

Treatment-Resistant Hypertension among Older Adults

Fatemeh Akbarian, MD, Dermatologist, Clinical Research Fellow, University of Toronto, Toronto, ON.

Vahid Ghafarian, MD, MPH, BSc.PT, Physiotherapist, Northpark Physiotherapy and Annex Retirement Residence, Toronto, ON.

Mohammad Ali Shafiee, MD, FRCPC, General Internist, Nephrologist, Department of Medicine, Toronto General Hospital, University Health Network; Clinician Teacher, University of Toronto, Toronto, ON.

Treatment-resistant hypertension (TRHTN) is a common challenge in geriatric practice and a significant cause of mortality and morbidity among older adults. In this overview, we will use a case-based approach to define the magnitude of the problem, identify characteristics of individuals with TRHTN, and explore the causes of uncontrolled hypertension including technical issues, patient-related and physician-related factors, and secondary causes of hypertension. We will then provide a simple approach to the problem, illustrating straightforward diagnostic workup and therapeutic options. In our approach most of the emphasis has been given to detailed history-taking and a targeted physical examination.

Key words: resistant hypertension, hyperaldosteronism, obstructive sleep apnea, older adults

Case

You are following a 68-year-old man with a few years history of hypertension that has been resistant to significant doses of angiotensin converting enzyme inhibitor (ACEI), beta-blocker, and thiazide diuretic medications. He is also overweight (BMI of 31), and complains of restless sleep. He is otherwise healthy and does not smoke or drink alcohol. His systolic and diastolic blood pressures range from 156 to 170 mmHg and 92 to 96 mmHg, respectively, and his pulse rate is 63 beats per minute. His physical examination, including ocular fundi and cardiovascular examinations, is normal. His serum electrolytes and creatinine levels are within normal limits, with no microalbuminuria. His 2D echo showed only mild left ventricular (LV) hypertrophy with normal LV function. What would be the proper approach to this patient for further assessment and management?

Introduction

Arterial hypertension is a leading risk for morbidity and mortality in Canada^{1,2} as well as the most frequent reason for a visit to the physician's office.³ Older adult populations have a higher prevalence of hypertension—over half of older Canadians have hypertension—and they are at greater risk for cardiovascular morbidity and mortality from it. However, they also have a greater reduction in cardiovascular risk with treatment than younger persons.^{2,3}

Definition

Treatment-resistant hypertension (TRHTN) is defined by a blood pressure higher than 140/90 mmHg, or higher than 130/80 mmHg among persons with diabetes or renal disease (urinary protein excretion > 300 mg/day or serum creatinine level > 133 µmol/L), despite adherence to appropriate treatments with full doses of at least three antihypertensive medications, including a diuretic.⁴

Prevalence

Although the exact prevalence of TRHTN is unknown, it is likely that this condition will become increasingly common, driven by an aging population, obesity, nonadherence trends, and effects of target-organ disease.⁵ The estimated incidence of true TRHTN from the entire cohort of the Anti-

GREAT NEWS! If you are a practicing Canadian physician, you can now access G&A's online, accredited CME program, and our archive of over 1,400 articles, by simply registering online! To access this month's FREE CME course, co-sponsored by the *Canadian Geriatrics Society* and the *University of Toronto*, complete the registration process by entering your unique **self-registration code** at

www.geriatricsandaging.ca/sr

Visit www.geriatricsandaging.ca/cme for our full list of courses and accreditation details.

hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALL-HAT)^{4,8} is approximately 15% of the hypertensive population.⁹ However, observations suggest that blood-pressure goals may be difficult to achieve in as many as 40% of patients.^{6,7}

Patient Characteristics

Treatment-resistant hypertension is associated with several characteristics that predispose patients to difficulty in achieving blood pressure (BP) goals. These features include obesity, diabetes, chronic kidney disease, and being of the

black race or female sex. Rates of TRHTN are also higher among individuals with target-organ damage, including left ventricular hypertrophy and renal disease.^{10,11} Resistant or difficult-to-control systolic hypertension is more common among persons over the age of

Table 1: Causes of Treatment-Resistant Hypertension	
Incorrect clinical diagnosis & technical issues	Pseudohypertension among older adults White-coat hypertension or office hypertension Measurement artifacts
Patient-related factors including;	
Dietary	Excessive sodium intake, excessive alcohol intake Licorice, ginger, bayberry
Lifestyle issues	Obesity, sedentary lifestyle, smoking Metabolic syndrome and insulin resistance
Medication-related issues	Nonadherence, psychiatric causes
Drug actions and interactions	Glucocorticoids, mineralocorticoids, NSAIDs*, COX-2 inhibitors, anorectics, appetite suppressants (e.g., sibutramine) Cyclosporin, erythropoietin, growth hormone Tricyclic antidepressants, MAOIs**, phenothiazines, tyramine and chemotherapeutic agents
Drugs that prevent absorption of antihypertensive medications	Cholestyramine (questran) (decreases absorption of diuretics) Rifampin (increases clearance of propranolol)
Over-the-counter drug interactions	Anabolic steroids, birth control pills Sympathomimetic amines, decongestants and diet pills
Herbal medications	Aniseed, St. Johns wort, cola alkaloids, ma huang (ephedra) Capsicum, blue cohosh, vervain, agnus cactus, pau de arco, Calamus amines, broom alkaloids, ginseng, guarana, coltsfoot
Substance interference	Nicotine, caffeine, amphetamines
Physician-related issues (almost half of the cases)	Inadequate patient education, inappropriate combinations Inadequate diuretic therapy, suboptimal medication regimen
Secondary causes of hypertension or concomitant conditions	Obstructive sleep apnea Hyperaldosteronism Renovascular, renal parenchymal Pheochromocytoma
*NSAID = nonsteroidal anti-inflammatory agents; COX-2 = cyclooxygenase 2; **MAOIs = monoamine oxidase inhibitors.	
Source: Adapted from Chobanian AV et al., 2003. ²⁴	

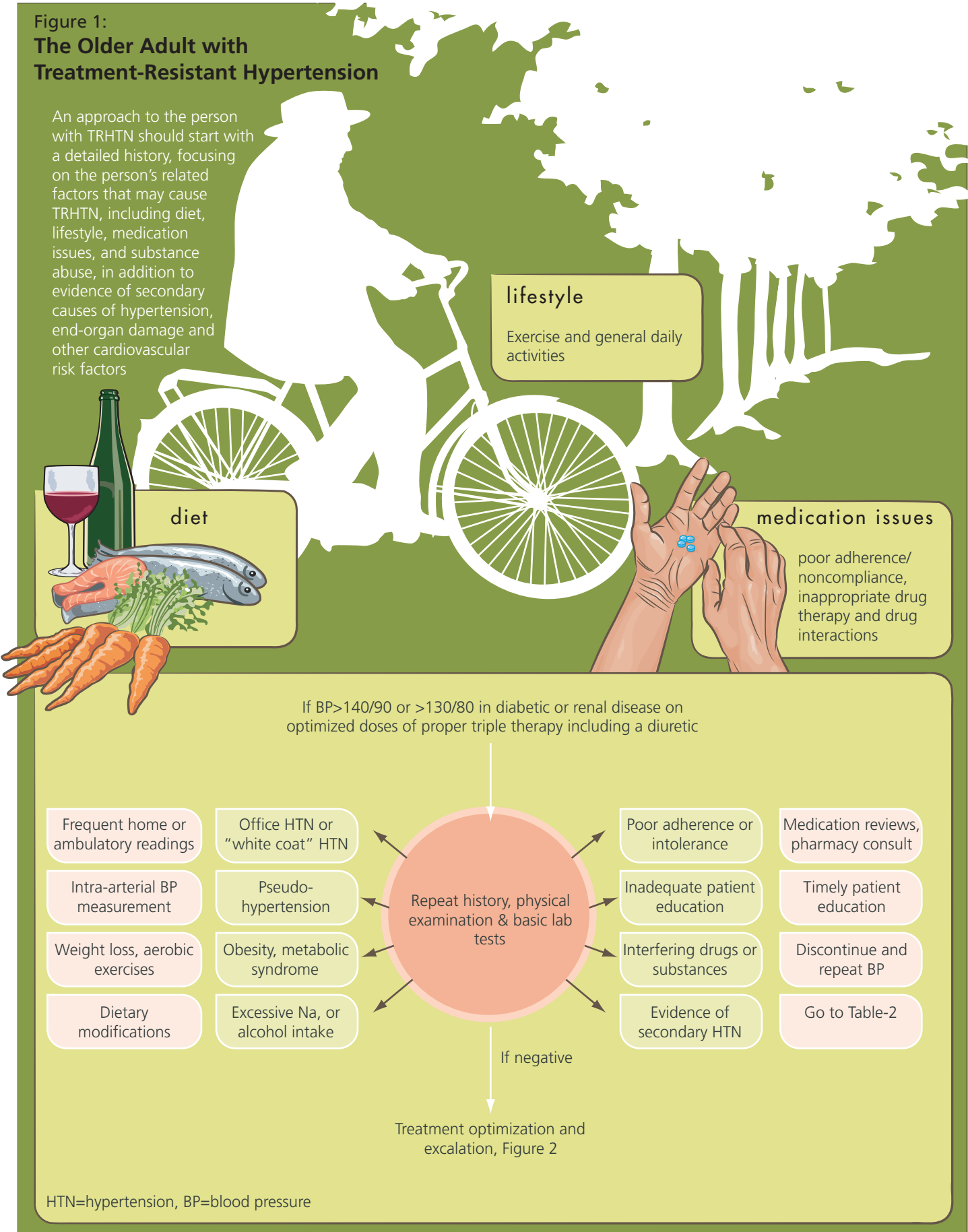
Table 2: Most Common Causes of Secondary Hypertension Presenting as TRHTN

Etiologies	Indication to Screen	Screening Tests	Treatment
Hyperaldosteronism	Spontaneous or diuretic induced hypokalemia <3.0 mmol/L, Incidental adrenal adenoma	Plasma renin-aldosterone ratio, 24-hour urinary aldosterone excretion	Aldosterone antagonists, surgical
Renovascular hypertension	Sudden onset or worsening of pre-existing hypertension Abdominal bruit, significant rise in serum creatinine with ACEIs or ARBs Recurrent pulmonary edema with hypertensive surges Presence of widespread vascular disease and atherosclerosis	Doppler ultrasound, CT or magnetic resonance angiography, postcaptopril renal flow scan	Angioplasty with stenting, ACEIs, or ARBs, plus loop diuretics
Renal Paranchymal	Nocturia, polyuria	Azotemia, proteinuria, cells, casts,	ACEIs, or ARBs, plus loop diuretics
Obstructive Sleep Apnea	Snoring, apnea, hypopnea, daytime somnolence, obesity	Sleep studies	Weight loss; nasal CPAP, aldosterone antagonists
Pheochromocytoma	Paroxysmal hypertension Hyperadrenergic symptoms/signs (e.g., headache, palpitations, sweating, and pallor) Hypertension triggered by beta-blockers, abdominal palpation, or micturition Incidental adrenal adenoma Multiple endocrine neoplasia (MEN) IIa, von Hippel-Lindau syndrome, von Recklinghausen's Neurofibromatosis	24-hour urine for catecholamine, metanephrines, imaging	Alpha-adrenergic inhibitor, followed by beta-blocker, surgical
Cushing syndrome	Truncal obesity, striae, moon face, muscle weakness, hyperglycemia	Urinary cortisol, dexamethasone suppression test, imaging (CT or MRI)	Mitotane, surgical, ketoconazole
Thyroid disease (Hypo or Hyper)	Weight loss or weight gain, tachycardia, anxiety, fatigue	TSH, free T3, T4	Anti-thyroid medication, levothyroxin
Hypercalcemia, Hyperparathyroidism	Polyuria, polydipsia, urolithiasis	Serum ionized calcium, iPTH	Diuretics, surgery
Coarctation of the aorta	Difference in BP in upper and lower extremities	Echocardiography; Imaging (CT or MRI)	Surgery, balloon angioplasty
Central nervous system tumors	Headache, nausea, vomiting, focal neurologic finding	Imaging (CT or MRI)	Surgery, radiation
Carcinoid syndrome	Flushing, diarrhea, abdominal pain, wheezing	Imaging (CT or MRI)	Surgery, octreotide chemotherapy
Premenstrual syndrome	Cyclical hypertension, puffiness, volume overload	Clinical symptoms linked to the menstrual cycle	Diuretics (thiazide, spironolactone)

Source: Adapted from Moser M and Setaro JF, 2006.³

Figure 1:
The Older Adult with
Treatment-Resistant Hypertension

An approach to the person with TRHTN should start with a detailed history, focusing on the person's related factors that may cause TRHTN, including diet, lifestyle, medication issues, and substance abuse, in addition to evidence of secondary causes of hypertension, end-organ damage and other cardiovascular risk factors



60 years than among younger individuals.¹²

Etiologies

The most common cause of TRHTN is a suboptimal medical regimen (43–58%), followed by poor adherence/noncompliance (10–16%), medication intolerance (14%), psychiatric causes (8–9%), office resistance (2–6%), interfering substance/ drug interaction (3%), and secondary causes of hypertension (5–10%).^{5,13,14}

Etiologies may be classified as technical issues, patient-related factors (such as noncompliance, dietary factors and obesity, alcohol abuse, and drug interaction), physician-related factors (including inadequate patient education, inappropriate drug therapy, inaccurate clinical diagnosis) and secondary hypertension (including primary

hyperaldosteronism, renovascular hypertension, and obstructive sleep apnea [OSA]). These causes are illustrated in Table 1 and Table 2.

Approach to the Older Adult with Treatment-Resistant Hypertension

An approach to the person with TRHTN should start with taking a detailed history, focusing on factors that may cause TRHTN, including dietary, lifestyle, medication issues, substance abuse, evidences of secondary causes of hypertension, end-organ damage, and other cardiovascular risk factors⁴ (Table 1) (Figure 1).

Subsequent to this, a proper and targeted physical examination must be performed. Blood pressure should be measured using a calibrated sphygmomanometer with properly sized cuff

and with the patient's arm supported at the heart level after he or she has been seated comfortably and quietly for five minutes with the legs uncrossed. Since smoking can elevate systolic blood pressure by 5–20 mmHg, and drinking coffee can elevate blood pressure by a few mmHg, the patient should be asked about smoking or drinking coffee within the previous 15–30 minutes.^{15,16}

Incorrect Clinical Diagnosis: Technical Issues

Office Hypertension or “White Coat” Hypertension

Isolated office TRHTN (known as the white coat effect, when a patient's blood pressure is 10 mmHg higher at doctor's office than in the home) may be found in 16% of individuals with hypertension.¹⁷ Repeated home measurements or 24-hour ambulatory monitoring are necessary to

Figure 2:
Stepwise Treatment Optimization

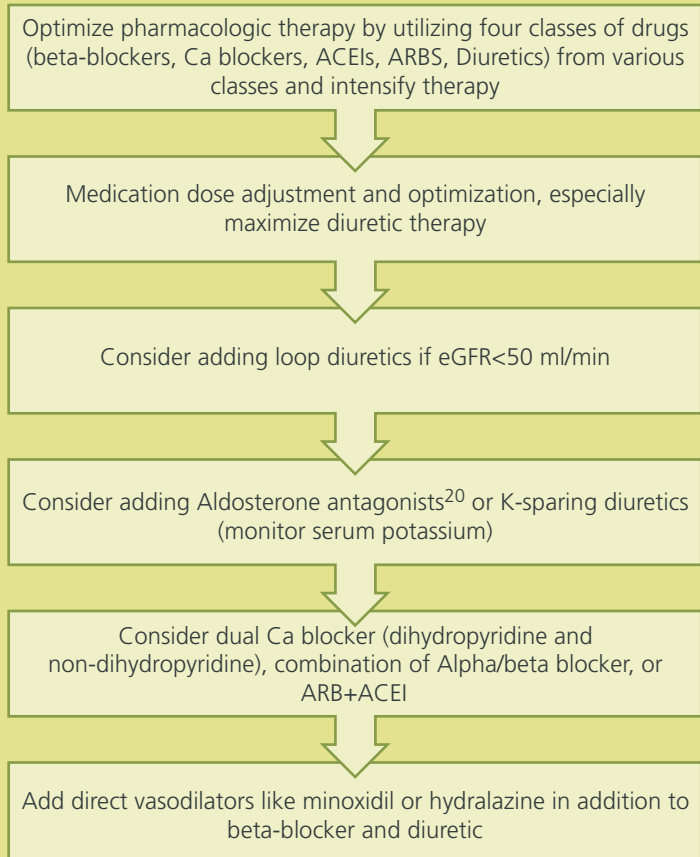
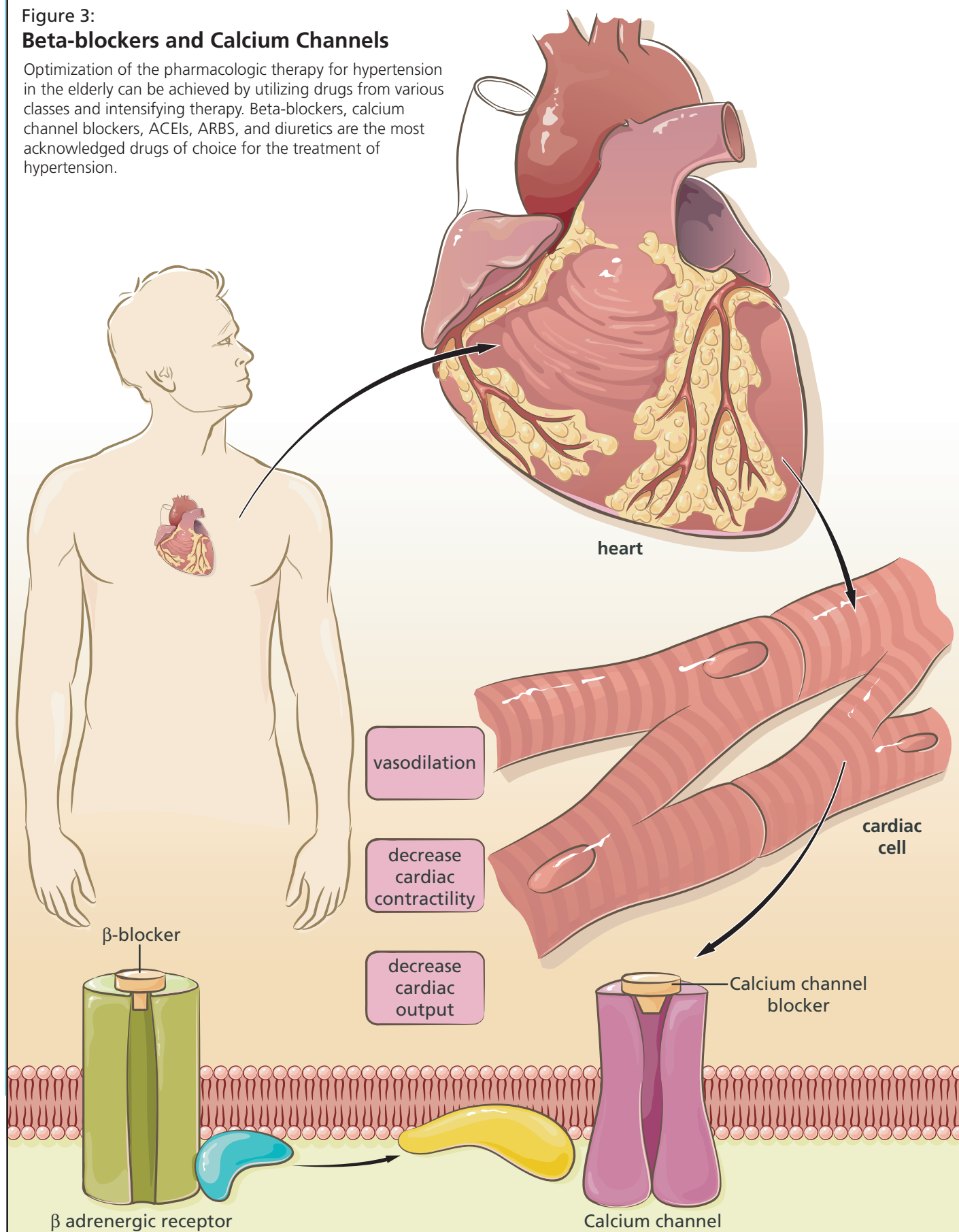


Figure 3:
Beta-blockers and Calcium Channels

Optimization of the pharmacologic therapy for hypertension in the elderly can be achieved by utilizing drugs from various classes and intensifying therapy. Beta-blockers, calcium channel blockers, ACEIs, ARBS, and diuretics are the most acknowledged drugs of choice for the treatment of hypertension.



differentiate this from true TRHTN.¹⁸ In one study, as many as one-third of persons with apparently resistant hypertension had average blood-pressure levels of less than 130/85 mmHg on 24-hour or home measurement.⁵ Some data suggest that blood pressure values obtained at home or during 24-hour ambulatory procedures correlate better with target-organ involvement, especially left ventricular hypertrophy, than do values obtained in the physician's office.¹⁵

Pseudo-hypertension

Pseudo-hypertension refers to false detection of hypertension by indirect measurement with a sphygmomanometer while direct measurement of intra-arterial blood pressure is in the normal range. Pseudo-hypertension should be suspected in the presence of marked hypertension in the absence of target organ damage, hypotensive symptoms with antihypertensive therapy in the absence of successful reduction of blood pressure, radiological evidence of pipe stem calcification in the brachial arteries, higher blood pressure in brachial artery than lower extremity, severe and isolated systolic hypertension, or a positive Osler's maneuver (palpable pulseless radial or brachial artery after inflating a blood pressure cuff above systolic pressure).^{24,19}

Laboratory Tests

Basic laboratory testing is also warranted, including measuring levels of serum electrolytes, creatinine, calcium, blood glucose, uric acid, lipids, and urinalysis, as well as an electrocardiography. In certain cases, other tests need to be taken in order to rule out secondary causes of hypertension or presence of end-organ damage. These include thyroid functions, urine albumin creatinine ratio, plasma aldosterone to renin ratio, chest X-ray PA lateral, renal ultrasound, and an echocardiography.²⁰

Optimization of Therapy

Optimization of therapy is essential, especially when there is evidence of end-organ damage. Following patient education for lifestyle modifications such as getting aerobic exercise, weight loss, increased fruit and vegetable intake, as well as dietary

Key Points

Resistant hypertension is a common problem; management should focus on eliminating compliance issues, interfering substances, lifestyle changes and secondary causes, as well as the use of optimizing drug therapy.

Diuretics are a key component to the successful treatment of treatment-resistant hypertension.

Primary aldosteronism is one of the most common secondary causes of HTN among individuals with TRHTN.

Recent clinical studies suggest that aldosterone antagonists are useful add-on agents for persons with TRHTN.

Obstructive sleep apnea is extremely common among persons with TRHTN.

Multiple drugs are often needed to manage TRHTN.

Consider dual Ca blocker (dihydropyridine and non-dihydropyridine), combination of alpha/beta blocker, or ARB+ACEI.

sodium restriction, the key is linking the patient to a readily accessible, skilled pharmacist in order to address the issue of adherence to medications as well as minimizing medications that interfere with antihypertensive drugs. Optimization of the pharmacologic therapy then can be done by utilizing drugs from various classes and intensifying therapy (Figure 2).

A low-renin status characterized two-thirds of patients with TRHTN who could be treated efficiently by aldosterone inhibition.²³ In case of renal failure estimated glomerular filtration rate (eGFR) less than 50 ml/min, adding a loop diuretic would be a more effective choice of diuretic.² Subsequent steps could be a dual calcium blocker (dihydropyridine and non-dihydropyridine), a combination of alpha blocker and beta blocker, or a combination of an angiotensin receptor blocker (ARBs) with an ACE inhibitor. Finally, adding a direct vasodilator like minoxidil or hydralazine to beta-blocker and diuretic medications would be another effective therapy (Figure 3).²⁹

Case Follow up

Further review of your case reveals the following additional findings: loud snoring, periods of silence followed by gasps, daytime sleepiness, headaches, morning headaches, trouble concentrating, forgetfulness and anxiety.

The patient's sleep study showed periods of apnea with an Apnea Hypopnea Index of five per hour. He was diagnosed as having OSA and assigned to an aerobic exercise and weight loss program. A calcium channel blocker (nifedipine) was initially added to his drug regimen in order to help with his blood pressure control. At a six-month follow up after 10 percent weight loss, his blood pressure was well controlled on minimum doses of ACE inhibitor and thiazide.

Discussion

Obstructive sleep apnea (OSA) is highly prevalent in and independently associated with TRHTN (odds ratio close to 5.0).^{17,20–22,25} Persons with TRHTN and OSA also have elevated aldosterone levels.^{21,22} Furthermore, a positive correlation between plasma aldosterone level and OSA severity among individuals with TRHTN has been demonstrated.²¹ However, it is not clear whether aldosterone excess worsens OSA severity or untreated OSA stimulates aldosterone release. Nevertheless, this supports aggressive screening of all persons with TRHTN for OSA. Additionally, spironolactone is an excellent antihypertensive drug for managing persons with TRHTN and OSA.^{21,23}



No competing financial interests declared.

References

1. Langille DB, Joffres MR, MacPherson KM, et al. Prevalence of risk factors for cardiovascular disease in Canadians 55 to 74 years of age: results from the Canadian Heart Health Surveys, 1986–1992. *CMAJ* 1999;161(8 Suppl):S3–9.
2. Papadopoulos PD, Papademetriou V. J Resistant hypertension: diagnosis and management. *Cardiovasc Pharmacol Ther* 2006;11:113–8.
3. Moser M, Setaro JF. Resistant or Difficult-to-Control Hypertension *N Engl J Med* 2006;355:385–92.
4. Fields LE, Burt VL, Cutler JA, et al. The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension* 2004;44:398–404.
5. Burnier M, Schneider MP, Chioléro A, et al. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. *J Hypertens* 2001;19:335–41.
6. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. *N Engl J Med* 2001;345:479–86. [Erratum, *N Engl J Med* 2002;346:544.]
7. Werlemann BC, Offers E, Kolloch R. Compliance problems in therapy resistant hypertension. *Herz*. 2004;29:271–5.
8. Epstein M. Resistant hypertension: prevalence and evolving concepts. *J Clin Hypertens* 2007;9:2–6.
9. Epstein M. Resistant hypertension: prevalence and evolving concepts. *J Clin Hypertens* 2007;9:2–6.
10. Garg JP, Elliott WJ, Folker A, et al. Resistant hypertension revisited: a comparison of two university-based cohorts. *Am J Hypertens* 2005;18:619–26.
11. Yakovlevitch M, Black HR. Resistant hypertension in a tertiary care clinic. *Arch Intern Med* 1991;151:1786–92.
12. Taler SJ. Treatment of resistant hypertension. *Curr Hypertens Rep* 2005;7:323–9.
13. Omvik P. How smoking affects blood pressure. *Blood Press* 1996;5:71–7.
14. Jee SH, He J, Whelton PK, et al. The effect of chronic coffee drinking on blood pressure: a meta-analysis of controlled clinical trials. *Hypertension* 1999;33:647–52.
15. Tamimi NA. Resistant hypertension: a methodological approach to diagnosis and treatment. *Saudi J Kidney Dis Transplant* 2007;18:337–45.
16. Oikawa T, Obara T, Ohkubo T, et al. Characteristics of resistant hypertension determined by self-measured blood pressure at home and office blood pressure measurements: the J-HOME study. *J Hypertens* 2006;24:1737–43.
17. Gaddam KK, Pratt-Ubunama MN, Calhoun DA. Aldosterone antagonists: effective add-on therapy for the treatment of resistant hypertension. *J Expert Rev Cardiovasc Ther* 2006;4:353–9.
18. Eide IK, Torjesen PA, Drolsum A, et al. Low-renin status in therapy-resistant hypertension: a clue to efficient treatment. *J Hypertens* 2004;22:2217–26.
19. Moses S, Family Practice Notebook. www.fpnotebook.com/CV/Pharm/MdctnCsOfHprtnsn.htm ©2008 [accessed on January 10, 2008]
20. Goodfriend TL. Treating resistant hypertension with a neglected old drug. *Hypertension* 2007;49:763–4.
21. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, et al. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest* 2007;131:453–9.
22. Grassi G, Whitworth JA. Resistant hypertension and aldosterone excess: new insights from ambulatory blood pressure monitoring. *J Hypertens* 2007;25:2006–7.
23. Feely J, Mahmud A. Spironolactone in resistant hypertension. *Hypertension* 2007;50:e57.
24. Chobanian AV, Bakris GL, Black HR, et al. The 7th report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. *Hypertension* 2003;42:1206–52.
25. Gonçalves SC, Martinez D, Gus M, et al. Obstructive sleep apnea and resistant hypertension: a case-control study. *Chest*. 2007 Dec;132(6):1858–62.