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# Review Article

## The Perplexing Problem of Resistant Hypertension – Evaluation and Treatment

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### Abstract

Resistant hypertension (HT) is a vexing problem and accounts for approximately 10% of all cases of HT. According to European and American Heart Association/American College of Cardiology guidelines, it is defined as blood pressure (BP) above target levels despite optimal dosing of three antihypertensive medications of which one is a thiazide diuretic. The other two are most often a calcium channel blocker and an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. It is imperative to first rule out all causes of pseudoresistant HT such as inaccurate BP measurement, prominent white coat effect, poor medication compliance, and inadequate optimization of treatment. Contributing lifestyle factors and secondary causes of HT must also be looked for and corrected before labeling the patient as having resistant HT. Investigations should include basic tests to evaluate for end-organ damage and in selected cases tests to rule out the common secondary causes such as sleep disorders, primary hyperaldosteronism, chronic kidney disease, and renovascular HT. When treating such patients, the first step is to change from hydrochlorothiazide to chlorthalidone or indapamide which are more effective diuretics. If a fourth drug is to be added, the strategy of choice is to add a mineralocorticoid receptor antagonist such as spironolactone eplerenone or amiloride. Beta-blockers, alpha-blockers, centrally acting drugs such as clonidine, and vasodilators such as hydralazine are other medicines that can be used for very resistant cases. For patients with very stubborn HT, newer interventional modalities may be tried. Among these, the most investigated is renal (sympathetic) denervation by either ultrasound or radiofrequency ablation. Another newer target is carotid baroreceptor modulation. Although an exciting frontier in the treatment of resistant HT, their efficacy, safety, and exact role await further randomized studies.

**Key words:** Drug therapy mineralocorticoids, interventional treatment, pseudoresistant hypertension, resistant hypertension

### Introduction

Hypertension (HT) is the leading risk factor for cardiovascular disease and ranks as a leading cause of disability worldwide.<sup>[1]</sup> In many patients, it remains poorly controlled and above the goal defined in various guidelines.<sup>[2]</sup> A smaller percentage of patients suffers from resistant HT, defined as the failure to reduce the systolic and/or diastolic blood pressure (BP) below 140 mmHg and 90 mmHg, respectively, despite the use of three or more anti-HT agents in optimal (best tolerated) doses. These must include an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), a calcium channel blocker, and a thiazide/thiazide-type –diuretic.<sup>[3,4]</sup> As stated in

the guidelines, home or ambulatory BP measurements should be used to confirm inadequate BP control and one needs to exclude pseudoresistant HT and secondary HT to establish the diagnosis of resistant HT.<sup>[3,4]</sup> When using such a strict definition, the overall incidence of true resistant HT is about 10%.<sup>[3,4]</sup> However, as per the recent American College of Cardiology (ACC)/ Heart Association (AHA) guidelines published in 2017, Stage 1 HT is defined as a systolic BP between 130 and 139 mmHg and/or a diastolic BP between 80 and 89 mmHg.<sup>[5]</sup> As the AHA statement defines resistant HT as failure to achieve target BP, if one was to follow these guidelines rather than the ESC-ESH guidelines, prevalence of resistant HT would be

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bound to increase. Irrespective of the guidelines that one follows, resistant HT is associated with increased risk of cardiovascular morbidity and mortality, chronic kidney disease (CKD), and other HT-mediated target organ damage.<sup>[6]</sup> When treating such a patient, it is imperative that the physician approaches the problem in a systematic way to ensure adequate control of the BP. This should be carried out in four stages.

1. Rule out pseudoresistance and confirm BP measurements and adherence to treatment
2. Identify contributing lifestyle factors
3. Rule out secondary causes of HT
4. Optimize treatment measures including addition of medication in their optimal doses.

### Pseudoresistance

The exclusion of pseudoresistance is paramount for diagnosing resistant HT accurately. Pseudoresistance is defined as persistently high uncontrolled BP at the clinic for reasons other than true resistance to drug treatment.<sup>[7]</sup> These could be due to numerous factors.

**Erroneous BP measurement technique:** This is a common cause and includes using a wrong size cuff, recording only a single reading, not baring the arm during measurement, or not having the patient in the proper position during the measurement.<sup>[3,4,7,8]</sup>

### White coat effect

Studies indicate that white coat HT (where clinic BP measurements are persistently elevated while out-of-office readings are significantly lower) is as common in patients with resistant HT as it is in the more general hypertensive population.<sup>[9]</sup> In a large Spanish study involving over 12,000 patients, a third of the patients initially diagnosed as resistant HT, were reclassified as having white coat resistant HT when subjected to a 24 h ambulatory blood pressure test.<sup>[10]</sup> Thus, it is imperative to perform this test before labeling patients as having resistant HT.

### Poor adherence to medications

Non-adherence to antihypertensive drug therapy is another common cause of lack of BP control,<sup>[3,4,7,11]</sup> with a prevalence of 31.2% in a pooled analysis of 24 studies in patients with treatment resistant HT was.<sup>[11]</sup> This prevalence varies depending on the mode of assessment and tends to increase with the longer the duration of treatment. During a 5–10 year follow-up, less than 40% of patients persist with their prescribed antihypertensive medication.<sup>[12]</sup> In a referral clinic setting, this phenomenon is less common, but it is still an important contributing factor to poor BP control in up to 16% of patients.<sup>[13]</sup> HT is a chronic disease often requiring the taking of multiple pills lifelong. Usually, more number of drugs prescribed less likely is the patient to adhere to those medications. Witnessing drug intake, though ideal, is not always possible and a variety of methods has been used to identify this problem such as patient interview and

diaries, pill counting, and examining prescription refill records.<sup>[7]</sup> Therapeutic drug monitoring, by repeatedly measuring serum or urine drug concentrations, has also been found to be a cost-effective way to ensure proper pill intake.<sup>[7]</sup>

### Physician-related problems

Physician inertia is one of the important contributors to apparent drug-resistant HT.<sup>[14]</sup> It has been found that doctors are reluctant to maximize therapy by either switching medications or increasing the dose of drugs to reach target levels. There is a huge discrepancy between guideline recommendations and their implementation in everyday practice which results in suboptimum blood pressure control.<sup>[14]</sup> Another physician-related cause of resistant HT is the use of irrational drug combinations some of which do not even contain a diuretic in the prescription.<sup>[15]</sup> Bridging this gap between knowledge and implementation could go a long way in effectively treating HT.

### Identify Modifiable Lifestyle Factors

Addressing contributing lifestyle factors are the second step in the approach to managing patients with resistant HT. These factors could be broadly classified into lifestyle factors, concomitant drug ingestion, and diagnosing secondary HT.

#### Lifestyle factors

##### *Obesity*

This is more commonly associated with severe and resistant HT and the need for multiple medications.<sup>[16]</sup> The pathophysiological mechanisms responsible are varied and include defective sodium excretion, in addition to increased activation of the sympathetic and the renin-angiotensin-aldosterone axis (RAAS).<sup>[17]</sup>

##### *Physical inactivity*

Reduced physical activity and a sedentary lifestyle are important independent risk factors for HT, however, there is a lack of clinical studies linking physical inactivity to resistant HT.<sup>[4]</sup> Indirect evidence that activity plays a role comes from a study which demonstrated that a regular exercise program resulted in significant lowering of ambulatory BP readings in patients with RH.<sup>[18]</sup>

##### *Dietary salt*

Apart from directly contributing to high BP, increased dietary salt is also responsible for blunting the BP lowering action of antihypertensive medication.<sup>[19]</sup> This is more important in the salt sensitive populations such as the elderly, African-Americans, and those with CKD. Although increased salt intake is widespread, it has been especially identified in patients with resistant HT.<sup>[4,20]</sup>

##### *Alcohol intake*

Increased alcohol ingestion (>30–50 g/day) has been recognized as an important risk factor for HT across many populations.<sup>[3,4,7,21]</sup>

Poor adherence to drug therapy is another reason why BP control is more difficult to achieve in heavy drinkers.

## Treatable/Secondary HT

### Drug-induced HT

Despite its frequent occurrence, primary care physicians often miss the diagnosis and hence a rare opportunity to treat this iatrogenic form of HT.<sup>[22]</sup> A variety of prescriptions and over-the-counter medications may induce HT [Table 1] or contribute to treatment resistance, and therefore, a detailed history of concomitant drug ingestion is important. The mechanisms whereby these drugs increase the BP are multiple.<sup>[22]</sup>

### Other causes of secondary HT

Before labeling a patient as having resistant HT, it is imperative to rule out the treatable causes of secondary HT. These are seen in about 5–10% of patients with HT.<sup>[7]</sup> Secondary HT is to be suspected when HT is first encountered at extremes of age, or is resistant, or presents as accelerated or malignant HT, when there is a disproportionate target organ damage for the degree of HT, or unprovoked or excessive hypokalemia.<sup>[23]</sup> A list of the possible causes is enumerated in Table 2, but among these, the most common are primary aldosteronism (PA), obstructive sleep apnea (OSA), CKD, and renovascular causes.<sup>[22,23]</sup> The diagnostic work-up for secondary HT is exhaustive and beyond the purview of this paper but some important tests that need to be carried out in suspected cases are listed in Table 3. Particular attention should be paid to a detailed history and physical examination, especially with regard to a history of snoring, daytime sleepiness and neck thickness, presence of abdominal bruits and peripheral pulses to rule out renal artery stenosis, aortic coarctation, and aortoarteritis. Assessment of end-organ damage, hypokalemia, active urinary sediment,

**Table 1:** Drugs responsible for increase in blood pressure

Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors

Oral contraceptives

Sympathomimetics

Illegal drugs such as cocaine, amphetamines, ecstasy (MDMA and other derivatives)

Glucocorticoids

Mineralocorticoids

Immunosuppressants – cyclosporine, tacrolimus

Erythropoietin

Supplements – containing ginseng, licorice, yohimbine

Antidepressants – venlafaxine, bupropion, desipramine

VEGF inhibitors

Cancer drugs such as bevacizumab

COX-2: Cyclooxygenase 2, MDMA: 3,4-methylene-methamphetamine,

VEGF: Vascular endothelial growth factor

blood chemistry, and kidney size on ultrasound to rule out CKD is important as is tests to rule out the endocrine causes HT if clinically suspected.<sup>[7,23]</sup>

### OSA

This is another risk factor that has been documented to be associated with resistant HT.<sup>[3,4,7,24]</sup> The pathophysiological basis includes intermittent hypoxia, sympathetic stimulation, and intrathoracic pressure swings all of which lead to fluid overload, aldosterone excess, and resultant HT.<sup>[24]</sup> Diagnosis is established with the help of a questionnaire (STOP-Bang, Berlin, Epworth Sleepiness Scale), measurement of neck circumference (>40 cm), and performance of a sleep study.<sup>[7]</sup> Continuous positive airways

**Table 2:** Causes of secondary HT

Drug induced

Renal

Renovascular

Renal parenchymal

Neurological

Increased intracranial pressure

Dysautonomia

Lead poisoning, porphyria

OSA

Guillain-Barre syndrome

Endocrine

Primary hyperaldosteronism

Pheochromocytoma

Cushing's disease

Thyroid disorders

Acromegaly

Aortic disease

Coarctation of aorta

Aortoarteritis

HT: Hypertension, OSA: Obstructive sleep apnea

**Table 3:** Basic testing in a patient with resistant HT

Ambulatory BP monitoring

12-lead electrocardiogram/chest X-ray

Transthoracic echocardiogram

CBC and blood chemistry (including urea, creatinine, electrolytes)

Urine analysis (proteins, erythrocytes, leukocytes)

Plasma aldosterone concentration and renin

Free plasma metanephrine/normetanephrine

Thyroid-stimulating hormone

Renal ultrasound

Renal artery Doppler

CBC: Complete blood count, HT: Hypertension

pressure although mildly useful in hypertensive patients is strongly recommended in those with resistant hypertension (RHT) and at least moderate OSA.<sup>[7]</sup> A recent study, however, brought into question the effectiveness of this therapy.<sup>[25]</sup>

### Primary hyperaldosteronism

This is now considered as one of the most common causes of secondary HT accounting at least for 20% of all cases of resistant HT.<sup>[7]</sup> In a recent large study from Greece involving 1616 patient with true resistant HT, high aldosterone/renin ratios were detected in 21% of cases.<sup>[26]</sup> Of these, only about half had true PA as confirmed by salt suppression test or response to spironolactone. It usually occurs between the ages of 30 and 60 years and only about 40% have hypokalemia.<sup>[27]</sup> Diagnosis is established by measuring the plasma aldosterone renin ratio, currently considered the most sensitive marker for diagnosing this disease. The result is affected by prior drug ingestion, age, and the method of collection.<sup>[7,27]</sup> A low ratio of morning plasma aldosterone in ng/dl to plasma renin activity in ng/ml/h (normal level between 20 and 40) is a test with a high negative predictive value.<sup>[7]</sup>

### CKD

The relationship between CKD and HT is bidirectional. More than 75% of patients with CKD have HT and the prevalence of resistant HT in CKD patient is more than 50%.<sup>[28]</sup> The cause of resistance is multifactorial, the most important factor being salt and water retention. In addition, there is activation of the sympathetic and the RAAS and renal ischemia due to structural and functional alterations in the kidney vasculature.<sup>[22,23]</sup> Another important contributory factor to HT seen in these patients is the restriction in the use of diuretics and the fact that when the glomerular filtration rate (GFR) is <40 ml/min; thiazide diuretics are ineffective.<sup>[22]</sup>

### Renovascular HT

This is predominantly atherosclerotic in origin and is common in older patients, with diabetes and evidence of atherosclerosis in other vascular beds.<sup>[7]</sup> In younger females (10% of this population), fibromuscular dysplasia is the etiological factor. In India, it is not uncommon to see renal artery stenosis due to aortoarteritis. Non-invasive diagnosis of this condition is tricky and remains an unfulfilled challenge for primary care physicians.<sup>[4,22]</sup>

### Management of Resistant HT

Management of resistant HT requires a multipronged approach. Before labeling the patient as having true resistant HT, we need to rule out pseudoresistant HT by correctly measuring the BP and corroborating the readings with a 24 h ambulatory BP record. Next, one should pay careful attention and address and all modifiable factors alluded to above.

### Maximize adherence

Simplification of the patient's prescription so that the number of pills he has to take decreases helps improve patient compliance. This is most easily done by prescribing long-acting formulations and also using combination medications where possible. Educating and counseling patients on the importance of adhering to their medication are also extremely important. A multidisciplinary approach using nurses, pharmacists, and nutritionists can improve the results of treatment care but is not always possible due to financial or other logistical considerations. Liberal use of home monitoring readings also helps to ensure compliance.<sup>[7,29]</sup>

### Non-pharmacological methods

**Weight loss:** This should be encouraged in all patients, especially those who are obese and overweight. It has been shown that a 10 kg loss in weight is associated with a 6.0 mmHg decrease in systolic and a 4.6 mmHg decrease in diastolic pressures in patients with HT.<sup>[30]</sup> Although not studied in patients with resistant HT, it is logical to conclude that this intervention would benefit patients with resistant HT and also help decrease the overall cardiovascular risk of the patient.

### Dietary advice and salt restriction

A reduced salt intake is well proven to decrease BP. A recent meta-analysis showed that a 1.0 g (43.5 mmol) reduction in daily sodium intake produces a 2.1 and 1.2 mmHg decrease in systolic BP in hypertensive and normotensive patients, respectively.<sup>[4]</sup> Although this has not been studied specifically in resistant HT, it is not unreasonable to advise salt restriction in this subgroup of patients. This would be especially in those with a high salt intake and those whose BP is salt sensitive such as elderly and African-American patients. It is advised that all patients with resistant HT should decrease the sodium intake to <100 mmol/24 h (2.3 g/day)<sup>[4]</sup> and to <65 mmol/day (1.5 g/day) in some recalcitrant cases. This requires a detailed history of the diet of the patient to allow adjustments so as to achieve this target. In accordance with the DASH diet, high intake of vegetables, fruit, nuts, and low-fat dairy products with a decreased consumption of saturated fats is effective in further reducing the BP.<sup>[4]</sup>

### Other lifestyle measures

Smoking cessation is a must as is curbing excessive caffeine use. Curtailing the alcohol intake to not more than 2 drinks per day in males and one drink in females or lighter weight people helps control BP better.<sup>[3-5]</sup> It is advisable that patients with resistant HT perform some aerobic exercise of at least 30 min duration on most days of the week.<sup>[4,7]</sup> This has been proven to decrease BP in all patients with HT including those with resistant HT. In addition, meditation and yoga techniques have been proven to improve the overall well-being of the patient and aid control of the BP.<sup>[4]</sup> All these adjustments in lifestyle, if properly adhered to, could go a long way in managing these patients without resorting

to increased medication or other new invasive modalities of treatment.

### Treatment of the secondary causes of HT

If an endocrine cause of HT such as PA, pheochromocytoma, or Cushing's disease is diagnosed, these patients should be referred to a specialist for effective treatment of that particular disease. If ingestion of drugs known to be responsible for BP is identified, the treating physician should ideally stop them altogether or lower their dosage or find a suitable alternative.

### Treatment of OSA

The greatest benefit is seen in those patients with severe OSA who are already on medication for HT. Although it is strongly recommended in those with RHT and at least moderate OSA,<sup>[4,7]</sup> data regarding its use in resistant HT are sparse. More recently, the efficacy of this has brought into question the effectiveness of this therapy.<sup>[25]</sup>

### Treatment of Renal artery stenosis

Intervention in the form of balloon angioplasty and stenting is almost always curative in those with fibromuscular dysplasia and is strongly recommended in this subset of patients. Restenosis rates can approach 20% at the end of 1 year.<sup>[7]</sup> In those with a stenosis due to atherosclerosis, results of clinical studies surprisingly show no great benefit and may be even harmful.<sup>[31,32]</sup> The overall consensus thus is that in this subgroup of patients, intervention is reserved for those with truly resistant HT and those with a demonstrated decline in renal function.<sup>[3,4,7]</sup>

### Pharmacological Treatment of Resistant HT

Patients with resistant HT are by definition on at least three antihypertensive agents. Common sense dictates that the drugs should preferably act by different mechanism and possibly have a synergistic action. The most widely used drug combination is of an ACEI or ARB with a calcium channel blocker (preferably of the dihydropyridine type) and a thiazide diuretic.<sup>[3,4,7]</sup> When deciding which drug to use, the clinical profile of the patient plays an important role.<sup>[3,5,29]</sup> For example, a patient with ischemic heart disease would benefit by addition of a beta-blocker while patients of African origin may not respond to RAS blockers. Before adding another drug to the therapeutic regimen of patients with resistant HT is to make sure, the patient is on a maximum dose of the three primary drugs. It must be remembered that the dose of diuretic is GFR dependent and often the dose of diuretic used is subtherapeutic which needs to be first addressed.<sup>[4]</sup> The next step is to change from hydrochlorothiazide to chlorthalidone or indapamide as these appear to be more effective antihypertensive agents.<sup>[3,4,7,33,34]</sup> A dose of 25 mg of chlorthalidone is equivalent to 50 mg of hydrochlorothiazide. If the GFR is <30–40 ml/min, then addition of a loop diuretic in single or multiple doses may help.

### Which Fourth Line Drug?

It is now realized that activation of the RAAS and consequent fluid retention is the important pathogenetic mechanism of resistant HT.<sup>[3,4,7]</sup> It, therefore, stands to reason that if a fourth drug is required, a mineralocorticoid receptor antagonist spironolactone or eplerenone would be the drug of choice.<sup>[3,5,7]</sup> This has now been incorporated in all recent guidelines.<sup>[3,4,5]</sup> The PATHWAY 2 trial clearly demonstrated the effectiveness and also superiority of such a strategy over using other antihypertensive drugs such as a beta-blockers and alpha receptor blockers (bisoprolol and doxazosin, respectively, which were used in this trial).<sup>[35]</sup> In this study, which was a double-blind four-way crossover trial, spironolactone in a dose of 25–50 mg was compared to bisoprolol (5–10 mg), doxazosin (5–10 mg) or placebo.<sup>[35]</sup> Spironolactone was found to be superior to all the other strategies with a mean reduction of mean BP by 8.78 mmHg with spironolactone versus 4.48 mm Hg with bisoprolol and 4.03 mmHg with doxazosin. Importantly, the percentage of patients achieving BP control was 60%, 43.3%, and 41.5% with spironolactone, bisoprolol, and doxazosin, respectively.<sup>[35]</sup> Important clinical data were also gleaned from three substudies conducted in these patients.<sup>[36]</sup> The first was that spironolactone was most effective in patients with low renin levels. Second, with this treatment, the thoracic fluid content decreased significantly by 6.6% highlighting the importance of fluid retention in the etiopathogenesis of resistant HT. Finally, in one substudy, amiloride was used instead of spironolactone with equally effective if not better results.<sup>[36]</sup> As a result of these findings, the European guidelines propose the use of amiloride in those in whom spironolactone is either not tolerated or is contraindicated.<sup>[3]</sup> Use of the newer agents such as eplerenone can also be used but because of a shorter half-life usually requires a twice daily dosage.<sup>[4]</sup>

### Other second-line drugs

These are only used if diuretics or mineralocorticoids cannot be administered and are usually not as effective as spironolactone. Alpha-blockers are vasodilators with an added benefit in patients with benign prostatic hyperplasia. If beta-blockers are to be used, those with additional alpha blocking properties such as carvedilol or labetalol may be preferred.<sup>[7]</sup> Bisoprolol and doxazosin were both found to be effective in the PATHWAY 2 trial.<sup>[35]</sup> Direct vasodilators such as hydralazine and centrally acting drugs such as clonidine and moxonidine have been used but there are problems of patient adherence due to multiple dosing required with these drugs and also side effects such as fluid retention and symptomatic hypotension.<sup>[7]</sup> To assess their efficacy, the resistant HT optimal treatment study compared the impact of clonidine and spironolactone in 187 patients with resistant HT.<sup>[37]</sup> The BP control as assessed in the office and with 24 h BP recordings was similar, however, the magnitude of 24 h reduction and also the reduction in daytime diastolic readings was more with spironolactone.<sup>[37]</sup> Many newer drugs such as endothelin receptor blocker (darusentan), aldosterone synthase inhibitors, canrenone, and neprilysin inhibitors are being developed for the

treatment of HT, however, there are little data regarding their use in patients with resistant HT.<sup>[7]</sup>

### Interventional treatment of resistant HT

Due to inadequate BP control even after optimal drug treatment, there have been new developments in technology resulting in a number of interventional procedures under review for the treatment of resistant HT.<sup>[38]</sup> These include renal nerve ablation (RNA), carotid baroreceptor stimulation, central arteriovenous anastomosis, carotid bulb restoration, and aortic stimulation.

### RNA

Catheter-based renal denervation acts by modulating the efferent sympathetic signals to the kidney that leads to reduced renal flow, RAAS activation, and fluid retention. It also decreases the afferent signals to the brain which are responsible for sympathetic action on the heart, vascular bed, and neurohumoral loops.<sup>[38]</sup> Initial studies (SYMPPLICITY 1 AND 2) demonstrated significant reductions in BP and generated huge interest in this modality in the treatment of HT.<sup>38</sup> However, the SYMPPLICITY 3 prospective, randomized trial comparing this procedure to sham studies did not reveal any significant difference in BP outcome between the two groups.<sup>[39]</sup> The study suffered from several pitfalls, but the lack of complete denervation involving a four quadrant interruption of the sympathetic nerve fibers was considered the main factor responsible for the negative outcome of this study.<sup>[40]</sup> To overcome these shortfalls, three new studies were carried out to retest this hypothesis. One of these studies, using a special designed spiral multielectrode catheter (SPYRAL HTN ON study), recruited patients whose BP was not controlled by one to three medications.<sup>[41]</sup> When compared to a sham procedure, RNA was associated with a greater improvement in office and ambulatory BP recorded readings. There was no documented damage to the renal artery or deterioration in renal function. Another recent study compared two different methods of carrying out RNA – namely, ultrasound ablation versus the radiofrequency method.<sup>[42]</sup> The former was associated with a greater decrease in BP as compared to the radiofrequency group. However, many questions continue to remain unanswered. Which modality is best (radiofrequency or ultrasound ablation), whether one needs to perform only the main artery RNA or to access all side branches and accessory arteries, which patients are likely to benefit the most. Till such time that these issues are not addressed, RNA will not become part of the mainstream treatment of resistant HT.

### Iliac vein and artery anastomosis

This is performed by placement of an arteriovenous coupler. The ROX CONTROL HTN study compared this procedure versus pharmacological treatment and it was found to be associated with a better control of both systolic and diastolic BP and the benefit persisted up to 1 year post-procedure.<sup>[43]</sup> However, the procedure suffered from a serious adverse effect in the form of

iliac vein stenosis requiring stenting in up to 33% of patients.<sup>[43]</sup> This procedure has, therefore, been abandoned.

### Carotid baroreceptor activation therapy

Stimulation of the carotid baroreceptors results in a sympatholytic response which results in lower BP due to a decreased heart rate and peripheral vasodilatation. The first device was studied in the RHEOS study in patients with resistant HT.<sup>[44]</sup> Although it resulted in a significant amelioration in blood pressure lasting for up to 1 year, it was associated with a significant procedure related facial nerve injury.<sup>[38]</sup> The newer device (the Barostim Neo) from the same company is much smaller and has shown good long-term effects both in resistant HT and heart failure.<sup>[45]</sup> This modality has become approved in Europe for the treatment of resistant HT, but in the US, it is only approved for the treatment of heart failure.<sup>[38,45]</sup> However, it is more invasive than RNA and the safety of the procedure has not been well established to be included in the mainstream therapies for resistant HT.<sup>[38]</sup> The MobiusHD carotid bulb expansion device which acts by stretching the carotid artery at the bulb, thereby reducing the BP, is a newer device used to treat HT.<sup>[38]</sup> Two trials are underway for exploring its use in difficult-to-treat HT and the results are eagerly awaited.

### Conclusion

During the past several years, newer data have emerged regarding various therapeutic options available to treat resistant HT. Before resorting to these, it is imperative for the treating physician to rule out pseudo-HT and identify and implement lifestyle modifications that will bring down the BP. It is also important to clinically assess and evaluate thoroughly for secondary causes of HT. If a fourth drug is to be added, studies show that a mineralocorticoid inhibitor such as aldosterone is the most effective and the drug of choice. For those who are intolerant to or develop side effects with spironolactone, eplerenone or amiloride are reasonable alternatives with a similar mode of action. Beta-blocker, alpha-blockers, centrally acting drugs, direct vasodilators, and some of the newer drugs are usually tried in only the very resistant cases. Several interventional and device-based modalities have been developed and are being investigated and recent studies have renewed interest in RNA in therapy of resistant HT. Carotid receptor stimulation and modulation are another emerging therapy which needs long-term studies to assess effectiveness and also address safety aspects. With all this armamentarium available to the treating physicians, the future outlook of patients with resistant HT appears to be bright.

### References

1. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, *et al.* Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA* 2017;317:165-82.
2. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, *et al.* Potential US population impact of the 2017 ACC/AHA high

- blood pressure guideline. *Circulation* 2018;137:109-18.
3. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, *et al.* 2018 ESC/ESH guidelines for the management of arterial hypertension; the task force for the management of arterial hypertension of the European society of cardiology (ESC) and the European society of hypertension (ESH). *Eur Heart J* 2018;39:3021-104.
  4. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, *et al.* Resistant hypertension: Diagnosis, evaluation, and treatment. A scientific statement from the American heart association professional education committee of the council for high blood pressure research. *Hypertension* 2018;72:e53-90.
  5. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Dennison Himmelfarb C, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH ASPC/NMA/PCNA guideline for prevention, detection, evaluation and management of high blood pressure in adults. A report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol* 2018;71:e127-248.
  6. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, *et al.* Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012;125:1635-42.
  7. Tsioufis CP, Kasiakogias A, Tousoulis D. Clinical diagnosis and management of resistant hypertension. *Eur Cardiol Rev* 2016;11:12-7.
  8. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, *et al.* Recommendations of blood pressure measurement in humans and experimental animals. Part 1: Blood pressure measurement in humans. A statement for professionals from the subcommittee of professional and public education of the American heart association council on high blood pressure research. *Circulation* 2005;111:697-716.
  9. Brown MA, Buddle ML, Martin A. Is resistant hypertension really resistant? *Am J Hypertens* 2001;14:1263-9.
  10. De la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, *et al.* Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension* 2011;57:898-902.
  11. Durand H, Hayes P, Morrissey EC, Newell J, Casey M, Murphy AW, *et al.* Medication adherence among patients with apparent treatment-resistant hypertension: Systematic review and meta-analysis. *J Hypertens* 2017;35:2346-257.
  12. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. *J Hypertens* 2005;23:2101-7.
  13. Garg JP, Elliott WJ, Folker A, Izhar M, Black HR, RUSH University Hypertension Service. Resistant hypertension revisited: A comparison of 2 university-based cohorts. *Am J Hypertens* 2005;18:619-26.
  14. Ferrari P. Reasons for therapeutic inertia when managing hypertension in clinical practice in non-Western countries. *J Hum Hypertens* 2009;23:151-9.
  15. Gupta CN, Akul SK, Mahapatra S, Lahiri A, Maji K, Sen S. Evaluation of antihypertensive drug prescription patterns, rationality and adherence to joint national committee-8 hypertension treating guidelines among patients attending medicine OPD in a tertiary care hospital. *Int J Contemp Med Res* 2019;6:J31-7.
  16. Bramlage P, Pittrow D, Wittchen HU, Kirch W, Boehler S, Lehnert H, *et al.* Hypertension in overweight and obese primary care patients is highly prevalent and poorly controlled. *Am J Hypertens* 2004;17:904-10.
  17. Hall JE. The kidney, hypertension, and obesity. *Hypertension* 2003;41:625-33.
  18. Dimeo F, Pagonas N, Seibert F, Arndt R, Zidek W, Westoff TH. Aerobic exercise reduces blood pressure in resistant hypertension. *Hypertension* 2012;60:653-8.
  19. Weinberger MH, Cohen SJ, Miller JZ, Luft FC, Grim CE, Fineberg NS. Dietary sodium restriction as adjunctive treatment of hypertension. *JAMA* 1988;259:2561-5.
  20. Nishizaka MK, Pratt-Ubunama M, Zaman MA, Cofield S, Calhoun DA. Validity of plasma aldosterone-to-renin activity ratio in African American and white subjects with resistant hypertension. *Am J Hypertens* 2005;18:805-12.
  21. Hussain K, Arisari RA, Ferder L. Alcohol-induced hypertension: Mechanism and prevention. *World J Cardiol* 2014;26:245-52.
  22. Faselis C, Doulmas M, Papademetriou V. Common secondary causes of hypertension and rational for treatment. *Int J Hypertens* 2011;2011:1-17.
  23. Chiong JR, Aronow WS, Khan IA, Nair CK, Vijayaraghavan K, Dart RA, *et al.* Secondary hypertension: Current diagnosis and treatment. *Int J Cardiol* 2008;124:6-21.
  24. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, *et al.* Obstructive sleep apnea: The most common secondary cause of hypertension associated with resistant hypertension. *Hypertension* 2011;58:811-7.
  25. Muxfeldt ES, Margallo V, Costa LM, Guimaraes G, Cavalcante AH, Azevedo JC, *et al.* Effects of continuous positive airway pressure treatment on clinic and ambulatory blood pressures in patients with obstructive sleep apnea and resistant hypertension: A randomized controlled trial. *Hypertension* 2015;65:736-42.
  26. Douma S, Petidis K, Doulmas M, Papaefthimiou P, Triantafyllou A, Kartali N, *et al.* Prevalence of primary hyperaldosteronism in resistant hypertension: A retrospective observational study. *Lancet* 2008;371:1921-6.
  27. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, *et al.* Endocrine Society. Case detection, diagnosis, and treatment of patients with primary aldosteronism: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2008;93:3266-81.
  28. Coresh J, Wei GL, McQuillan G, Brancati FL, Level AS, Jones C. Prevalence of high blood pressure and elevated serum creatinine level in the United States: Findings from the third national health and nutrition examination survey (1988-1994). *Arch Intern Med* 2001;161:1207-16.
  29. Aronow WS. Approaches for the management of resistant hypertension in 2020. *Curr Hypertens Rep* 2020;22:1-9.
  30. Aucott L, Poobalan A, Smith WC, Avenell A, Jung R, Broom J. Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes: A systematic review. *Hypertension* 2005;45:1035-104.
  31. Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, Baigent C, *et al.* Revascularization vs. Medical therapy for renal-artery stenosis. *N Engl J Med* 2009;361:1953-62.
  32. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, *et al.* Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014;370:13-22.

33. Roush GC, Sica DA. Diuretics for hypertension: A review and update. *Am J Hypertens* 2016;29:1130-7.
34. DiNicolantonio JJ, Bhutani J, Lavie CJ, O'Keefe JH. Evidence-based diuretics: Focus on chlorthalidone and indapamide. *Future Cardiol* 2015;11:203-17.
35. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, *et al.* Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomised, double-blind, crossover trial. *Lancet* 2015;386:2059-68.
36. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, Ford I, *et al.* Endocrine and haemodynamic changes in resistant hypertension and blood pressure responses to spironolactone or amiloride: The PATHWAY-2 mechanisms substudies. *Lancet Diabetes Endocrinol* 2018;6:464-75.
37. Krieger EM, Drager LF, Giorgi DM, Pereira AC, Barreto-Filho JA, Nogueira AR, *et al.* Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: The ReHOT randomized study (resistant hypertension optimal treatment). *Hypertension*. 2018;71:681-90.
38. Doulas M, Imprialos KP, Kallistratos MS, Manolis AJ. Recent advances in understanding and managing resistant/refractory hypertension. *F1000Res* 2020;9:1-10.
39. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, *et al.* A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;370:1393-401.
40. Papademetriou V, Stavropoulos K, Doulas M, Tsioufis K. Now that renal denervation works, how do we proceed? *Circ Res* 2019;124:693-5.
41. Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, *et al.* Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018;391:2346-55.
42. Fengler K, Rommel KP, Blazek S, Besler C, Hartung P, von Roeder M, *et al.* A three-arm randomized trial of different renal denervation devices and techniques in patients with resistant hypertension (RADIOSOUND-HTN). *Circulation* 2019;139:590-600.
43. Lobo MD, Ott C, Sobotka PA, Saxena M, Stanton A, Cockcroft JR, *et al.* Central iliac arteriovenous anastomosis for uncontrolled hypertension: One-year results from the ROX CONTROL HTN trial. *Hypertension* 2017;70:1099-105.
44. Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, *et al.* Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension. Results from the double-blind, randomized, placebo-controlled Rheos pivotal trial. *J Am Coll Cardiol* 2011;59:765-73.
45. Lohmeier TE, Hall JE. Device-based neuromodulation for resistant hypertension therapy. *Circ Res* 2019;124:1071-93.

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