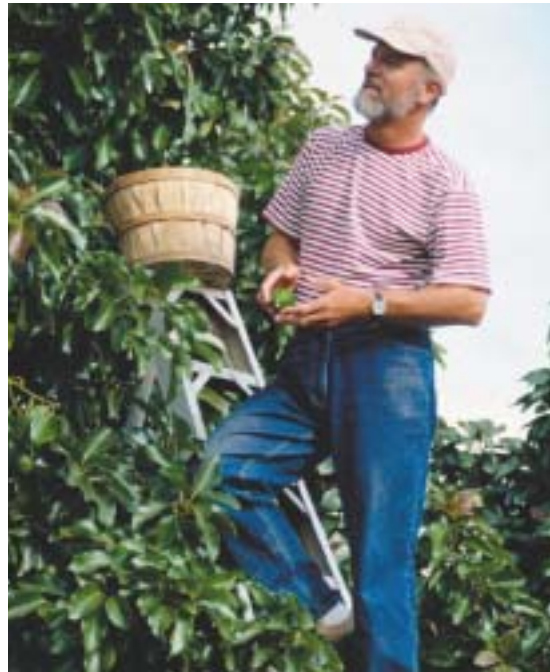

“Resistant” hypertension: Following the clues



By Richard Ogilvie, MD, FRCPC, FACP

CASE

JM, a 50-year-old male non-smoker returns to my office after an interval of 18 months. His blood pressure (BP) had been labile and borderline in the past, but now measures 160/95 mmHg on repeated determinations over six weeks.

He weighs 85 kg with a body mass index of 28, claims to be physically active and has a normal physical exam and laboratory investigations, including serum electrolytes, creatinine, sensitive thyrotropin (sTSH), lipids, urinalysis and electrocardiography (ECG).

I had initiated hydrochlorothiazide 25 mg/day without modifying his BP, and added ramipril 10 mg/day. Four months after starting drug treatment, his BP has changed little and I am considering the addition of a third drug, amlodipine.

Is this a case of “resistant” hypertension?

Resistant Hypertension

Determining “resistant” hypertension

Commonly, the label of “resistant” hypertension is applied when three drugs are being used without adequate control. It is useful to consider steps to rule out the causes of therapy failure. This exercise is part of the ongoing care you should consider before you reach the point of adding a third antihypertensive agent.

Drugs: Is the patient truly compliant? Is he or she using other medications that could interfere with the antihypertensive treatment, such as nonsteroidal anti-inflammatory drugs (NSAIDs)? Does the patient binge-drink alcohol over the weekend and then visit you on Monday afternoon?

Diet: Does the patient abuse salt? Asking for a 24-hour urine collection for volume, sodium (ideal 100 mmol/day), potassium, creatinine and protein is a useful way of discovering individuals who use excessive sodium in their diet. Have you ever looked at the sodium content of mineral water that your patient ingests? Can you persuade him or her to lose 4 kg and reduce waist size by one inch?

This particular patient has a normal blood sugar and lipid pattern. Sometimes the use of a statin in hypercholesterolemic patients, or the use of metformin in diabetic patients, can improve BP control without further modification of antihyper-



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Asthma is
a variable
disease.



Resistant Hypertension

First Steps to Consider:

Here are the first steps to consider when determining whether the patient has resistant hypertension:

1. **Drugs:** Is the patient truly compliant?
2. **Diet:** Does the patient abuse salt?
3. **Activity:** Is the patient active?
4. **Wrong cuff size:** Is a proper size used?
5. **Reactivity:** Is the patient properly instructed?

tensive drugs or doses. Endothelial dysfunction probably modulates the BP-lowering effect of most drugs.

Activity: I am repeatedly surprised at how converting sloth into activity results in improved BP control. A minimum

of 30 minutes of brisk walking per day is required. Although this might not induce a large weight loss, this activity is absolutely necessary to maintain any weight loss that has been achieved by dietary modifications.

Wrong Cuff Size: Every office should have a small, large and a thigh cuff to fit adult arms that are either too small or too large for standard-sized cuffs. Frequently patients with “resistant” hypertension have normotension when a proper cuff size is used.

Reactivity: About 25% of individuals have a reaction to cuff inflation, resulting in higher BP readings when done in your office. As a result, you cannot use office BP values as a guide to therapy. Ambulatory BP monitoring is the best method to document BP and to guide treatment. Sometimes self-determined BP readings can be substituted. The patient will have to be taught the right technique and the cuff to be used should be calibrated in your office. I instruct my patients to take their BP after sitting for five minutes.

Three BP determinations should be recorded in a row. It is best to do this in the morning when waking up and in the evening upon return from work for three consecutive days. Usually the third determination and the third day will have the lowest values, as the reactivity is modulated, similar to the progression of values during ambulatory monitoring. A normal, self-determined BP value is a systolic pressure below 135 mmHg and a diastolic pressure below 83 mmHg.

Resistant Hypertension

Persistent Blood Pressure Elevation

If the BP is still elevated after consideration of the five preceding steps, I begin other investigations to rule out secondary causes of hypertension, such as renal artery stenosis, primary aldosteronism, pheochromocytoma, and sleep apnea.

Other Steps to Consider:

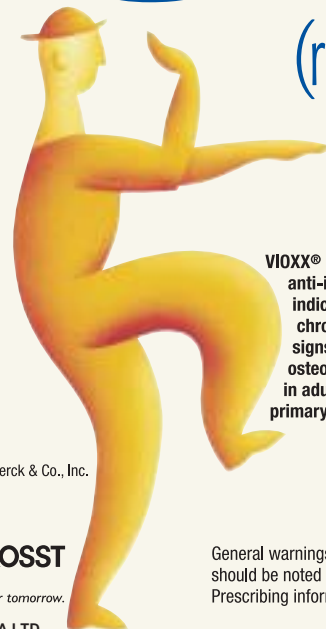
Here are other investigations to rule out secondary causes of hypertension:

1. **Renal artery stenosis**
2. **Primary aldosteronism**
3. **Pheochromocytoma**
4. **Sleep apnea**

Renal Artery Stenosis: Clues, such as the abrupt onset or rapid progression of hypertension, an epigastric bruit, a history of smoking or atherosclerotic vascular disease (i.e., carotids or iliofemoral) or severe dyslipidemia, or a rise in serum creatinine with use of an ACE inhibitor (ACEI), are absent in this patient. I probably would not order a differential renal scan and flow while on the ACEI until the addition of a third drug, amlodipine, had failed. If the scan and flow are positive, a volumetric computed tomography (CT) renal angiogram or, for diabetics, a magnetic resonance renal angiogram, would complete the investigation.

Primary Aldosteronism: This patient was normokalemic before starting hydrochlorothiazide. His serum potassium was normal, but slightly reduced to 3.6 mmol/L on the drug. His level returned to 4.0 mmol/L when ramipril was added. He did not complain of muscle aches, cramps or excessive fatigue. He did not eat licorice. Spontaneous

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hypokalemia, in the absence of diuretic therapy, would be a stronger clue. There are, however, reports of normokalemic primary aldosteronism.

The 24-hour urine collection I had ordered previously contained less than 100 mmol of potassium — a value that is often exceeded with the syndrome. The best screening test is a plasma renin activity and serum aldosterone while on the ACEI or two hours after a single dose of captopril 25 mg.

Failure of the plasma renin activity to increase from a suppressed low value, plus failure of the serum aldosterone to be suppressed below 350 pmol/L, should prompt additional investigation. I usually order a CT examination of the adrenal glands looking for an adenoma, however, magnetic resonance imaging (MRI) provides better resolution of small adenomas.

I then order differential adrenal vein sampling for serum aldosterone and cortisol to document the function of the adenoma. Meanwhile I hold back on treatment with drugs modifying aldosterone, such as spironolactone, ACEIs or angiotensin receptor blockers (ARBs) for 48 hours, then restart the treatment immediately after the sampling. Calcium blockers, thiazide diuretics or alpha and beta blockers can be continued, if necessary, for BP control.

Pheochromocytoma: The commonly reported clues of episodic hypertension (associated symptoms of headaches, sweating, flushing or pallor, gut upset or weight loss) need not be present and persistently elevated BP can be present. The diagnosis of pheochromocytoma is less common than primary aldosteronism.

I usually wait until the patient fails the third drug therapy before obtaining a 24-hour urine for volume, metanephrines, total catecholamines and creatinine. The collection bottle must contain acid before the collection is started. Creatinine must be determined to assess the ratio of metanephrines to creatinine content. The hormone to creatinine ratio is used for diagnosis as it does not rely upon a threshold amount of the hormone in the urine collection. It is more reliable than trying to determine if the patient collected urine for 15 hours or 30 hours which could modify the total amount of the hormone reported by the lab. A vanillylmandelic acid (VMA) determination is not useful.

Sleep Apnea: There are several reports of improved blood pressure response after the initiation of nasal continuous positive airway pressure (CPAP) therapy in hypertensive individuals with sleep apnea. Often these subjects are overweight with a large neck size, have a history of snoring and respiratory pauses

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at night. These individuals also complain of excessive daytime sleepiness or nocturnal awakening with choking or sweating. I include questions about these symptoms in my initial workup of hypertensive patients and repeat them in all subjects who fail to respond to three antihypertensive drugs.

What happened with this patient?

None of these steps or investigations was fruitful in following this patient. I had to prescribe full doses of the three drugs, hydrochlorothiazide, ramipril and amlodipine, along with dietary and activity measures, before target BP was achieved. Do you have other suggestions to help me treat this patient? [Dx](#)

Good luck with your “resistant” hypertensives. They can be a frustrating challenge!



One depression
can lead to another.