compliant, but certain clues are indicative. For example, patients taking a diuretic should have increased uric acid levels, so normal uric acid levels in a patient on a diuretic could be a clue that he or she is not taking the medication. If poor adherence is suspected, patients should be admitted to the hospital to take the medications under close observation.

Many factors can contribute to true resistance

Many cases of resistant hypertension are drug-induced, particularly in patients taking a nonsteroidal anti-inflammatory drug or a cyclooxygenase II inhibitor. Use of ginseng, ma huang, and bitter lemon should also be suspected. Drugs or herbal preparations contributing to high blood pressure should be discontinued or minimized.

Alcohol intake in excess of two drinks (1 oz of alcohol) per day for men and half that amount for women can also contribute to hypertension.

Volume overload is common and has many causes, including a compensatory response to vasodilators, excessive salt intake, or an undetected reduction in the glomerular filtration rate causing retention of salt and water.

Drug considerations

A common cause of apparent resistant hypertension is physicians not following blood pressure treatment guidelines by not increasing the dosage when needed or by prescribing inappropriate drug combinations.

We commonly see furosemide (Lasix) being misused, ie, being prescribed once daily for hypertension. (It has a shorter duration of action than thiazide diuretics, the usual class of diuretics used for hypertension.)

For a patient who is already on many medications but whose hypertension is not responding, the first step should be to give a diuretic of an appropriate class in an appropriate dosage.

Diuretics are often inappropriately stopped if a patient develops hypokalemia. Potassium supplementation should always be an adjunct to diuretic therapy. Potassium itself is a potent vasodilator and, given as a supplement, has been shown to reduce stroke risk in rats.

The combination of an angiotensin receptor blocker and an angiotensin-converting enzyme inhibitor should not be used for patients with true resistant hypertension. The direct renin inhibitor aliskiren (Tekturna) should not be used in combination with these drugs, and the combination of aliskiren and valsartan (Valturna) has now been taken off the market.

Spironolactone (Aldactone) is sometimes used for resistant hypertension in the belief that in some cases primary aldosteronism is the underlying cause. A study in 1,400 participants confirms that it lowers blood pressure,[9] but the reason is unclear: the blood pressure response was unrelated to levels of renin, angiotensin, or the plasma aldosterone-to-renin ratio.

Identify secondary causes of hypertension

Poor patient adherence is hard to prove, but certain clues point to it

Patients should be evaluated for kidney disease, which is the most common secondary medical reason for resistant hypertension. For patients with poor renal function (estimated glomerular filtration rate < 50 mL/minute), hydrochlorothiazide is not effective against hypertension, but chlorthalidone is. In addition, patients with poor renal function should be given loop diuretics such as furosemide two or three times daily, or the long-acting drug torsemide (Demadex) should be used instead.

Genetic variation can cause different rates of metabolism of drugs, contributing to resistant hypertension. Certain people metabolize hydralazine very fast, making it less effective. The same is true for some beta-blockers.

Obesity and diabetes can also contribute to resistant hypertension.

Ancillary neurohumoral studies are occasionally indicated to rule out identifiable causes of secondary hypertension that may be correctable. There are many identifiable causes of hypertension, but detailing each is beyond the scope of this article.

TABLE 1

Step-by-step guide for evaluating and managing patients with resistant hypertension

Exclude factors that cause apparent resistance

Measure office blood pressure properly

Exclude:
- White-coat effect
- Pseudohypertension (in the elderly due to calcified arteries)

Evaluate patient's adherence to therapeutic regimen

Identify any target-organ involvement

Identify and reverse factors contributing to true resistance

Discontinue or minimize the use of any pharmacologic agents that may increase blood pressure

Identify any lifestyle factors:
- Alcohol intake
- Salt intake (limit daily intake to < 100 nmol/L or 2.4 g Na or 6 g NaCl)
- Physical inactivity

Evaluate for the presence of kidney disease

Obtain a neurohumoral and hemodynamic profile as guide to therapy

Perform a thorough search for secondary hypertension as indicated

Pharmacologic principles

Suboptimal dosing regimens or inappropriate antihypertensive drug combinations are most common causes of true resistant hypertension

As volume expansion is a frequent pathogenic finding in these patients, an appropriate diuretic to decrease volume overload remains a cornerstone of therapy

Dual renin-angiotensin system blockade is not recommended for patients with true resistant hypertension

Ultimately, patient characteristics (age, pathogenetic mechanisms involved, and concomitant disease) will determine the best combination of agents needed to achieve the blood pressure goal

Refer to a hypertension specialist if not controlled on more than three optimal medications

Patients should be tested for thyroid disease. Hypothyroidism can cause high blood pressure, although usually diastolic rather than systolic hypertension. Hyperthyroidism can cause marked systolic hypertension.

TABLE 1 provides a step-by-step guide for evaluating and managing patients with resistant hypertension.

EXPERIMENTAL DRUG THERAPY

Endothelin receptor antagonists are currently under investigation for the treatment of resistant hypertension. The protein endothelin-1 (ET-1) is a potent vasoconstrictor (30–50 times more potent than angiotensin II and norepinephrine) and has a long duration of action. ET-1 binds to two receptors with opposing effects: ET-A promotes vasoconstriction, and ET-B promotes vasodilation and clears ET-1.

Darusentan, a selective blocker of ET-A, was tested in the phase III DORADO trial, which was discontinued because the initial results did not meet primary outcome measures. Initial findings had indicated that it might not be as useful as hoped. Side effects included headache, flushing, and edema.

EXPERIMENTAL NONPHARMACOLOGIC THERAPIES

Electrical stimulation of carotid sinus baroreceptors is being tried under the assumption that a high sympathoexcitatory state contributes to resistant hypertension. Devices are placed around the carotid artery bifurcation, and stimulation is believed to increase the depressor influences that modulate blood pressure. Large-scale trials are under way, but it is too early to tell if the approach will be useful. Patients complain of neck pain from the device.

Renal denervation is another experimental approach.[12] The kidney has a central role in blood pressure regulation: efferent nerves regulate renal vascular resistance, renal blood flow, and renin release from the juxtaglomerular apparatus; afferent nerves modulate sympathetic output from the central nervous system. The results of the Renal Denervation in Patients With Uncontrolled Hypertension (Symplicity HTN) trials 1 and 2 have been encouraging. The Symplicity HTN-3 trial will begin soon in the United States.

OUR PATIENT UNDERGOES ADDITIONAL STUDIES

To rule out the white-coat effect in our patient, we measured her blood pressure with an automated device that takes several readings without the clinician in the room. (This topic has

been reviewed by Vidt et al in this journal[13]). The average of the automated readings was 183/113 mm Hg, and her average pulse was 109 beats per minute, arguing against a white-coat effect.

Her blood pressure was also markedly elevated (average 198/129) during 24-hour ambulatory blood pressure monitoring.

Findings on physical examination were unremarkable except for grade III hypertensive retinopathy. She had no carotid or abdominal bruits. Her peripheral pulses were strong and synchronous bilaterally.

Laboratory testing found the patient had normal serum electrolyte levels and good renal function but relatively low urinary sodium, 90 mmol/day (normal 40–220), and very low renin activity, 0.7 µg/L/h (normal upright 0.8–5.8 µg/L/h, supine 0.5–1.8 µg/L/h), calling into question the wisdom of treatment with an angiotensin receptor blocker.

Hemodynamic studies were performed using impedance cardiography and found very high systemic vascular resistance with normal cardiac output, indicating that the patient had a high preload, which could be from hypervolemia or intense venous constriction. It is especially interesting that her vascular resistance was high despite her treatment regimen that included an angiotensin receptor blocker and a vasodilator, perhaps an indication of nonadherence with her medications.

Diuresis reduces her blood pressure

The patient was admitted to the hospital, and because her laboratory results indicated that plasma renin activity was suppressed, the angiotensin receptor blocker valsartan was discontinued.

On day 1, her weight was 162 lb and average blood pressure was 194/128 mm Hg. After 4 days of diuresis with escalating doses of furosemide, her weight was 153 lb and blood pressures ranged from 140 to 158 over 82 to 98 mm Hg. Her heart rate was 90 beats per minute. The hospital stay showed that volume overload was one of the factors maintaining her hypertension. She was discharged on metoprolol succinate (Toprol-XL) 100 mg twice daily and furosemide 80 mg twice daily.

Her blood pressure fluctuates widely after discharge

Over the next 5 days after discharge, the patient's blood pressure rose steadily to 180/122 mm Hg, her heart rate was in excess of 100 beats per minute, and her weight increased to 158 lb. Blood screening found that the level of metoprolol was undetectable, and a diuretic screen showed no furosemide in the urine. Both the patient and her husband were adamant that she was taking her medications.

Hydrochlorothiazide 25 mg daily was added, and nadolol (Corgard) 80 mg once daily was started in place of metoprolol. On a return visit, her blood pressure and heart rate were finally good at 138/86 mm Hg and 60 beats per minute (sitting) and 134/92 and 63 (standing).

On 24-hour monitoring, some fluctuations of elevated blood pressure were still evident, with an average of 142/91 mm Hg, so nifedipine (Procardia) 60 mg daily was added.

Her final list of medications is hydrochlorothiazide 25 mg, nadolol 80 mg, and nifedipine XL 60 mg, all taken once daily.

Volume overload complicated by nonadherence

In summary, the main pathogenetic mechanism that sustained this patient's hypertension was volume overload. Her urinary sodium level indicated that she was not taking excessive amounts of sodium. The volume overload may have been a compensatory response to the concomitant use of peripheral vasodilators plus sympatholytic agents.

In addition, she was not adherent to her antihypertensive regimen. The fact that her heart rate was 109 beats per minute despite having a drug regimen that included five sympathetic blocking agents was a strong clue. She eventually admitted that she did not like taking diuretics because they made her skin wrinkle.

In general, in a case like this, I try to minimize the number of drugs and give a diuretic as well as different classes of appropriate drugs. ■

Diuretics are often inappropriately stopped if a patient develops hypokalemia

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