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HYPERTENSION (DS GELLER AND DL COHEN, SECTION EDITORS)

Resistant Hypertension Updated Guidelines

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Abstract

Purpose of Review To discuss the current definition as well as recommendations for diagnosis and treatment of resistant hypertension (RH) based on the 2018 American Heart Association (AHA) guidelines and recent literature.

Recent Findings RH is defined as uncontrolled blood pressure (BP) on ≥ 3 anti-hypertensives, one of which should be a diuretic, prescribed at maximally tolerated doses and appropriate dosing frequency. The diagnosis of RH requires exclusion of white coat effect and medication non-adherence, underscoring the importance of out-of-office BP measurements. Secondary causes of hypertension must be excluded in all patients with RH. A step-wise approach to treatment focusing on lifestyle modifications and medication optimization can be effective in > 50% of the patients with RH. Device-based interventional therapies for RH are currently investigational.

Summary Out-of-office BP measurements are central to the diagnosis of RH. Medication optimization is successful in most patients. Further studies are needed to define the role of device-based interventions.

Keywords Resistant hypertension · Hyperaldosteronism · White coat hypertension · Ambulatory BP monitoring · Renal denervation · Pseudoresistance

Introduction/Definition of RH

Resistant hypertension (RH) is defined by the 2018 American Heart Association (AHA) guidelines as the blood pressure (BP) of a hypertensive patient that remains above goal despite concurrent use of 3 or more anti-hypertensive agents of different classes administered at maximally tolerated doses and appropriate dosing frequency [1••]. Typically, the 3-drug regimen includes a diuretic, a long-acting calcium channel blocker (CCB), and a renin–angiotensin system inhibitor (RAASi) (angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)). Notably, patients who are on 4 or more anti-hypertensives and achieve goal BP are included in this definition and are referred to as having "controlled resistant hypertension." The term "refractory" hypertension does not have a consistent definition in the literature and will not be used in this review [2–4].

The 2018 AHA RH definition (Table 1) differs in several important ways from prior 2008 guidelines. (1) The revised definition is more descriptive and notes a commonly used and effective 3-drug combination as mentioned earlier. (2) White coat hypertension (WCH) is excluded from the definition of RH. "White-coat effect" is defined as BP above goal at the office but at or below goal on ambulatory or home blood pressure monitoring. Therefore, out-of-office BP readings are important to obtain and WCH needs to be ruled out. (3) Medication non-adherence needs to be excluded before a diagnosis of RH is established.

If information regarding medication dose, adherence, or out-of-office BP readings (i.e., causes of pseudoresistance) is unavailable in uncontrolled hypertensives on ≥ 3 medications, they are termed as having apparent treatment RH (aTRH).

Prevalence

The prevalence of RH varies significantly between populations: clinic-based hypertension studies versus clinical trials

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Table 1 2018 AHA definition of resistant hypertension

1. Above goal BP despite 3 or more BP meds commonly including a long-acting CCB, RAS blocker, and a diuretic at maximally tolerated doses and appropriate dosing frequency
2. WCH is excluded with ABPM or home BP monitoring
3. Medication non-adherence is excluded
4. Goal BP should be defined based on current clinical guidelines

[1••]. Population or clinic-based studies report prevalence of RH around 12–18%. Given issues around pseudoresistance, these statistics likely reflect prevalence of aTRH rather than true RH. The higher prevalence of RH (34–39%) noted in clinical trials likely has to do with selection bias of a study population at higher risk for cardiovascular outcomes [1••].

Prognosis

Patients with RH are at a two-fold higher risk of cardiovascular events compared to those with controlled hypertension [1••]. A large retrospective study comparing hypertensives with RH (controlled and uncontrolled) versus those that did not have RH found a 32% increased risk of developing end-stage renal disease, a 25% increased risk of an ischemic heart event, a 46% increased risk of heart failure, a 14% increased risk of stroke, and a 6% increased risk of death in the RH group [5••].

Diagnosis

The new definition of RH highlights the importance of accurate and standardized BP measurement techniques, out-of-office BP measurements as well as ensuring medication adherence.

Medication Non-Adherence Exclusion

Medication non-adherence is an important cause of aTRH and falsely increases the prevalence of RH. Studies utilizing direct plasma/urine drug measurements of anti-hypertensives have reported non-adherence rates anywhere from 25 to 68% among hypertensive patients, with the higher rates reported among patients labeled as "resistant" [6, 7•, 8, 9•, 10, 11]. Unfortunately, medication compliance history from the patient is unreliable and administered patient questionnaires are often filled inaccurately [11]. Among patients identified as non-adherent by pharmacy refill records, providers accurately characterized only 37% as non-adherent based on patient history [12]. Perceived non-adherence is a barrier to therapy intensification partly due to clinician inertia which contributes further to suboptimal BP control in the patient [12, 13]. No current consensus exists on the best way to confirm adherence prior to labeling the patient as having RH. Direct methods, such as urine or plasma liquid chromatography, are expensive and not widely available. A multisystem team-based care approach incorporating patient education, patient self-report adherence assessment tool, and pharmacy refill databases may be preferred. Use of cost-effective medications with once-daily dosing or combination drugs to reduce pill burden can help improve medication adherence; more formalized guidelines await further trials [1••, 14, 15].

WCH Exclusion

Approximately 37% of patients with aTRH have WCH [16]. However, prognostically, they are very distinct from patients with true RH. Long-term cardiovascular risk in patients with WCH is similar to that of well-controlled hypertensives [17, 18]. A 2019 meta-analysis of 11 large studies concluded that the risk of deterioration to sustained hypertension was significantly higher in the WCH group (RR 2.85, range 2.32–3.49) but failed to detect any significant differences in risk for stroke, cardiac outcomes, or all-cause mortality [19]. The need to exclude WCH in patients with presumed RH places a greater emphasis on out-of-office BP measurements. Given the limited availability of 24-h ambulatory blood pressure monitoring (ABPM), clinicians often rely on home BP measurements [20]. There is a good correlation between ABPM and home BPs; however, home BPs tend to overestimate BP by a factor of 8.8/0.2 mmHg with a lower sensitivity (55%) but a high specificity (91%) to detect controlled BP [21•]. Therefore, if the BP based on home BP monitoring is above goal, ideally, an ABPM should be done next [22]. Both modalities are superior to office BP in predicting cardiovascular risk [23, 24]. It is worth noting that, while recent guidelines define BP control as < 130/80 mmHg in the office, control as determined by 24-h ABPM is defined as BP average < 125/75 mmHg [25••]. A March 2019 scientific statement from the AHA extensively lays out considerations for in-office, at-home, and ambulatory BP measurements [26•].

Once the diagnosis of RH has been established, the next step is to evaluate for secondary causes of hypertension.

Excluding Secondary Causes

Current AHA guidelines recommend screening all patients who strictly fit the definition of RH for secondary causes [1••].

Drug-Induced RH

Numerous drugs (prescription, over-the-counter, and illicit) are known to elevate BP. Non-steroidal anti-inflammatory agents (NSAIDs) are thought to be one of the more common causes of drug-related hypertension, raising systolic BP by

5 mmHg on average [27, 28]. Inhibition of renal prostaglandins leading to decreased afferent arteriolar vasodilation and natriuresis is the putative mechanism and may explain the relative ineffectiveness of ACEi/ARBs in patients taking NSAIDs [29]. Oral contraceptives (combined estrogen and progesterone) and hormone replacement medications are another common culprit. These are associated with the greatest BP increase (~ 3–6 mmHg) [30, 31]. Proposed mechanism is increased angiotensin production, though much of the knowledge in this field is based on older studies [32]. Less common drugs include illicit substances (cocaine and amphetamines) where the hypertensive effect is mediated via sympathetic nervous system activation and medications such as calcineurin inhibitors, recombinant human erythropoietin, anti-depressants, and tyrosine kinase inhibitors that act via a variety of complex mechanisms to raise BP [33–36]. Practitioners should at least screen for the presence of these substances in the RH population while acknowledging that the effects of all the agents described in this section are highly variable with effects unpredictable at the individual level.

Secondary Causes

Upon excluding the contribution of exogenous substances, the practitioner should initiate a targeted work-up to assess for causes of secondary hypertension. Initial testing is guided by the prevalence of the various disorders in the RH population and the individual features of the patient. Most common secondary causes of hypertension include obstructive sleep apnea (OSA), renal parenchymal disease (i.e., chronic kidney disease or CKD), renal vascular disease (specifically, renal artery stenosis), and primary hyperaldosteronism (PH). Pheochromocytoma and corticosteroid excess (or Cushing syndrome) are rare. Initial work-up for any patient with RH should include a basic metabolic panel, urinalysis (including assessment of proteinuria), and serum aldosterone and plasma renin activity (PRA) measurements [1••]. Further biochemical or imaging studies are recommended based on patient risk factors and clinical features. This will be briefly discussed in the subsequent texts and summarized in Table 2. The reader is directed to some excellent reviews on the topic.

Primary Hyperaldosteronism Primary hyperaldosteronism (PH) is a condition marked by inappropriately high and autonomous aldosterone production most commonly due to an aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia, with adrenal carcinoma being an important rare cause [37]. The prevalence of PH in patients with RH is 10 to 20% (vs. < 10% in general hypertensives) [38–40]. Accordingly, the 2016 Endocrine Society clinical practice guidelines recommend screening all patients with RH for primary hyperaldosteronism with a morning plasma renin assay (PRA) and serum aldosterone level [40]. A positive test is defined by an aldosterone/renin ratio (ARR) > 30 or > 20 if the plasma aldosterone concentration (PAC) is ≥ 16 ng/dL [40]. It is worth noting that some investigators use additional criteria where PAC ≥ 15 ng/dL in addition to elevated ARR in order to account for patients with very low renin values; however at least one study had confirmable cases of aldosterone excess with PAC values < 15 ng/dL, and, thus, a PAC cut-off is not currently included in the Endocrine Society guidelines [40•, 41]. Next steps include confirmatory testing with 1 of 4 recommended tests that are reviewed extensively in the referenced guidelines; in our practice, we typically use an oral-salt loading test coupled with a 24-h urine aldosterone measurement. A confirmatory test is not required in a patient with spontaneous hypokalemia, an undetectable PRA, and a PAC > 20 ng/dL. These constellation of findings can only be seen in PH [40•]. Finally, subtype classification (unilateral versus bilateral disease) is pursued starting with adrenal computed tomography (CT) and followed by adrenal venous sampling (AVS) for those patients who are potential surgical candidates. In young patients with unilateral disease surgical, management with adrenalectomy is recommended, while patients with bilateral disease and those who are not surgical candidates should be treated with a mineralocorticoid receptor antagonist, such as spironolactone [40•].

Chronic Kidney Disease Hypertension and chronic kidney disease are bidirectionally interrelated with hypertension resulting in progressive CKD and advanced CKD contributing to sodium and water retention and RAAS overactivation with consequently poor BP control. The prevalence of RH is very high in patients with CKD. A 2016 report from the Chronic Renal Insufficiency Cohort Study examined over 3000 hypertensive patients with chronic kidney disease and determined that ~ 40% of this population had RH when using a BP cut-off of 140/90 mmHg [42•]. Among patients on > 3 antihypertensives within this cohort, only 40–49% had controlled BP when using a goal 130/80 mmHg and 61–69% when using a more liberal goal of 140/90 mmHg [43]. Given these findings, guidelines recommend screening all patients with RH for the presence of chronic kidney disease; treatment guidelines will center around the understood pathophysiology as reviewed later.

Renal Vascular Disease (Renal Artery Stenosis) In the elderly, atherosclerotic renal vascular disease remains an important secondary cause of RH. Recent case series indicate that ~ 24% of elderly patients with RH have significant renal vascular disease/stenosis [44]. In older studies, the prevalence of renal occlusive disease was as high as 35% in patients with secondary forms of hypertension (though not strictly defined as RH) [45]. Landmark trials, including ASTRAL and CORAL, failed to demonstrate significant benefit related to renal and cardiovascular outcomes with renal artery

Table 2 Secondary causes of resistant hypertension and suggested work-up

Cause	Prevalence in RH	Signs/symptoms	Recommended screening	Test interpretation
Primary hyperaldosteronism	10–20%	None specific Only a minority of patients (< 35%) are hypokalemic	Morning aldosterone and plasma renin activity (PRA) in *all* patients with RH	Aldosterone to plasma renin ratio (ARR) > 30 or > 20 if plasma aldosterone concentration (PAC) is ≥ 16 ng/dL
Chronic kidney disease	High prevalence of RH in CKD population (~ 40%) indicates bidirectional cause and effect relationship between hypertension and CKD	None at early stages of CKD Signs and symptoms of volume overload (edema, shortness of breath) and uremia (nausea, vomiting, fatigue) at late stages	Basic metabolic panel and urinalysis in all patients with RH	Chronic kidney disease stages as defined by the estimated glomerular filtration ratio (eGFR)
Renal artery stenosis	~ 25% of elderly patients	Abdominal bruit (non-specific); comorbid coronary or peripheral arterial disease (CAD, PAD); unexplained atrophic kidney or size discrepancy > 1.5 cm between kidneys; flash pulmonary edema; unexplained drop in eGFR	Renal duplex ultrasonography OR computed tomographic angiography OR magnetic resonance angiography in select patients	Depending on imaging modality For renal duplex ultrasonography: Reno-aortic velocity ratio (renal artery peak systolic velocity (RAPSV)/aortic peak systolic velocity) greater than 3.5 and RAPSV > 180 cm/s correlate to 60% + stenosis
Obstructive sleep apnea	70–90%	Loud snoring, frequent nocturnal arousals, witnessed apnea, excessive daytime sleepiness	Screening for symptoms in all patients with hypertension Polysomnography in select patients	Apnea-hypopnea index (AHI) > 15 events/h
Pheochromocytoma	Rare, < 5%	-Paroxysmal hypertension -All patients with an incidental adrenal mass	Plasma-free metanephrines *or* 24-h urine-fractionated metanephrines	Laboratory reference intervals differ regionally; positive biochemical test results should be followed up by CT imaging
Cushing syndrome	Rare, < 5%	Easy bruising Striae Dorsal fat deposition Osteoporosis Proximal myopathy	Urine cortisol *OR* late night salivary cortisol *OR* 1 mg overnight or 2 mg 48-h dexamethasone suppression test in select patients	An abnormal test based on local laboratory reference intervals should be referred to an endocrinologist

angioplasty/stenting compared to conservative medical management despite achieving a lower systolic BP in the stenting arm in the CORAL trial [46, 47]. Based on these trials, current treatment approach favors medical management focused on RAAS blockade and use of statin and aspirin. Large data registries indicate that ACEi/ARBs confer a mortality benefit in this population [48, 49]. Despite lack of data, there is a select group of patients that may still benefit from revascularization. Patients with uncontrolled BP despite maximized medical therapy and those with accelerated loss of eGFR and/or recurrent flash pulmonary edema were excluded from most trials and should be considered for treatment with revascularization; detailed considerations are outlined in a 2014 Expert Consensus statement [50].

Obstructive Sleep Apnea and Other Sleep Disorders Poor sleep quality from numerous causes, including restless leg syndrome, insomnia, as well as OSA, has been implicated as a contributor to elevated BP [51, 52]. Studies have reported a very high prevalence (> 70%) of severe OSA in patients with RH, attributed to fluid retention leading to upper airway edema [53, 54]. Activation of the sympathetic nervous system and the role of aldosterone/RAAS have been described as potential mechanisms [55, 56]. All patients with RH should be screened for symptoms for OSA (Table 2) and polysomnography performed in patients who screen positive [1••]. Use of continuous positive airway pressure (CPAP) treatment is recommended in all patients with OSA though studies have routinely shown modest SBP reduction of 2–5 mmHg with this treatment, including in patients with RH [57, 58]. Given the mechanistic role of the RAAS and sympathetic activation, it is reasonable to utilize RAAS blockers and central α-agonists for BP control though no specific guidelines currently address this topic [59, 60].

Pheochromocytoma and Cushing Syndrome Catecholamine-producing chromaffin cell tumors, such as pheochromocytoma and excessive glucocorticoid exposure (endogenous or exogenous) leading to Cushing syndrome, are both rare causes of RH, estimated to account for < 5% of cases [61, 62]. See Table 2 for further details.

Management

General Principles

Patients with RH are complex and require a multi-modal approach to achieve BP control. Most patients can be managed with medication optimization, including use of combination therapies, to improve adherence and lifestyle interventions. There may be a role for invasive treatment modalities in a small subset of patients. A rational step-by-step approach to BP management in RH based on the most recent AHA guidelines will be summarized in Fig. 1.

Lifestyle Interventions

Low Sodium Diet Association between high sodium intake and hypertension is well known. AHA guidelines recommend a low salt diet (100 mmol/day or < 2.3 g daily) for all patients with hypertension [25, 63]. In a study of 204 patients with confirmed RH, 33% had 24 h urinary sodium excretion > 200 mEq [64]. A randomized crossover trial with 12 patients with RH assessed multiple parameters on low salt (50 mmol/d) and high salt (250 mmol/d) diets for 7 days each. The average drop in BP was 22.7/9.1 mmHg in the low salt versus the high salt group [65]. A similar study in 20 adult patients with stage 3–4 CKD had average BP drops of 10/5 mmHg [66]. Patients with CKD, obesity, and RH may be particularly sensitive to sodium. As decrement in BP is linear to the decrease in sodium intake, perhaps more stringent control of dietary sodium intake may be beneficial in high-risk populations [63]. More trials are needed to evaluate this approach.

Caloric Restriction and the DASH Diet General hypertension guidelines recommend > 5–10% of body weight loss for overweight/obese hypertensives; alcohol restriction (< 10 g/d for women and < 20 g/d for men); as well as potassium-rich and low-fat diets, such as DASH (Dietary Approaches to Stop Hypertension), as being effective means to lower BP [1••, 79]. A recent meta-analysis has reported decrease in BP of 4.5/3.2 mmHg in hypertensive patients with weight loss [25••, 67]. No studies to date have addressed weight loss and utility of DASH diet specifically in the RH population, but the results can be reasonably applied to this group of patients [25••, 68]. Caution must be exercised with DASH diet in patients with CKD due to the risk of hyperkalemia.

Exercise Numerous studies have established the role of exercise in BP control. The largest meta-analysis thus far reported a decrease in BP by 8.3/5.2 mmHg after several weeks of aerobic and endurance exercises [69]. Several small studies in patients with RH reported similar effects when evaluating both short-term and long-term effects of aerobic exercise on 24-h blood pressure [70, 71]. Data are lacking on the combined effects of lifestyle interventions in BP control, and this remains a promising area of research. Given the effect size of these interventions, it is reasonable to employ all the above-mentioned recommendations in the management of complex RH patients.

Pharmacologic Treatment

Suboptimal medication management is identified as a major cause of RH [72]. Referral to a hypertension specialist and medication optimization can achieve BP control in > 50% (and as high as 90%) of cases [3, 72, 73]. By definition, patients with RH should already be on maximally tolerated doses of a diuretic, ACEi/ARB, and a long-acting CCB. Within each class, drug choice may be guided by some existing data derived from studies in the general hypertensive population; however, specific data in RH patients is lacking. Studies demonstrate a greater BP-lowering effect (~ 10 mmHg) with azilsartan medoxomil as compared to olmesartan, valsartan, and ramipril [74, 75]. Among long-acting CCBs, small studies suggest better BP control with nifedipine compared to amlodipine; however, use is limited due to more edema-related side effects [76, 77]. Short-acting CCBs are not recommended for use in RH. Currently, there are no data supporting the use of a specific RAASi or long-acting CCB for patients with RH [1••].

Volume excess and high sodium intake play an important role in the pathogenesis of RH as indicated by the high prevalence (67–75%) of low renin state in RH [65, 78]. Therefore, effective volume control is a vital initial step towards BP control in this group. A diuretic class appropriate for estimated glomerular filtration rate (eGFR) should be used: The current guidelines in RH recommend using a long-acting thiazide-like diuretic, such as chlorthalidone (CTD) or indapamide, in RH patients with an eGFR > 30 mL/min and a long-acting loop diuretic, such as torsemide, if eGFR is < 30 mL/min [1••]. The use of hydrochlorothiazide (HCTZ) becomes less predictable at eGFR < 45 mL/min, and switching to CTD or indapamide is recommended in patients with eGFR 30 to 45 mL/min if a thiazide-class diuretic is desired [79]. In fact, several studies support an improved day time and nocturnal BP effect of CTD as compared to same-dose HCTZ (5–7 mmHg lower SBP on average) [80, 81].

The pathogenesis of RH is complex, and underlying mechanisms beyond volume excess exist. Sympathetic activation and vascular dysfunction may play a bigger role than volume

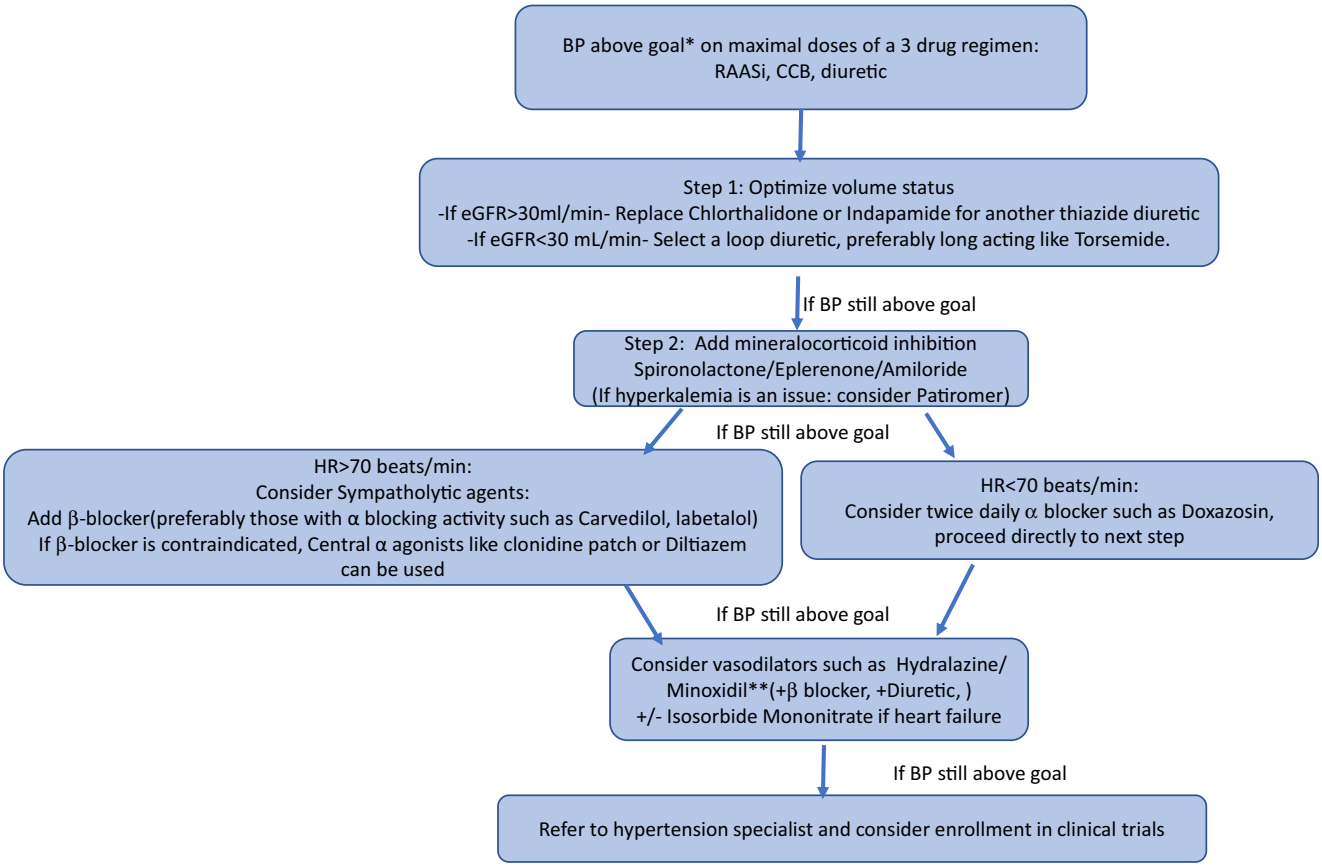

Fig. 1 A step-wise approach to pharmacological management of resistant hypertension. RAASi, renin–angiotensin aldosterone system inhibitor; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate. * BP goal is defined by the latest AHA hypertension guidelines. ** Hydralazine can cause tachycardia and should be used with a β-blocker. Minoxidil can cause significant fluid retention and should be used with a diuretic

in a subset of RH patients, where diuretic up-titration may not be an effective means to control BP. One study evaluated RH patients on ≥ 5 anti-hypertensives who underwent cardiac magnetic resonance imaging and were found to have no evidence of intravascular volume overload based on normal cardiac chamber volumes, suggesting that treatment resistance in this high risk cohort was due to factors other than volume excess [82]. Researchers have investigated the role of objective volume measurement in guiding drug choice in RH. Drug dosing based on bioimpedance measurements was compared to drug adjustments made by a hypertension specialist without such data and demonstrated goal BP control in 56% of patients in the bioimpedance group versus 33% in the specialist group [83].

Choice of the 4th Drug There is extensive literature support for the use of mineralocorticoid receptor antagonists, specifically spironolactone, as the fourth agent in RH. A meta-analysis of 5 randomized controlled trials totaling 553 patients with RH showed a 24-h SBP decrease of ~ 10 mmHg when spironolactone was added to a 3-drug regimen as opposed to placebo [84•]. The PATHWAY-2 trial compared spironolactone to placebo, bisoprolol, and doxazosin in a randomized double-blind crossover trial. Spironolactone lowered SBP by an additional 8 mmHg as compared to placebo and by 4–5 mmHg as compared to the other active treatment groups [85•]. It is worth mentioning that spironolactone was primarily effective in patients with low serum renin levels; at high renin levels, it was no longer superior to other drug classes [85•]. In fact, some authors argue for checking renin levels to guide therapy. Low plasma renin values are indicative of volume excess and favor utilizing diuretics and MR antagonists. On the other hand, high plasma renin levels favor the use of ACEis and ARBs. In a small trial of 77 patients, 74% of those randomized to this strategy achieved BP control as compared to 59% in the control group, though the results did not reach statistical significance [86]. Overall, the current weight of evidence does not support using specific laboratory or imaging tests to guide medication choice, and the decision is left up to the individual practitioner.

Recently published sub-studies of the PATHWAY-2 trial offer further support of the idea that RH is a salt-retaining state and identify amiloride as a viable alternative to spironolactone for the treatment of RH [87]. In a subset of 146 RH patients,

12-week treatment with amiloride resulted in similar SBP-lowering effects from baseline as spironolactone (20.4 mmHg vs. 18.3 mmHg SBP) [87]. Therefore, in RH, amiloride may be an effective 4th agent in patients responsive but intolerant to spironolactone due to adverse effects, such as gynecomastia and erectile dysfunction. It is worth noting that a small (~ 0.3–0.5 meq/L) but persistent increase in serum potassium has been observed with MR antagonists, and treatment-limiting hyperkalemia remains of particular concern in patients with comorbid RH and CKD [85•]. Newer potassium-binding drugs, such as patiromer, may allow use of RAAS inhibitors, including MR antagonists, in patients with RH. In a recent study, patients receiving patiromer and RAAS inhibitors 15% developed hyperkalemia as compared to 60% in the control group (RAASi and placebo) [88]. A trial investigating combination therapy with patiromer and spironolactone in patients with RH and CKD is currently underway [79].

What Drug to Use Next? Empirical evidence for which drugs to choose after spironolactone is minimal, but recommendations are presented here based on the 2018 AHA guidelines and practice at our institution. Assessment of sympathetic tone as evidenced by heart rate is a reasonable next step, and sympatholytic drugs may be considered. Combined α/β-blockers (such as carvedilol, nebivolol, and labetalol) may have a therapeutic advantage over β-blocker monotherapy [89]. If contraindicated, clonidine patch should be considered. While not included in the AHA guidelines, in our opinion, it is reasonable to use an α-blocker (such as doxazosin twice daily) for the patients with heart rate < 70 beats/min. Next, hydralazine should be added but care should be taken that it is only used in conjunction with a diuretic and a negative inotrope given the propensity of hydralazine to increase sodium retention and sympathetic tone. Nitrates are of limited use alone but can be combined with hydralazine for patients with heart failure and reduced ejection fraction (HFrEF) [90]. Similarly, sacubitril/valsartan is indicated for use primarily in patients with HFrEF [91]. Patients who remain refractory despite all of these interventions should be referred to a hypertension specialist and may be considered for device therapy and/or clinical trials [1••].

Device-Based Treatment

Sympathetic overactivity is one of the postulated mechanisms for RH. Device-based treatments for hypertension focus on reducing central sympathetic outflow. These treatments are currently investigational in the United States and will be discussed briefly in this review.

Renal sympathetic nerve ablation or denervation is probably the best known of the interventional therapies as early studies demonstrated encouraging results. However, the key study in the field, SYMLICITY HTN-3 trial, was a prospective sham-controlled randomized study with over 500 patients that failed to demonstrate any difference in BP among patients with RH after radiofrequency renal denervation compared to sham controls [92]. Improved catheters and more aggressive radiofrequency denervation techniques have been trialed since. One such sham-controlled study, SPYRAL HTN-OFF MED, evaluated the effect of more complete denervation(main renal artery and branches using a spiral catheter) in hypertensives off of their medications and demonstrated significant reductions in 24-h ABPM while demonstrating procedural safety [93•]. This has led to the ongoing SPYRAL HTN-ON MED trial evaluating denervation therapy specifically in patients with RH [94•]. Studies have evaluated using ultrasound energy rather than radiofrequency for full circumferential thermal ablation of the renal sympathetic nerves with success [95]. A recent trial comparing the various denervation approaches found endovascular ultrasound ablation to be superior to radiofrequency ablation of the main renal artery and similar in efficacy to the more aggressive radiofrequency ablation around both the main renal artery and smaller branches [96].

Carotid sinus baroreceptor activation involves carotid sinus stimulation via an electronic pulse generator system which causes reduced central sympathetic outflow and increased vagal activity resulting in reduced cardiac workload and enhanced arterial dilatation. Several small studies appear promising, but efficacy data from controlled trials are lacking [97, 98].

Several ongoing trials listed on ClinicalTrials.gov will further define the utility of device-based therapies in RH.

Conclusion

Resistant hypertension is an important cause of cardiovascular morbidity and mortality. Diagnosis requires exclusion of white coat hypertension and medication non-adherence. Evaluation for secondary causes of hypertension is important. A step-wise treatment approach focusing on lifestyle intervention and medication optimization is often effective means of treatment. Invasive interventions utilizing device-based therapies are currently investigational, and their role in the treatment of RH is yet to be determined.

Compliance with Ethical Standards

Conflict of Interest Irene Chernova and Namrata Krishnan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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