



## DIAGNOSIS AND TREATMENT OF RESISTANT HYPERTENSION: A REVIEW

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### ABSTRACT

Resistant hypertension is growing clinical condition worldwide associated with major target organ damage and poor prognosis with compared with non-resistant hypertension. The significant prevalence of resistant hypertension and high cardiovascular risk of patient with resistant hypertension is necessary to identify the main causes to control the blood pressure and to reduce its morbidity and mortality. The diagnosis of resistant hypertension requires use of good blood pressure technique to confirm persistently elevated blood pressure level, pseudo resistance, and white coat hypertension must be excluded. The treatment involves lifestyle modification and use of adequate combination of antihypertensive agent from different class with adequate doses. The recent data derived from two multicentre randomized trials, namely PATHWAY-2 pointed Mineralocorticoid receptor antagonist spironolactone is preferable fourth drug therapy in patient with confirmed resistant hypertension. The Resistant hypertension required more than four drugs for controlling blood pressure. New combination, drugs and device management should be tested, aiming to reduce the burden of resistant hypertension.

**Key words:** Resistant hypertension, Ambulatory blood pressure monitoring, Obstructive Sleep Apnea, Antihypertensive therapy, Combination drug therapy, Spironolactone, Renal Denervation.

## INTRODUCTION

The term resistant hypertension refer to patient with blood pressure persistently greater than 140/90 mmHg despite of taking three or more antihypertensive agent of different class , one of which should be diuretics and all agent should be prescribed at optimal dose[1]. Resistant Hypertension also includes patients whose blood pressure is controlled with use of more than three medications. Resistant hypertension represent 10- 20 % of all cases of stage II hypertension and epidemiological evidence suggest that it is associated with older age, obesity, impaired renal function, diabetes mellitus and obstructive sleep apnea[2-5]. The burden of RH tend to have obvious increment with adoption of the 2017 hypertension guideline setting of cutoff criteria on greater than 130/80 mmHg[6]. Beyond the increasing prevalence, resistant hypertension gained particular attention due to higher rate of target organ damage [7] and poor prognosis compared to non-resistant counterparts[8, 9]. Hypertension is associated to an elevated morbidity and mortality, contributing directly to higher risk of cardiovascular event and renal disease [10, 11]. It is well established that antihypertensive treatment effectively reduces high blood pressure and consequently reduce cardiovascular risk like heart failure, myocardial infarction, stroke and kidney disease hence greatest challenge worldwide to achieves sustained Blood pressure control of hypertensive patient[10, 11].The RH is more common in patient with diabetes mellitus, obesity, dyslipidemia, physical inactivity, chronic kidney disease and left ventricular hypertrophy [1, 12, 13].

Individual with elevated office blood pressure due to white coat hypertension, inaccurate blood pressure measurement or inappropriate dose or combination of agent to treatment may have pseudoresistant hypertension [4, 14, 15]. In a Spanish ambulatory blood pressure monitoring (ABPM) registry blood pressure was assessed in 68,045 patients with HTN. Of these 8295(12.2%) appeared to have resistant hypertension (office blood pressure  $\geq$ 140/90 mmHg while receiving  $\geq$ 3 drugs including diuretics) but 37.5 % had normal BP when assessed using ABPM [16].

## DIAGNOSTIC APPROACH

Before the diagnosis of resistant hypertension it is recommendable to evaluate the common causes of pseudo resistance hypertension, namely inaccurate measurement of blood pressure, especially size of cuff as in obesity, white coat blood pressure, poor drug adherence and inadequate antihypertensive therapeutic scheme [1]. Drug of choice is very important, specially to verify the prescription of diuretic in adequate dosages as well as use of at least two other synergic drug that reduce cardiovascular morbidity and mortality [1, 10, 11]. Moreover, therapeutic adherence is very complex challenge in the management of resistant hypertension. The uses of greater number of drug not only for hypertension but also for other co morbidities like diabetes mellitus and dyslipidemia hinders adherence. In recent study female sex, physical inactivity, depressive symptom and history of coronary artery disease were the principle factors associated with low adherence in resistant hypertension patient[12].

### Evaluation of patient:

The evaluation of patient with Resistant hypertension should be directed towards the confirming the diagnosis, identifying the causes contributing to treatment resistance and documented target organ damage [1]. In most cases treatment resistance is multifactorial in etiology with excessive sodium intake and listed in table: 1.

**Table 1: Common causes of Resistant hypertension**

- Chronic kidney disease
- Renovascular disease
- Obstructive sleep apnoea
- Coarctation of the Aorta
- Pheochromocytoma
- Primary hyperaldosteronism
- Cushing syndrome
- Thyroid disease
- Intracranial mass

The medical history should be documented duration, severity and progression of hypertension, treatment adherence, response to prior medication, current medication uses and symptom of possible secondary causes of hypertension. Daytime sleepiness, loud snoring is suspicious for obstructive sleep apnea. A history of peripheral or coronary atherosclerotic disease increases the risk of renal artery stenosis. Hypertension in association with palpitation and diaphoresis suggest Pheochromocytoma.

### Physical examination:

The presence of carotid, abdominal or femoral bruits increased the possibility of renal artery stenosis. Diminished femoral pulse suggests aortic coarctation or significant aortoiliac disease. Cushing disease is suggested by abdominal pigmented striae, moon faces and prominent interscapular fat deposition [1]. A Funduscopic examination should document the presence and severity of retinopathy.

### Lab investigation:

All Resistant hypertension patients should have laboratory examination to rule out Diabetes mellitus, Dyslipidemia and renal function ( blood urea, serum creatinine, microalbuminuria, and proteinuria) because of high association of Resistant hypertension with diabetes mellitus, Dyslipidemia and chronic kidney disease [1, 12, 13, 17]. Impaired renal function represented by renal parenchyma disease is related to excessive activation of Renin Angiotensin Aldosterone system and fluid retention [17]. Electrocardiogram should be performed to rule out left ventricular hypertrophy because resistant hypertension is also associated with left

ventricular hypertrophy. Measure the plasma aldosterone / Renin ratio and plasma renin activity, to screen for primary aldosteronism. The aldosterone / renin ratio is an effective screening.

**Table 2: Basic investigations in patient with Resistant Hypertension**

- Ambulatory blood pressure monitoring
- 12-lead electrocardiogram
- Tran thoracic echocardiogram
- Complete blood count
- Serum glucose, urea, Creatinine, electrolytes, Lipids
- Urine analysis- protein, erythrocytes, leukocytes
- Plasma aldosterone concentration and renin
- Thyroid stimulating hormone
- Renal echocardiogram

Test for primary aldosteronism[18]. Collection of urine for 24 hours during ingestion of normal diet can be helpful in estimating dietary sodium and potassium intake, calculating creatinine clearance and aldosterone excretion. Measurement of 24 hour urinary metanephrines or plasma metanephrines is effective screening for patient in whom Pheochromocytoma is suspected [19]. Imaging for suspected cases of renal artery stenosis like young female , whose presentation suggest the presence of fibromuscular dysplasia and older patient at increased risk of atherosclerotic disease[1].

#### **TREATMENT OF RESISTANT HYPERTENSION:**

Treatment of resistant hypertension comprises the reversal of lifestyle factors contributing to treatment resistance, accurate diagnosis and appropriate treatment of secondary causes of hypertension and the use of effective multidrug regimens. Lifestyle changes that should include weight loss, regular exercise, ingestion of a high fiber, low-fat, low salt diet, and avoid heavy alcohol intake.

#### **Non pharmacological treatment:**

##### **Weight Loss:**

The weight loss in case of treatment of resistant hypertension has benefit in terms of reducing blood pressure and often allows for reduction in the number of prescribed medications. Long-term weight loss studies have indicated that a 10-kg weight loss is associated with an average reduction in systolic blood pressure of 6.0 mm Hg and a reduction in diastolic blood pressure of 4.6 mm Hg [20]. Considering that patients with resistant hypertension are frequently overweight or obese, weight loss should be strongly encouraged as a relevant part of the global management of these patients.

### **Physical Activity:**

Regular aerobic exercise produced average reductions of 4 mm Hg in systolic and 3 mm Hg in diastolic blood pressure[21]. In a small group of African-American men with severe hypertension, an aerobic exercise regimen lowered systolic blood pressure by 7 mm Hg and diastolic blood pressure by 5 mm Hg [22]. So patients should be encouraged to exercise for a minimum of 30 minutes per days.

### **High-Fiber, Low-Fat Diet:**

Ingestion of a diet rich in fruits and vegetables, high in low-fat dairy products, potassium, magnesium, and calcium; and low in total saturated fats will reduced systolic blood pressure in hypertensive patients by 11.4 mm Hg and diastolic blood pressure by 5.5 mm Hg more [23]. The high amount of fruits and vegetables in this diet lowers blood pressure and improves endothelial function in this group by means of nutritional factors in addition to potassium, magnesium, and fiber [24].

### **Dietary Salt Restriction:**

The dietary salt reduction is well documented in general hypertensive patients, in whom it is associated with reductions of 5 to 10 mmHg in systolic blood pressure and of 2 to 6 mm Hg in diastolic blood pressure[25]. The reductions in dietary salt should also health benefits in adults by lowering rates of cardiovascular events and death and reducing medical costs [26]. A very recent study to assess the effects of low dietary salt ingestion in patients with resistant hypertension showed that dietary salt restriction reduced both office and 24-hour ambulatory blood pressure. The degree of blood pressure reduction induced by dietary salt restriction in this group of resistant hypertensive patients is larger than reductions observed in normotensive populations. In fact, high dietary salt ingestion is an important cause of resistant hypertension. This effect is related to excess intravascular fluid retention, which persists in spite of the use of conventional thiazide diuretics [27]. The intensive dietary salt restriction is ideally less than 100 mEq of sodium per 24 hours, should be recommended for all patients with resistant hypertension [1].

### **Cessation of Heavy alcohol intake:**

The cessation of heavy alcohol ingestion can significantly improve hypertension control. Daily intake of alcohol should be limited to no more than 2 drinks (1 ounce of ethanol) per day (egg, 24 ounces of beer, 10 ounces of wine, or 3 ounces of 80 pro of liquor) for most men and 1 drink per day for women or lighter-weight persons [28].

### **Withdrawal of interfering medication:**

Medication that interfere with blood pressure control mainly NSAIDS, Corticosteroids, and oral contraceptive pills should be avoid in patient with Resistant Hypertension. If complete avoidance is difficult then lowest effective dose should be used [1].

**Table 3: Drugs avoided during treatment of resistant Hypertension:**

Non-steroidal anti-inflammatory drug
Oral contraceptives
Corticosteroids
Tricyclic antidepressant
Monoamine oxidase inhibitors
Other substance like caffeine, cocaine, alcohol

**Treatment of obstructive sleep apnea:**

In patient with obstructive sleep apnea, continuous positive airway pressure (CPAP) reduces 24-hour ambulatory BP and contribute to a better prognosis in terms of adverse cardiovascular even [29]. High risk for obstructive sleep apnea is highly prevalent and associated with resistant hypertension [30]. In an observational study of CPAP use, the mean difference in mean arterial pressure was  $-5.6$  mm Hg in resistant hypertensive's and  $-0.8$  mm Hg in patients with controlled blood pressure at the end of follow-up period. A beneficial response to CPAP therapy was found mainly in the patients with the most severe hypertensive disease [31].

**Pharmacological Treatment:****First three drugs:**

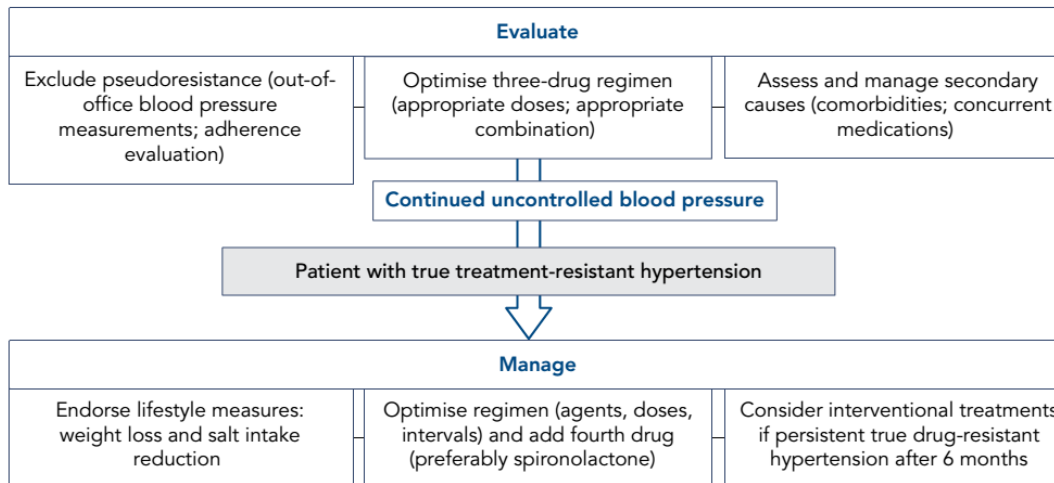
In patient with Resistant Hypertension have subclinical volume retention so effective diuretic therapy is essential to control blood pressure [32]. Thiazide diuretics are effective in majority of resistant hypertension patient and Chlorthalidone because of longer duration of action. Loop diuretics are preferable in patient with chronic kidney disease when Glomerular filtration is less than 30 ml in one minute per 1.73metre square body surface area. The other two drugs should be capable for reducing cardiovascular morbidity and mortality [11, 33]. Full dose of Angiotensin converting enzyme inhibitors or Angiotensin II receptor blockers, calcium channel blockers and beta blockers are generally effective and well tolerated, should prescribed according to current guidelines[11, 33].

**Best Fourth Drug Therapy:**

Mineralocorticoid receptor antagonist (spironolactone) provides a significant reduction of BP when compared with placebo [34]. More recently, evidence also points to an advantage of spironolactone compared to other drugs [35-37] and as compared to renal Denervation [38]. Among these, the PATHWAY-2—a double blind, placebo controlled trial and this trial tested the hypothesis that resistant hypertension is primarily caused by excessive sodium retention, evaluating whether the addition of spironolactone as a fourth-line anti-hypertensive led to a greater reduction of BP than intensive anti-hypertensive therapy with other blood pressure reduction regimens [35].

The PATHWAY-2 study included 314 patients with resistant hypertension using a combination of three drugs: a thiazide diuretic, an ACE inhibitor or Angiotensin receptor blocker, and a calcium channel blocker. Participants received four different medications (spironolactone 25 to 50 mg/day, Bisoprolol 5 to 10 mg/day, Doxazosin 4 to 8 mg/day, and placebo), each for 12 weeks, with a random order. Spironolactone was superior to other drugs in reducing systolic BP at home, and approximately 60% of the patients reached Bp control that is systolic blood pressure are less than 135 mmHg [35]. The current evidence so far pointed spironolactone is preferable fourth drug therapy for resistant hypertension.

The ReHOT investigation, a multicenter randomized study comprising stage 2 hypertension patients from all region of Brazil, compared spironolactone versus Clonidine as a fourth drug therapy for patient with confirmed resistant hypertension[39]. After 12 weeks of standard triple regimen treatment to select true Resistant hypertension patient and additional 12 weeks for testing the effect of these two drugs, the ReHOT showed that spironolactone and Clonidine treatment resulted in similar BP control as determined by both office BP monitoring and 24 ambulatory blood pressure monitoring [40]. Per protocol analysis (limited to those with  $\geq 80\%$  adherence to spironolactone or Clonidine use) showed similar results in the primary endpoint. Overall, the adherence and tolerance of both drugs were similarly good (only a higher percentage of somnolence was observed in the Clonidine group). However, data from the secondary endpoints showed that patients randomized to the spironolactone group had a greater decrease in their 24-h systolic and diastolic BP and diastolic daytime ambulatory BP than those to the Clonidine group. Spironolactone was considered preferable for the fourth drug therapy in the ReHOT trial.



**Figure 1:** Flow chart showing treatment of resistant hypertension.

## **New drug in Development:**

New drugs in development are the inhibitors of neprilysin (degradative enzyme for natriuretic peptides) and endothelin converting enzyme (endothelin system). Together with the well-known Angiotensin-converting enzyme inhibitor, they form a group called vasopeptidase inhibitors, which likewise have many theoretical benefits, but none is yet available in clinical practice [41]. Darusentan, an endothelin antagonist receptor, was also tested in RH, but not used due to high incidence of side effects [42]. Other molecules under development include aldosterone synthase inhibitors, other endothelin antagonists, nitric oxide donors and many other molecules in a preclinical stage. None of them have any practical application until now [41].

## **Device management:**

Several devices are currently studied to control blood pressure in resistant hypertension including baroreceptors activation therapy, renal Denervation and iliac artery vein fistula.

### **(a) Baroreceptors activation therapy**

Baroreceptors activation therapy is new technique to control blood pressure is under the research by reducing peripheral sympathetic activation. It is a surgically implantable device that Work by stimulating carotids sinus baroreceptors causes a reduction in sympathetic response and consequently BP reduction. The Rheos Pivotal Trial [43] was a double blind, randomized, placebo-controlled device trial conducted in RH patients. There was a mean reduction in office systolic BP of up to 35mmHg after 12 months, and over 50% of subjects achieved systolic BP control. This effect was sustained over longer follow-up of 22–53 months. It is important to note that this trial did not evaluate ambulatory BPs, just office BP reduction. Therefore, future of this procedure is uncertain, so more research is required.

### **(b) Renal sympathetic Denervation (RSD)**

The ablation of renal sympathetic nerve with radio-frequency catheter causes reduction of blood pressure. Renal sympathetic out flow is activated in essential hypertension, and basically the aim of the treatment is, by endovascular technique, to interrupt this activation causing BP reduction. A randomized study (Symplicity HTN-2 trial) enrolled 106 patients and demonstrated a mean reduction of 32/12mmHg at 6 months in office systolic and diastolic BP, respectively [44] and this effect was maintained after 2 years of follow-up. Nevertheless, the results were based on office BPs, whereas ABPM data were available only in a small subgroup, showing a less impressive BP reduction (11/7mmHg in 24-h BP) after 6 months [44] Moreover, it is not clear if BP reduction was sustained over long-term follow-up [45].

### **(c) Iliac Artery –vein Fistula**

The self-expanding device creates a 4mm arteriovenous fistula between iliac artery and iliac vein generating a sustained calibrated shunt volume within a short period of time [46]. In the first randomized controlled trial of this technology at 6 months, the intervention group showed a reduction in office systolic BP of 27 mm Hg compared with a fall of 4 mm Hg in the normal care group,



corroborated by ABPM and main side effect is unilateral leg edema. The iliac artery – vein anastomosis remain an established in additional treatment of Resistant hypertension [47].

## CONCLUSION

The Resistant hypertension patients are requiring more than four drugs for controlling blood pressure. Patient with Resistant hypertension are risk of major cardiovascular or cerebrovascular event so effectively managed to reduce the risk of such event. Both pharmacologic and nonpharmacologic therapies have shown benefits in patient with resistant hypertension and assessment of specific multidrug regimen are need to better therapy. There are two interventional approaches like, Renal Denervation and Baroreflex activation therapy, these approaches are used in clinical practice for the treatment of resistant hypertension and other approach like arteriovenous fistula and renal artery Stenting is less commonly used due to several complications. New drugs combination and device based intervention should be tested and used to reduce the burden of resistant hypertension.

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