

Resistant Hypertension- A Review of Management Strategies

Dharmendra Jain *, Niraj Kumar **

Abstract

Resistant hypertension (RH) is defined as the condition in which the blood pressure remains above goal in spite of concurrent use of 3 antihypertensive agents of different classes. Prevalence of resistant hypertension is 10-20% of the general hypertensive population. Patients with resistant hypertension are at high risk for adverse cardiovascular events. After excluding pseudoresistance, two most important causes of resistant hypertension are concomitant use of drugs and secondary causes. Management includes careful selection of antihypertensive drugs, lifestyle changes, treatment of secondary causes of hypertension, and discontinuation/ minimizing drugs that can cause hypertension. Invasive treatment option at present is an era to be explored.

Keywords: Hypertension, pseudoresistant hypertension, truly resistant hypertension, white- coat effect.

Introduction

Resistant hypertension (RH) is defined as the condition in which the blood pressure remains above goal in spite of concurrent use of 3 antihypertensive agents of different classes, one of them usually a diuretic with all the agents at optimal dose.¹ “Optimal dose” of medication is the maximum tolerated dose, not necessarily the maximum dose. Presence of diuretic is recommended but not mandatory. Patients whose blood pressure is controlled with four or more medications are also considered to have resistant hypertension.

Exact prevalence of resistant hypertension is unknown. According to an analysis of US NHANES among hypertensive adults treated with medications, approximately 13% people have resistant hypertension. Prevalence of resistant hypertension of 10-20% of the general hypertensive population is found in observational studies.²

Patients with resistant hypertension are at high risk for adverse cardiovascular events. Though prognosis of patients with resistant hypertension has not been evaluated, probably, it is impaired in comparison to non resistant hypertension as these

patients usually have long- standing history of poorly controlled hypertension and commonly have associated cardiovascular risk factors such as diabetes, obstructive sleep apnea, left ventricular hypertrophy (LVH), and/ or CKD. According to one study, patients with resistant hypertension are almost 50% more likely to have an adverse cardiovascular event over a median follow- up of 3.8 years compared with patients with controlled blood pressure.³

Patient’s characteristics associated with resistant hypertension include older age esp. more than 75 years, chronic high baseline blood pressure, obesity, excessive dietary salt ingestion, target organ damage (chronic kidney disease, diabetes, left ventricular hypertrophy), aortic stiffening, atherosclerotic vascular disease, black race and female sex.^{4,5,6}

Etiology of resistant hypertension includes:

- a) Pseudo resistance
 - 1) Poor Blood Pressure Technique - most common mistakes are measuring the blood pressure before the patient sits quietly and use of too small a cuff. They will result in falsely high blood pressure readings.

* Assistant Professor, Cardiology, Institute of Medical Sciences, BHU, Varanasi

** Senior Resident, Cardiology, Institute of Medical Sciences, BHU, Varanasi

Correspondence to: Dr. Dharmendra Jain, Assistant Professor, Cardiology, IMS, BHU, Varanasi.

E- mail: djaincard@gmail.com

- 2) Poor Adherence - approximately 40% of patients with newly diagnosed hypertension discontinue their antihypertensive medications during the first year of treatment.
- 3) White- Coat Effect

b) True resistance

- 1) Obesity
- 2) Dietary Salt
- 3) Alcohol
- 4) Drug- Several classes of drug increases blood pressure and contribute to treatment resistance. NSAIDS including aspirin, selective COX-2 inhibitors, sympathomimetic agents (decongestants, diet pills, cocaine), oral contraceptives, cyclosporine, erythropoietin, herbal compounds (ephedra or ma huang).
- 5) Secondary Causes - Secondary causes of hypertension are common in patients with resistant hypertension, although the overall prevalence is unknown. Common causes include obstructive sleep apnea, renal parenchymal disease, primary aldosteronism, renal artery stenosis.

c) Other causes are pheochromocytoma, Cushing syndrome, hyperthyroidism, aortic coarctation, intracranial tumors.

Management

- a) Confirm treatment resistance
- b) Exclude pseudo resistance
- c) Identify and reverse contributory life style factors
- d) Discontinue or minimize drugs that can cause hypertension
- e) Screen for secondary causes of hypertension
- f) Pharmacological treatment

Chlorthalidone is more effective than hydrochlorothiazide in reducing blood pressure because it is more potent and lasts longer. In addition, it may reduce cardiovascular events to a greater extent than hydrochlorothiazide.

When glomerular filtration rate is <30 mL/min, a loop diuretic usually is needed.

The addition of Spironolactone as 4th drug with careful attention to potassium level is an evidence-based strategy for the treatment of RH. (NICE clinical guideline)

As per Cambridge $\alpha\beta\Delta$ guideline, plasma renin label is useful in deciding drugs- a beta- blocker (β) in case of high renin levels, an alpha- blocker (α) in case of normal renin levels, while in case of low renin levels the diuretic drug is changed or its dose increased (Δ).⁷

Other pharmacologic strategies for treating resistant hypertension are vasodilating β - blocker (e.g., labetalol, carvedilol, nebivolol); a direct vasodilator (e.g., hydralazine); or a centrally acting agent such as clonidine (transdermal or oral) or guanfacine. In men with comorbid benign prostatic hyperplasia, an α -blocker (e.g., terazosin) is a reasonable addition. Another strategy useful in patients with comorbid diabetes or CKD is adding a CCB of the alternate class (e.g., adding a nondihydropyridine to a dihydropyridine). Particular attention should be given to possible drug interaction. For e.g. a nondihydropyridine CCB combined with a β - blocker may promote bradycardia, which can be worsened by clonidine. Role of other agents such as endothelin receptor antagonists is being evaluated.⁸ Dual RAAS blockade is not recommended because of a lack of evidence in resistant hypertension, no proven added value and increased risk of adverse events seen in high risk patients enrolled in the ONTARGET trial. Moxonidine, although frequently prescribed, leads to increased morbidity and mortality in heart failure patients.⁹

Invasive treatment as renal sympathetic denervation gives a new therapeutic option for the treatment of resistant hypertension. However, with the negative result of SIMPLICITY HTN-3 trial¹⁰ the definitive role of the technique is questionable.

Another invasive method is baroreflex stimulation (electrical stimulation of the carotid sinus nerve). The method proved very effective in lowering blood pressure. In contrast to renal sympathetic denervation, baroreflex stimulation is a reversible method; the system can be switched off in the event of hypotension or shock and be adapted to the requirements of a circadian blood pressure rhythm by external programming via radiofrequency telemetry. Baroreflex stimulation has been approved at certain places for the treatment of patients with resistant hypertension and a high cardiovascular risk. However, it is reserved to selected centers with great expertise.

Conclusion

A sizable proportion of hypertensive patients have resistant hypertension. These patients are at higher risk for target organ damage. Proper history and examination may detect pseudo resistant hypertension. Among true RH, volume overload is the most common etiology so use of diuretics or increasing dose or changing class of diuretics may suffice in many. Invasive treatment is the best hope for future.

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