

Review Article

Resistant Hypertension: Overview

K. Krishnakumar

Department of Cardiology, Senior Interventional Cardiologist, PRS Hospital, Trivandrum, Kerala, India

Abstract

Resistant hypertension (RH) is defined as office blood pressures (BP) which is uncontrolled on ≥ 3 or controlled on ≥ 4 different classes of antihypertensive medications at optimal doses and preferably including a diuretic.

- RH is important as many patients in this subgroup have secondary causes of hypertension.
- Most important aspect of treatment in RH is to divide RH into true RH and pseudo-RH.
- Three factors, namely patient adherence, optimal dosing of antihypertensive medications, and out-of-office BP recordings, are important in classifying RH to true RH and pseudo-RH.
- Many RH patients are volume expanded and respond to intensified diuretic therapy, sodium restriction, dual calcium-channel blocker, or α -adrenoreceptor blocker. Plasma renin activity can be used for personalized therapy in RH.

Key words: Resistant hypertension, insulin resistance, artifacts, adherence, secondary hypertension, indapamide, valsartan, escalating diuretics, renin guided therapy

Introduction

Resistant hypertension (RH) is defined as blood pressures (BP) uncontrolled on ≥ 3 or controlled on ≥ 4 different classes of antihypertensive medications at optimal doses and preferably including a diuretic.

- Insulin resistance and obstructive sleep apnea are two common associations of RH.
- True RH and pseudo-RH are two subsets of RH which have to be identified and treated.

BP measurement artifacts

- It is important to obtain accurate BP values before labeling as RH. Standard BP measurement protocols are required to segregate true RH from apparent RH.
- To minimize measurement artifacts.
- To get a BP value which represents true out-of-office BP.
- BP has to be measured accurately in office setting by trained individuals to avoid problem of white-coat effect.
- Automated office BP in which a series of BP measurements are made in office usually mimicks daytime recordings.^[1]

Address for correspondence:

Dr. K. Krishnakumar, Senior Interventional Cardiologist, PRS Hospital, Trivandrum - 695 002, Kerala, India.
E-mail: krishnasarith@rediffmail.com

Received: 10-10-2018; Accepted: 01-12-2018

doi: 10.15713/ins.johtn.0147

Optimal therapy

- It is important to define what is optimal therapy before classifying patients as true RH.

What medications and what dose ?

Patient should be on three different classes of antihypertensive medications including a diuretic.^[2]

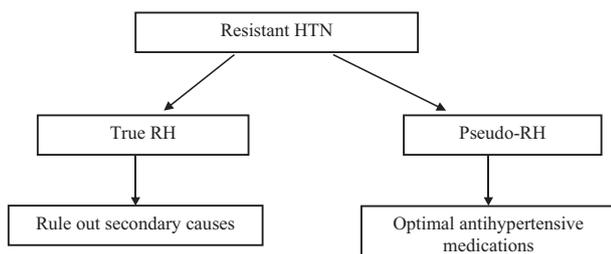
Antihypertensive dose should be $\geq 50\%$ of maximum recommended dose.

Patient adherence

Can be assessed by direct questions – Are you regularly taking medications?

- Indirect question: Regarding concern for cost or side effects.
- In apparent RH, clinicians appear to have opportunities to improve BP control by optimizing antihypertensive medication dosing.
- Once a diagnosis of true RH is made, one has to evaluate for the cause of secondary hypertension (HTN).





Prognosis

In patients with apparent-resistant HTN based on the measurement of office BP, the subject with nonhypertensive out-of-office BP values has a favorable prognosis. This is where ambulatory BP recordings are useful. Both self-monitored BP and ambulatory BP recordings provide prognostically important information beyond office BP, in this group of patients.^[1]

Pharmacotherapy of RH

Commonly prescribed three drugs regimen for RH include ARB + CCB + thiazide diuretic. Beta blockers could be added for specific indications.^[3]

Drugs and Dosing for RH

Diuretic	ACE/ARB	CCB ^[4]	Aldo Receptor blocker	Beta blocker
Indapamide 1.25 to 2.5 mg daily	Lisinopril 20-40 mg	Amlodipine 5-10 mg	Sprinolactone 25-50 mg	Bisoprolol 10-20 mg
Hydrochlorothiazide 12.5-25 mg	Perindopril 4-8 mg		Eplerenone 25-50 mg	Metoprolol 100-200 mg
Chlorthalidone 6.25-25 mg	Valsartan 160-320 mg			
Torsamide 20-40 mg				

Rationale

Low-dose aldosterone antagonist, spironolactone 12.5–50 mg, lowers BP in RH. Spironolactone at a dose of 25 mg daily lowered BP by 25–50 mmHg (systolic)/10–15 mmHg (diastolic). Eplerenone is an alternative aldosterone antagonist devoid of sex steroid effects.

Beta Blockers

Aldosterone is projected to play a major role in BP regulation in long term than renin–angiotensin system.^[5] Aldosterone raises BP by increasing number and activity of epithelial sodium channels. Amiloride which is epithelial sodium channel blocker has similar effect as Aldosterone antagonist.

However target organ protection is seen only with Aldosterone antagonist. Patients with serum K⁺ value >4.5 and eGFR <45 ml/min are not ideal candidates for spironolactone. Target organ protection is a major advantage of Aldosterone antagonists.

Diuretics

Escalating diuretic potency from hydrochlorothiazide to chlorthalidone to torsemide as GFR decline from >45 to <30 ml/1.73 m²/min helps to reduce fluid retention and helps in BP control.

Diuretics	EGFR
HCTZ	>50 ml/1.73m ² /min
Chlorthalidone	45-50 ml/1.73m ² /min
Torsemide	<45 ml/1.73m ² /min

Personalized Therapy for RH

Renin-guided therapy, i.e. Plasma renin activity (PRA), can be used to guide antihypertensive therapy without increasing number of medications.^[6]

Low PRA-better response	High PRA-better response
Diuretics	Renin/Angiotensin blocker
CCB	β Blockers
α Blockers	
Aldosterone antagonist	

Control of other cardiovascular risk factors is important

- Diabetes
- Dyslipidemia – statins have shown 36% reduction of coronary events.
- Choose antihypertensive medication depending on other compelling indications like CAD, CKD, CHF, Diabetes.

Summary

RH should be clearly defined into true RH and pseudo-RH. Screening for secondary causes is important in true resistant HTN.

Clinicians should identify and address pseudo-resistance, screen for secondary hypertension, initiate changes to lifestyle and pharmacotherapy to improve BP control.

Personalized drug therapy depending on PRA may be a choice for truly RH.

Device-based therapy may evolve in future for the treatment of RH.

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How to cite this article: Krishnakumar K. Resistant Hypertension: Overview. *Hypertens* 2019;5(1): 32-34.

Source of support: Nil, **Conflict of interest:** None

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