AHA Scientific Statement

Resistant Hypertension: Detection, Evaluation, and Management
A Scientific Statement From the American Heart Association

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Abstract—Resistant hypertension (RH) is defined as above-goal elevated blood pressure (BP) in a patient despite the concurrent use of 3 antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic. The antihypertensive drugs should be administered at maximum or maximally tolerated daily doses. RH also includes patients whose BP achieves target values on ≥4 antihypertensive medications. The diagnosis of RH requires assurance of antihypertensive medication adherence and exclusion of the "white-coat effect" (office BP above goal but out-of-office BP at or below target). The importance of RH is underscored by the associated risk of adverse outcomes compared with non-RH. This article is an updated American Heart Association scientific statement on the detection, evaluation, and management of RH. Once antihypertensive medication adherence is confirmed and out-of-office BP recordings exclude a white-coat effect, evaluation includes identification of contributing lifestyle issues, detection of drugs interfering with antihypertensive medication effectiveness, screening for secondary hypertension, and assessment of target organ damage. Management of RH includes maximization of lifestyle interventions, use of long-acting thiazide-like diuretics (chlorthalidone or indapamide), addition of a mineralocorticoid receptor antagonist (spironolactone or eplerenone), and, if BP remains elevated, stepwise addition of antihypertensive drugs with complementary mechanisms of action to lower BP. If BP remains uncontrolled, referral to a hypertension specialist is advised. (*Hypertension*. 2018;72:00-00. DOI: 10.1161/HYP.0000000000000084.)

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Hypertension is the world's leading risk factor for cardiovascular disease (CVD), stroke, disability, and death. Even with steady improvement during the past 30 years in hypertension awareness, treatment, and control rates, a large proportion of hypertensive adults, despite conscientious clinical management, still fail to achieve their recommended blood pressure (BP) treatment targets on 3 antihypertensive medications or require ≥4 medications to achieve their targets. These individuals, designated as having treatment-resistant hypertension (RH), remain at increased risk for target organ damage, morbidity, and mortality despite ongoing antihypertensive drug therapy.

New recommendations for the detection, evaluation, and management of hypertension have been published in the 2017 American College of Cardiology/American Heart Association (AHA) clinical practice guideline for the prevention, detection, evaluation, and management of high BP in adults.[1] Among its recommendations, the 2017 guideline reduces both the BP threshold for initiating antihypertensive therapy to ≥130/80 mm Hg for adults with existing CVD or 10-year atherosclerotic CVD risk ≥10% and the BP goal of treatment to <130/80 mm Hg for most individuals. These recommendations affect the BP threshold for diagnosis of RH and thus will increase its prevalence in the hypertensive population. The current scientific statement is consistent with the 2017 American College of Cardiology/AHA guideline.[1]

In 2008, the AHA issued its first scientific statement on RH that included recommendations for diagnosis, evaluation, and treatment.[2] Since 2008, a large number of studies of RH have improved our understanding of its pathogenesis, evaluation, and treatment. This first revision of the AHA scientific statement[2] is intended to place this new evidence into the context of our understanding of RH from prior literature and to identify gaps in knowledge requiring additional research in the future.

Definitions of RH

RH is defined as the BP of a hypertensive patient that remains elevated above goal despite the concurrent use of 3 antihypertensive agents of different classes, commonly including a long-acting calcium channel blocker (CCB), a blocker of the renin-angiotensin system (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]), and a diuretic. All agents should be administered at maximum or maximally tolerated doses and at the appropriate dosing frequency. Albeit arbitrary with respect to the number of medications required, RH is defined in this manner to identify patients who are at higher risk for morbid CVD events and death. Moreover, they are more likely to have medication adverse effects, more likely to have a secondary cause of hypertension compared with hypertensive patients without drug resistance, and may benefit from special diagnostic or therapeutic approaches to control their BP. RH also includes patients whose BP achieves target values on ≥4 antihypertensive medications, a condition that has been referred to in the literature as controlled RH. Thus, the term RH refers to hypertension with both uncontrolled and controlled BP, depending on the number of antihypertensive agents used.

Errors in BP measurement can account for the misdiagnosis of RH. The preparation of the patient, environmental conditions, cuff size, and technique of BP measurement can have a substantial influence on BP results.[1,3] In particular, inherent BP variability dictates that diagnostic BP recordings include an average of at least 2 readings obtained on at least 2 separate occasions.[1,3] Therefore, before the diagnosis of RH is made, it is critical to ensure accurate BP measurement. Similarly, out-of-office BP and self-monitored BP require proper technique.[1,2,4] BP should be measured at any site according to current guidelines.[1]

The "white-coat effect" is defined as office BP above goal but out-of-office BP levels measured by ambulatory BP monitoring (ABPM) (or, if ABPM is unavailable, by home BP monitoring) below goal in a patient on ≥3 antihypertensive agents. The risk of CVD complications in patients with a white-coat effect is similar to the risk in hypertensive patients with controlled BP.[5–7] Out-of-office BP monitoring is generally required to make the diagnosis of true RH.

Nonadherence in taking prescribed antihypertensive medications must also be excluded before RH is diagnosed. Medication nonadherence is highly prevalent in patients with apparent RH.[8,9] It has been estimated that as many as 50% to 80% of hypertensive patients prescribed antihypertensive medications demonstrate suboptimal adherence.[10] This relatively high proportion with nonadherence that may mimic RH is related, at least in part, to the large pill burden, dosing complexity, expense, high frequency of adverse reactions with multidrug antihypertensive regimens, poor patient-clinician relationship, and clinician inertia with reduced insistence on adherence when patients are consistently nonadherent.[11] Exclusion of nonadherence should include frank and nonjudgmental clinician-patient discussion, monitoring of prescription refills and pill counts, and, if available, biochemical assay of drugs or their metabolites in urine or plasma.

In summary, the definition of RH has been modified from that of the 2008 AHA scientific statement in 4 important ways: (1) BP should be measured and the BP threshold for diagnosis and treatment goals should be in accord with current clinical practice guidelines[1]; (2) patients should be taking ≥3 antihypertensive agents, commonly including a long-acting CCB, a blocker of the renin-angiotensin system (ACE inhibitor or ARB), and a diuretic at maximum or maximally tolerated doses; (3) patients with the white-coat effect should not be included in the definition of RH; and (4) the diagnosis of RH requires the exclusion of antihypertensive medication nonadherence.

Prevalence of RH

As stated, RH requires patient adherence to prescribed medications and that the uncontrolled subset has elevated BP outside the office setting. The term apparent treatment RH (aTRH) is used when ≥1 of the following data elements are missing: medication dose, adherence, or out-of-office BP; thus, pseudoresistance cannot be excluded.[12] Among treated adults with hypertension, prevalent aTRH occurs in ≈12% to 15% of population-based[13–16] and 15% to 18% of clinic-based reports.[17–20] Prevalent aTRH occurs in a higher percentage of the population- and clinic-based samples when an at-risk

Table 1. Prevalence of aTRH in Adults With Treated Hypertension as Reported From Selected Population-, Clinic-, and Intervention-Based Studies

Population Based	Time Period	n	Uncontrolled With ≥3 BP Medications, %	Controlled With ≥4 BP Medications, %	aTRH, %
NHANES[13]	1988–1994	2755	8.3	1.1	9.4
NHANES[13]	1999–2004	3031	8.8	2.9	11.7
NHANES[14]	2003–2008	3710	…	…	12.8
NHANES[13]	2005–2008	2586	9.7	4.8	14.5
REGARDS[15]	2003–2007	14731	9.1	5.0	14.1
REGARDS[16] (CKD)*	2003–2007	3134	…	…	28.1
Clinic based					
EURIKA[17] (diabetes mellitus)	2009–2010	5220	13.0†	3.1	16.1
Spanish ABPM[18]	2004–2009	68045	12.2	2.6	14.8
CRIC (CKD)[19]‡	2003–2008	3939	21.2	19.2	40.4
South Carolina[20]§	2007–2010	468877	9.5	8.4	17.9
Clinical trials					
ALLHAT[21]	1994–2002‖	14684	11.5	1.2	12.7
ASCOT[22]	1998–2005	19527	48.5	…	…
ACCOMPLISH[25]	2003–2006¶	10704	39	…	…
INVEST[26]	1997–2003#	17190	25.1	12.6	37.8

Uncontrolled aTRH is defined as BP ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic on ≥3 BP medications. Controlled aTRH is defined as BP <140 mm Hg systolic and <90 mm Hg diastolic on ≥4 BP medications unless otherwise specified.

ABPM indicates Ambulatory Blood Pressure Monitoring Registry; ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcome Trial; aTRH, apparent treatment-resistant hypertension; BP, blood pressure; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort; EURIKA, European *Study* on Cardiovascular Risk Prevention and Management in Usual Daily Practice; INVEST, International Verapamil-Trandolapril Study; NHANES, National Health and Nutrition Examination Survey; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

*Mean estimated glomerular filtration rate in adults with CKD and aTRH: 60.8 mL·min⁻¹·1.73 m⁻².

*Mean estimated glomerular filtration rate in adults with CKD and aTRH: 60.8 mL·min^{-1}·1.73 m^{-2}.

†aTRH defined as BP >130/>80 mm Hg.

‡Mean estimated glomerular filtration rate in adults with CKD and aTRH: 38.9 mL·min^{-1}·1.73 m^{-2}.

§Includes untreated hypertensive patients.

‖Excluded 7628 patients with uncontrolled hypertension on <3 BP medications.

¶Prevalent uncontrolled aTRH estimated from report on BP control 6 months after randomization.

#Excluded 5386 treated participants with BP <130/<80 mm Hg.

group is selected, for example, patients with treated hypertension and chronic kidney disease (CKD).[16,19] The higher prevalence of aTRH among treated hypertensive adults in clinical trials (34%–39%) is likely explained by the selection of patients with demographic and comorbidity characteristics that place them at high risk for the fatal and nonfatal CVD outcomes of interest.[21–26] Moreover, in population- and clinic-based studies, some RH cases may go unrecognized because patients are not prescribed ≥3 drugs at maximal doses despite uncontrolled BP. In contrast, clinical trials usually include forced titration schemes that unmask RH by reducing the prevalence of suboptimal treatment.[12]

The prevalence of aTRH estimated from selected population-based, clinic-based, and clinical trial-based reports is shown in Table 1 (for details, see the Data Supplement).

Prognosis of RH

Observational studies using the 2008 criteria have shown that patients with RH are at higher risk for poor outcomes compared with patients without RH.[23,27–30] In a retrospective study

of >200000 patients with incident hypertension, those with RH were 47% more likely to suffer the combined outcomes of death, myocardial infarction, heart failure, stroke, or CKD over the median 3.8 years of follow-up.[23] Differences in CVD events in this study were driven largely by a higher risk for the development of CKD.[23] In another study of >400000 patients, compared with patients without RH, patients with RH had a 32% increased risk of developing end-stage renal disease, a 24% 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.[29] Prospective studies using ABPM have suggested an almost 2-fold increased risk of CVD events in patients with true RH compared with those with hypertension responsive to treatment.[30–33] Together, these studies suggest that RH is associated with an increased risk of adverse outcomes and represents an important public health problem.

RH is associated with worse outcomes among patients with some comorbid conditions. In patients with CKD, RH is associated with higher risk of myocardial infarction, stroke, peripheral arterial disease, heart failure, and all-cause

mortality compared with patients without RH.[19] Similarly, in patients with ischemic heart disease, RH is associated with higher rates of adverse events, including death, myocardial infarction, and stroke.[26,34,35] Conversely, RH is not associated with increased adverse clinical events in patients with heart failure with reduced ejection fraction and may lower the risk for heart failure–related rehospitalization.[36]

Among patients with RH, lower BP is associated with reduced risk for some cardiovascular events.[28,37] In the REGARDS study (Reasons for Geographic and Racial Differences in Stroke), uncontrolled RH was associated with a 2-fold increased risk of coronary heart disease compared with controlled RH. Control status was not associated with differences in stroke or mortality.[28] In another study of >118 000 treated hypertensive adults, including >40 000 individuals with RH and 460 000 observation-years, BP control was associated with significantly lower rates of incident stroke and coronary heart disease with no difference in rates of incident heart failure.[37] BP control reduced the risk of incident stroke, coronary heart disease, or heart failure by 13% among those with RH compared with a 31% lower risk of these outcomes among patients without RH.[37] Although BP control is associated with a lower risk for some CVD outcomes, it is possible that the benefit of BP lowering may be less in patients with RH compared with patients with non-RH.

Patient Characteristics

Demographic correlates of RH include black race, older age, and male sex.[38] RH is characterized by the variable clustering of distinct demographics, comorbidities, physiological aberrations, and metabolic abnormalities. However, these factors are not mutually exclusive because, in fact, they can be substantially interdependent (eg, nondipping or reverse dipping BP and sympathetic nervous system overactivity, visceral obesity, and excess aldosterone).

Multiple comorbidities have been associated with RH. Obesity,[39–41] left ventricular hypertrophy,[42] albuminuria,[14,43] diabetes mellitus,[14,38,39] CKD,[38,39,44] higher Framingham 10-year risk score,[39] and obstructive sleep apnea (OSA)[45,46] are more common in RH than non-RH. Very high proportions (60%–84%) of individuals with RH have sleep apnea.[33,47–49] Other sleep abnormalities are also manifest in RH (relative to those with controlled hypertension or normotensives), including shorter sleep duration, reduced sleep efficiency, and less rapid eye movement sleep.[50]

Physiological aberrations in RH include vascular disease/dysfunction as evidenced by high rates of peripheral[39] and carotid artery atherosclerosis,[42] impaired endothelial function,[51,52] reduced arterial compliance, and raised systemic vascular resistance,[40] all of which may be more pronounced in RH compared with non-RH. The normal nocturnal decline in BP is also attenuated in a high proportion (43%–65%) of individuals with RH.[32,53,54] The attenuated nocturnal decline in BP is even more pronounced in uncontrolled compared with controlled RH.[52] Nondipping ambulatory BP in individuals with RH has been linked to reduced heart rate variability, a marker of sympathetic nervous system overactivity.[53] Reverse dipping, in which nocturnal BP paradoxically rises, may be associated with

increased subclinical organ damage and possibly CVD events. Reverse dipping is also associated with increased sympathetic nervous system activity at night.[55] In adults with severe uncontrolled RH and self-reported sleep apnea in the SYMPLICITY HTN-3 trial (Renal Denervation in Patients With Uncontrolled Hypertension), renal denervation lowered office systolic BP (SBP) more effectively relative to sham controls at 6 months (−17.0 mm Hg versus −6.3 mm Hg; *P*<0.01).[56] Renal denervation did not lower office SBP in patients without sleep apnea.

RH has also been linked to metabolic derangements, including hyperuricemia,[17] aldosterone excess,[47] and suppressed circulating renin levels (≈60% of those with RH have suppressed renin levels).[57] In general, RH is characterized by exquisite salt sensitivity of BP. Reducing dietary sodium intake to levels significantly below the level of usual intake in Western societies (eg, 50 mmol/d) promptly and impressively lowered BP in many individuals with RH.[58] Moreover, the severity of sleep apnea in those with RH is positively related to dietary sodium intake, at least in those with hyperaldosteronism.[49] Plasma osmolality-adjusted copeptin concentrations, a surrogate marker for vasopressin release, are almost twice as high in individuals with RH compared with those with nonresistant, controlled BP.[59]

There are distinct patterns of antihypertensive drug prescribing and administration in individuals with RH. Suboptimal antihypertensive drug regimens substantively contribute to the likelihood of being diagnosed with RH.[41,60,61] Accordingly, drug treatment regimens in RH infrequently include either spironolactone or chlorthalidone, 2 highly effective BP-lowering agents, in this high-risk group of hypertensives.[60,61] Bedtime dosing of once-daily antihypertensive agents (relative to morning or twice-daily dosing) appears to significantly affect diurnal BP patterns because there are fewer patients with nondipping of BP and >24-hour BP control and higher rates of nocturnal normalization of BP[62] with this dosing strategy.

Genetics/Pharmacogenetics

BP has a genetic basis, as evidenced by its heritability in family-based studies,[63–65] with estimates for long-term average BP that as much as 50% to 60% of BP variability can be attributed to additive genetic factors.[66] However, there has been limited study of the heritability of RH or of the BP-lowering response to specific antihypertensive agents. A disproportionately higher prevalence of RH among blacks[67,68] has been suggested to reflect a contribution by genetic factors, but environmental or psychosocial determinants of BP control are also possible.[69]

Common genetic variants influencing BP have been identified at >300 independent loci but require scores to hundreds of thousands of individuals for their detection.[70–91] These genetic variants typically have effects on the order of 1.0–mm Hg SBP and 0.5–mm Hg diastolic BP per BP-raising allele. Individually, these variants explain ≤0.1% of BP variability and, in aggregate, only 3% of total BP variance. This is consistent with the complex nature of BP regulation, involving multiple compensatory systems such as vascular tone, sodium excretion and plasma volume, autonomic nervous system

function, and myocardial performance, as well as many as-yet unknown factors.

The majority of genetic studies of RH have been limited to candidate genes and have lacked adequate sample sizes to survive the multiple testing burden across the many such candidate gene studies performed.[92–96] Much larger studies of well-characterized individuals with RH and of individuals before and after treatment with specific antihypertensive therapies are needed to better define the role of common and rare genetic variation in causing RH and modulation of drug response. For a more detailed discussion of genetics and pharmacogenetics in RH, please see the Data Supplement.

Diagnosing RH

Identifying and Correcting Medication Nonadherence

Overview

The term *adherence* is defined as remaining attached (to the medication regimen) and is distinct from *compliance*, which means submitting to a request, wish, or demand. Medication adherence is an important determinant of hypertension control. However, a quarter of patients who are newly initiated on antihypertensive therapy fail to fill their initial prescription.[97,98] During the first year of treatment, the average patient has possession of antihypertensive medications only 50% of the time, and only 1 in 5 patients has sufficiently high adherence to achieve the benefits observed in clinical trials.[98,99] Nevertheless, the trend to improved BP control (<140/90 mm Hg) rates among those on antihypertensive treatment to >70% suggests that recent strategies to improve antihypertensive medication adherence and care have been successful.[100]

Assessing and ensuring optimal medication adherence are essential steps in the evaluation and management of patients with RH. By definition, these patients are taking ≥3 antihypertensive drugs, and information on the level of adherence to the prescribed regimen is crucial to guide clinical reasoning and decision making. A major criterion of success is the ability of the patient to follow the recommendations on a daily basis (adherence) and to stay on therapy (persistence), with the latter aspect most critical in clinical practice.[101] In fact, the diagnosis of RH is predicated on the patient's adherence to the prescribed regimen, and failure to identify inadequate adherence contributes to overestimation of the prevalence of "true" RH. Adequate adherence necessary for patients to experience benefit from full exposure to prescribed pharmacological therapy is generally defined as taking at least 80% of doses, although the scientific basis for this cutoff is unclear.[102] Although data are limited, a review of studies of medication adherence in aTRH identified rates of nonadherence in this population ranging from 7% using pharmacy refill records in a managed care population to >60% using serum drug levels in a referral clinic.[102]

Assessment of Adherence

Identification of patients with inadequate adherence among those with aTRH will avoid unnecessary and potentially harmful treatment intensification and allow implementation of strategies to improve adherence and more cost-effective allocation of health resources. Furthermore, assessment of change in adherence as a major potential confounder is essential in trials assessing new treatment modalities of RH.[103] Thus, a systematic approach with reliable, practical methods for measuring medication adherence would facilitate providers' abilities to optimize their antihypertensive regimens.

Although counterintuitive, 1 analysis found that the SBP response to therapeutic intensification for uncontrolled hypertension was not different across quintiles of adherence.[104] Specifically, SBP fell an average of 2.1 mm Hg in the highest adherence quintile (≥98% adherence) and 2.4 mm Hg in the lowest adherence quintile (<80% adherence; mean, 62%) with each therapeutic intensification. Clinicians are less likely to intensify medications when their assessment suggests that the patient is nonadherent. However, clinician assessment of adherence is poor.[105] Thus, although work continues to optimize methods for assessing medication adherence, clinicians should be cautious when deciding against therapeutic intensification in a patient with uncontrolled hypertension whom they perceive to be nonadherent. It is important for providers to use effective strategies for improving adherence such as those described subsequently.

Because of the complex and dynamic nature of adherence, it is difficult to measure, particularly by any single assessment. Clinician impression and techniques such as pill count often are inaccurate. However, increasingly reliable and sophisticated indirect and direct methods are available for assessing medication adherence.[106] Indirect methods, including patient self-report medication adherence assessment tools such as the Morisky Medication Adherence Scale[107] and the Hill-Bone Compliance Scale,[108] have demonstrated predictive validity in a variety of hypertensive populations and identify adherence risk factors that can be used to tailor messages targeting improved adherence. Using a nonthreatening, nonaccusatory approach, which requires excellent communication skills, is preferred when interviewing patients about adherence. An example is the following: "When taking multiple medications, it is common to miss doses throughout the week. How many times do you miss taking your BP medication in a week?"

Pharmacy databases for medication possession and refills provide a valid measure of adherence. Measurement of pharmacodynamic parameters (eg, heart rate for β-blockers, lack of rise of plasma renin activity [PRA] for renin-angiotensin inhibitors, *N-acetyl*-seryl-aspartyl-lysyl-proline measurements for ACE inhibitors) may have limited specificity. Direct methods include witnessed drug intake, the Medication Event Monitoring System, and drug monitoring in body fluids. Witnessed medication taking followed by monitoring of effect on BP has been effective in identifying suspected nonadherence in trials of novel treatment modalities, although this approach has not been widely used in general practice. Medication Event Monitoring System monitoring of the date and time that a medication bottle is opened and closed has superior sensitivity compared with other methods, although ingestion of the medication is not confirmed. Urine or blood measurement of drug or metabolites with mass spectroscopy reliably determines whether a drug is present or absent but does not determine whether it was taken regularly or at a therapeutic level. A novel approach, urine fluorometry, recently was reported as a safe, easy, and reliable method to assess

adherence.[109] In addition, a new technology moving toward clinical application involves a sensor in the pill that emits a signal on interacting with gastric acid, which is detected by a sensor on the skin.[110]

There is no gold standard for measuring adherence. Indirect methods such as pill count, self-report, and prescription refill data are simple, inexpensive, and widely used. However, they can easily be manipulated to overestimate adherence. A direct method such as urine or blood measurement of drug or metabolites is considered more robust but is relatively expensive, is of limited availability, and does not perfectly reflect level of adherence. All methods have limitations, and ideally, accurate assessment of adherence should involve a combination of approaches.

Multisystem Intervention to Improve Adherence

Factors contributing to poor adherence are myriad and multilevel. Barriers to adherence exist at the levels of patient (eg, multiple comorbid conditions, resource constraints, suboptimal health literacy, lack of involvement in the treatment decision-making process), clinician (eg, prescription of complex drug regimens, communication barriers, ineffective communication of information about adverse effects, provision of care by multiple providers, clinician inertia), and healthcare system (eg, office visit time limitations, limited access to care, lack of team-based approaches and health information technology).[107] Because barriers to medication adherence are complex and varied, solutions to improve adherence at the population level must be multifactorial.[108,111,112]

Several systematic reviews and meta-analyses have assessed the impact of interventions, including modification of antihypertensive therapy, on adherence to antihypertensive medications.[112–120] Evidence specific to improving adherence in the RH population is sparse. However, evidence-based approaches effective in the general hypertension population can be applied. No single intervention is uniquely effective, and a sustained approach using multiple strategies, including health system solutions and those that target the individual patient's barriers to adherence, is likely to be most effective. Interventions demonstrated to be effective in improving adherence are outlined here and organized by health system, clinician, and patient levels.

Health system–level interventions to improve the quality of hypertension care, medication adherence, and BP control use multidisciplinary team-based care.[121] A variety of patient-centered, team-based hypertension care models have been demonstrated to increase the proportion of individuals with controlled BP.[121–125] An effective, multifaceted approach often includes systems support for clinical decision making (ie, treatment algorithms), collaboration between clinician and patient, medication adherence, BP monitoring, and patient self-management.[126,127] Further systems-level support such as use of electronic health records, registries, clinical decision support (ie, treatment algorithms), technology-based remote monitoring, self-management support tools, and monitoring of performance augments and intensifies team-based care efforts.[128–132]

Effective strategies for improving adherence to antihypertensive medications include (1) using agents that are dosed once daily over those that require multiple daily doses and using fixed-dose combination agents when available[113,116–120,133]; (2) using low-cost and generic antihypertensives, particularly when cost of care is a barrier[134] (patients with RH often have multiple chronic conditions requiring pharmacotherapy); and (3) consolidating refills, that is, minimizing the number of trips to the pharmacy to obtain all prescribed medications.[134]

Patient-centered care and patient engagement in deciding which antihypertensive medications are included in their treatment regimen (patient-centered decision making) improve adherence.[135,136] In addition, a patient-centered approach to consider overall adverse effect profile and preferential use of agents that are well tolerated may help. Medication adherence scales may be useful.[107,108] Many clinicians may benefit from training to enhance communication skills and to increase cultural competence in their interactions with patients.

At the individual patient level, it is essential to educate patients, their families, and caregivers about hypertension, the consequences of hypertension, and the possible adverse effects of medications. An informed patient is better able to collaborate to establish shared goals of therapy and a plan of care. To maintain contact with patients for ongoing follow-up and monitoring, telehealth or mobile communication approaches may be helpful.[132,137] Patients must integrate pill taking into their routine activities of daily living with the use of adherence support tools such as reminders, pillboxes, packaging, or other aids. Individual barriers to adherence such as low health literacy can be difficult to identify in a busy practice setting. Moreover, only 12% of US adults have the health literacy skills needed to manage the demands of our complex health system.[138] The Health Literacy Universal Precautions Toolkit recommends assuming that all patients may have difficulty understanding and creating an environment with supportive systems where all patients receive written and oral communication in plain language that promotes empowerment and self-management.[138] Key recommendations include using visual, interactive education and providing a medication list or pictorial medication schedule. Another approach, the teach-back method, offers clinicians a nonthreatening way to confirm whether patients understand what has been explained to them. If a patient understands, he/she is able to "teach back" the information accurately. Motivation interventions are also effective in supporting medication adherence and lifestyle modification efforts.[139] The creation of an encouraging, blame-free environment in which patients are recognized for progress toward treatment goals, empowered to ask questions, and given "permission" to answer questions related to their treatment honestly is essential to identify and address nonadherence.

Poor BP Measurement Technique

Inaccurate measurement of BP can result in the appearance of treatment resistance. In a study comparing standard triage BP measurements by clinic staff with an automated device obtaining up to 6 BP measurements 1 minute apart while the patient was alone and seated in a quiet room, triage SBPs were a median of 17 mm Hg higher, and the difference was highest in the group of patients with initial SBPs >160 mm Hg.[140] In

this study of patients referred for RH, inaccurate BP measurement was estimated at 33%.[140]

Certain aspects of BP measurement technique have been standardized with the widespread acceptance of oscillometric devices to measure BP in the hospital, workplace, and home. For example, potential measurement confounders such as observer bias, end-digit preference, and the presence of an auscultatory gap are not an issue with non-auscultatory methods.[3] However, cuff size, body and arm positions, and measurement environment are common features of auscultatory and oscillometric methods that affect the accuracy of BP measurement. Proper BP measurement technique entails (1) preparing the individual by emptying a full urinary bladder and then sitting with legs uncrossed and back, arm, and feet supported in a quiet room, ideally 5 minutes before the first reading is obtained; (2) choosing a BP cuff with a bladder length of at least 80% and width of at least 40% of the arm circumference; (3) placing the cuff directly on the skin of the upper arm at the level of the heart on the supported arm; and (4) obtaining a minimum of 2 readings 1 minute apart.[1,3]

Cuff-measured BP may differ from intra-arterial pressure. Severe arterial stiffness or medial calcification of the brachial artery may result in an inaccurate detection of Korotkoff sounds when BP is measured with the auscultatory method. The inappropriately elevated cuff pressure in patients with severe arterial disease has been called pseudohypertension.[141] The degree to which arterial stiffness or brachial artery calcification affects BP measurement with oscillometric devices has not been established but is suspected to be less pronounced. In addition, the auscultatory method has been shown to overestimate diastolic BP among hypertensive individuals, likely unrelated to calcified arteries.[142]

White-Coat Effect

The white-coat effect is the observation of repeated BP elevations in the office with controlled or significantly lower BP outside the office in a hypertensive patient on medication. The white-coat effect has been attributed to an alerting reflex triggered by the healthcare provider or the clinic environment that activates the sympathetic nervous system.[143] Some degree of BP rise is seen with in-office measurement in the majority of people; however, the white-coat effect can be magnified in individuals diagnosed with hypertension, women, and older individuals.[144] A clinically significant white-coat effect may be present in 28% to 39% of individuals with aTRH by office BP measurement.[18,32,145] Short duration of hypertension and the absence of diabetes mellitus or CKD are also associated with pseudoresistance from a white-coat effect.

In RH populations, the CVD risk of overdiagnosing RH from the white-coat effect is comparable to that in treated controlled hypertensive patients.[31] In a Brazilian cohort of patients with RH, ambulatory BP was an independent predictor of all-cause mortality and a composite outcome of CVD events, whereas office BP showed no prognostic value.[32] These findings are consistent with outcome studies in the general population. An analysis of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes, which included >12 000 participants from across the world, found that after age was accounted for, the white-coat effect did not contribute to CVD risk.[7] Recognizing the risk disparity between white-coat–related BP elevation and RH, randomized clinical trials in RH have excluded patients whose BP is controlled by measurement with either ABPM or home BP monitoring.[20,145]

The white-coat effect can be easily identified by 24-hour ABPM. However, ABPM is not readily available in all countries and, because of limitations in insurance reimbursement, is not even commonly used in the United States.[146] Oscillometric digital devices that can automatically record 3 to 6 BP measurements without a clinician in the examination room are now available for clinical use, a process called automated office BP. BP measurement by automated office BP attenuates the white-coat effect. Self-measured home BPs (with appropriate instruction in the BP measurement technique) correlate with average daytime BPs measured by 24-hour ABPM and can be used to identify the white-coat effect.[146] However, it is important to consider that individuals may alter their BP logs or underreport high or low BP values. In general, upper arm cuff-based home BP monitors are preferred over wrist BP monitors. Although wrist monitors may be convenient, particularly for obese patients who require very large cuff sizes, they have the potential for measurement error in individuals with arrhythmias, during arm movement, or when the wrist is not placed at heart level.[1,3] Finger BP monitors are not recommended because of error and artifactual readings. Although BP control is <130/80 mm Hg in the office, control by 24-hour ABPM is defined as <125/75 mm Hg.

Treatment Inertia

Suboptimal antihypertensive therapy accounts for a large subset of patients not achieving BP targets (Figure 1).[140] During 2007 to 2010, only 49.6% of patients with uncontrolled aTRH identified in a community-based practice network in the United States were prescribed an optimal antihypertensive regimen.[20] More than 90% of the 84 193 patients with aTRH were appropriately prescribed a diuretic; however, antihypertensive medications were administered at <50% of their maximally recommended dose in 42.1% of patients with uncontrolled aTRH. Patients who were more likely to be prescribed an optimal regimen were black or were diagnosed with CKD, diabetes mellitus, or coronary heart disease.[20]

Overcoming clinician treatment inertia can be accomplished through an integrated health system model of care. Hypertension control rates exceed the national average in the Kaiser Permanente and Veterans Affairs health systems, where the approach to BP control is systematic and multidisciplinary. Identifying patients with hypertension, standardizing BP measurements, and using a stepwise treatment algorithm have led to an increase in BP control rates from 54% in 2004 to 84% in 2010 in the Kaiser Permanente Southern California health system.[147]

Lifestyle Factors

The 2017 American College of Cardiology/AHA clinical practice guideline for the prevention, detection, evaluation, and management of high BP in adults provides a detailed discussion of the relationships between several lifestyle factors
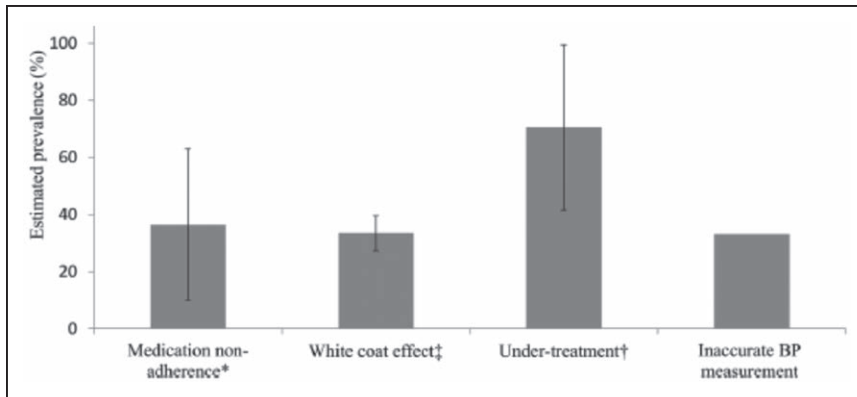
Figure 1. Estimated prevalence of each of the causes of pseudoresistant hypertension. BP indicates blood pressure. Modified from Bhatt et al[140] with permission from the American Society of Hypertension. Copyright © 2016, American Society of Hypertension. *Indicates reference 102. †Indicates references 20 and 140. ‡Indicates references 18, 32, and 145.

and high BP.[1] The following sections focus specifically on the role of behavioral activities in the pathogenesis of RH.

Obesity

Excess body fat ranks among the most important factors responsible for the increasing prevalence of hypertension.[148] Visceral adiposity in particular plays a fundamental role in causing high BP through a variety of mechanisms culminating in enhanced salt sensitivity, vascular dysfunction, and activation of the sympathetic nervous system and renin-angiotensin system.[148,149] Mounting evidence further supports the importance of heightened mineralocorticoid activity in RH.[149–151]

Recent findings from the NHANES (National Health and Nutrition Examination Survey) of 13 375 hypertensive adults demonstrate that body mass index (BMI) ≥30 kg/m^2 approximately doubles the risk for aTRH.[13] In 14 461 patients with RH in the Spanish Ambulatory Blood Pressure Monitoring Registry, a BMI ≥30 kg/m^2 was also an independent risk factor for RH (odds ratio, 1.62; 95% CI, 1.32–1.99).[152] Even among 3367 hypertensives with CKD, increasing levels of obesity were independently associated with higher risks of aTRH, ranging from an odds ratio of 1.52 (BMI ≥30 kg/m^2) to 2.26 (BMI ≥40 kg/m^2).[19] Finally, in a large data set (>470 000) from the Kaiser Permanente Southern California health system, obesity (BMI ≥30 kg/m^2) was also found to be an independent risk factor for RH (odds ratio, 1.62; 95% CI, 1.42–1.51).[38] Although obesity has the potential to promote spurious elevations in BP (eg, use of a smaller-than-optimal BP cuff),[148] these findings nonetheless strongly support a direct role for excess adiposity in promoting RH.

Dietary Sodium

Higher dietary sodium intake is incontrovertibly linked to increases in arterial BP.[153–155] However, relatively large interindividual variations exist in "salt sensitivity" of BP. The mechanisms are complex and likely involve a host of responses beyond excess volume retention, including vascular dysfunction, arterial stiffness, sympathetic activation, impaired renin-angiotensin axis suppression, mineralocorticoid receptor activation, and immune cell modulation.[156,157]

It is more difficult to precisely quantify the importance of excess dietary sodium specifically in regard to causing RH for several reasons, including the complexities in accurately characterizing routine intake in the relevant populations.[158] However, a number of recently published studies suggest a

role. Among 279 patients with RH, brain natriuretic peptide was higher and PRA was lower than in control patients, supporting a component of relative volume excess (although 24-hour urinary sodium levels were not increased).[159] In a study of 204 patients with true RH confirmed by ambulatory monitoring, one-third displayed evidence for excess sodium intake (ie, 24-hour urine levels >200 mEq).[160] Further indirect evidence can be derived from large population studies in which chronic renal insufficiency, a well-established cause of heightened salt sensitivity of BP, has been repetitively linked to aTRH.[13,38,152] Perhaps the most compelling support comes from the few clinical trials demonstrating marked reductions in BP among patients with RH following a reduced sodium diet.[58,161]

Alcohol

Alcohol intake has been linked to increases in BP and the risk for developing hypertension.[162–164] The dose-response association may differ between men (linear) and women (J shaped)[164] and can be modified by metabolic genes.[163] Nonetheless, heavy alcohol intake (>30–50 g/d) is a well-established risk factor for hypertension.[165]

Physical Inactivity

Both reduced physical activity and lower physical fitness are independent risk factors for hypertension.[166–171] Graded inverse associations between activity and fitness level with the risk for developing high BP have been shown in young adults,[168] men,[169] and women.[170] There is further evidence that a sedentary lifestyle itself (eg, more television watching) independently promotes the onset of hypertension.[167,172] Conversely, there is a paucity of studies that have reported associations between physical inactivity and RH. Along with other poor lifestyle factors, self-reported inactivity was not predictive of RH among patients in the REGARDS cohort.[173] On the other hand, indirect support for the important role of activity comes from a randomized study demonstrating that a thrice-weekly treadmill walking exercise program for 8 to 12 weeks significantly lowered daytime ambulatory BP (6±12/3±7 mm Hg; P=0.03) among 50 treated patients with RH.[173]

Dietary Pattern and Other Risk Factors

The Dietary Approaches to Stop Hypertension (DASH) eating pattern is well established to reduce BP, by 6.7/3.5 mm Hg in a recent meta-analysis.[174,175] Nonetheless, as with other lifestyle

Table 2.   Drugs and Other Substances With Potential to Induce or Exacerbate Elevated BP and Hypertension

NSAIDs
Oral contraceptives
Sympathomimetic
Cyclosporine, tacrolimus
Erythropoietin
VEGF inhibitors
Alcohol
Cocaine
Amphetamines
Antidepressants
Glucocorticoids, mineralocorticoids

BP indicates blood pressure; NSAIDs, nonsteroidal anti-inflammatory drugs; and VEGF, vascular endothelial growth factor.

factors in the REGARDS cohort, a low DASH diet questionnaire score was not independently associated with aTRH.[166] Further studies are needed to clarify the precise role of poor diet in the pathogenesis of RH. Psychosocial stressors (eg, occupational stress, low social support), negative personality traits (anxiety, anger, depression), and reduced sleep duration/quality have also been associated with high BP[176–178]; however, data linking them specifically to RH are lacking. Finally, a variety of environmental exposures, including loud noises (eg, traffic), colder temperatures (eg, winter), higher altitudes, and air pollutants, promote high BP.[179] Future studies are required to elucidate the potential impact of these commonly encountered environmental factors on RH.

Drug-Related RH

Several classes of pharmacologic agents can increase BP and contribute to drug-induced RH (Table 2). However, the effects of these agents are found to be highly individualized, with the majority of individuals manifesting little or no effect and others demonstrating severe elevations in BP levels.

Nonsteroidal Anti-Inflammatory Agents

Nonsteroidal anti-inflammatory agents (NSAIDs) increase BP by reducing the production of prostaglandins E_2 and I_2, leading to reduced vasodilation and sodium excretion. With their widespread use, NSAIDs are considered one of the most common offending agents affecting BP control.[180,181] In general, all nontopical NSAIDs in doses adequate to reduce inflammation and pain can affect BP levels in both normotensive and hypertensive individuals.[182] The results of meta-analyses have indicated that the average increase in mean arterial pressure is highly variable, with a range of reports from 2 to 5 mm Hg.[183] Furthermore, NSAIDs affect the treatment effect of several antihypertensive medication classes, including diuretics, ACE inhibitors, ARBs, and β-blockers.[184,185] It is important to note that antihypertensive medication interactions have typically not been shown with CCBs,[186] and the effect of NSAID use on α- and β-blocker efficacy might also be minimal.[187]

Although the effect of NSAIDs on the incidence of hypertension has been reported as described earlier, there are significant variations in the magnitude of changes in BP in hypertensive patients taking antihypertensive medications.[188–192] Several studies found no effect of NSAIDs on BP in patients who were using diuretics.[193–195] The SBP increase with NSAIDs in ACE inhibitor users ranged from 5 to 10 mm Hg.[196–199] The inhibition of prostaglandins by NSAIDs is proposed as the mechanism that explains the loss of the BP-lowering effect of ACE inhibitors.[200,201]

BP effects from the use of NSAIDs vary by type, with selective COX-2 (cyclooxygenase-2) inhibitors such as celecoxib having less BP effect than traditional NSAIDs.[192,202] The BP effect[188–190] appears to be dose-dependent, involving the inhibition of COX-2 in the kidneys, with a reduction in sodium excretion and an increase in intravascular volume.[186] In contrast, low-dose aspirin does not have COX-2–inhibiting or BP-increasing effects, as indicated by results from the HOT study (Hypertension Optimal Treatment).[191] However, these conclusions cannot be extrapolated to larger doses of aspirin.

Oral Contraceptives and Hormone Replacement

Oral contraceptives raise BP and induce hypertension by increasing angiotensin biosynthesis.[203,204] The Nurses' Health Study of >60 000 normotensive women followed up for 4 years found that women using oral contraceptives had an 80% higher risk of developing hypertension compared with women not using oral contraception agents.[205] However, only 41.5 cases of hypertension per 10 000 person-years could be attributed to oral contraceptive use, and this number rapidly declined with cessation of therapy. Similarly, another study in hypertensive women reported that women taking oral contraceptives had more severe hypertension and poorer BP control rates than women using other contraceptive methods.[206] The type of oral contraceptives is important, with combined oral contraceptives (progestin and estradiol) associated with BP elevations at greater rates than lower-dose estradiol-only and progestin-only oral contraceptives.[207,208] Epidemiological studies of high-dose estrogen use found mean elevations in SBP of 3 to 6 mm Hg, with ≈5% of women developing new hypertension.[209] Cessation of estrogen use typically leads to a return to baseline BP within 2 to 12 months, but proteinuria may persist.[209,210] The mechanism responsible for the hypertensive effect of oral contraceptives may involve the renin-angiotensin system because estrogen stimulates the production of angiotensinogen.[211]

Postmenopausal hormone replacement therapy uses much lower estrogen doses than oral contraceptives, combined with progestin for women with an intact uterus. Estrogen replacement therapy and hormone replacement therapy appear to have a neutral effect on BP, as illustrated by the following observations from 2 large randomized trials. The Women's Health Initiative, a randomized placebo-controlled trial, assessed the effect of estrogen-progestin replacement on outcomes in postmenopausal women[211] and found that at 5.2 years hormone replacement therapy produced only a small increase (1.5 mm Hg) in SBP compared with placebo.[212] Similar findings were noted in the PEPI trial (Postmenopausal Estrogen/Progestin Interventions) in which estrogen replacement therapy, with or without progestins, did not affect BP after 3 years.[213]

Sympathomimetic Amines

Sympathetic amines increase BP by activation of the sympathetic nervous system. The association of sympathomimetic amines with dose-related increases in BP has been well established.[214,215] Although sympathomimetic-induced hypertension may not be clinically significant in healthy patients, these BP levels can be concerning in individuals with comorbid conditions.[214–217] Sympathomimetic amines include amphetamines and similar compounds such as pseudoephedrine and ephedrine. Historically, these compounds were contained in some over-the-counter cough and cold preparations and appetite suppressants, with several, most notably phenylpropanolamine, taken off the current market.

Immunosuppressive Agents

Cyclosporine

Cyclosporine and tacrolimus increase BP by inducing systemic and renal vasoconstriction and sodium retention. Hypertension is reported in the majority of patients undergoing renal, hepatic, or heart transplantation treated with cyclosporine.[218] Cyclosporine is associated with enhanced renal vasoconstriction leading to volume-dependent (low renin) hypertension.[219,220] Cyclosporine-induced hypertension is usually treated with vasodilatory CCBs. Although diuretics are effective treatment, they may exacerbate prerenal azotemia. Another immunosuppressive agent, tacrolimus, is thought to have some hypertensive effects.

Other Agents

Recombinant Human Erythropoietin

Recombinant human erythropoietin can increase BP by complex mechanisms in a dose-dependent fashion, resulting in hypertension in 20% to 33% of recipients.[221] Long-term use of erythropoietin promotes vascular smooth muscle cell growth, vascular remodeling, and medial hypertrophy, with maintained elevated BP.[222,223] Erythropoietin-induced hypertension can be controlled with antihypertensive medications, often with a single agent.[224]

Tyrosine Kinase Inhibitors

In patients being treated for malignancies, antineoplastic drugs that target the VEGF (vascular endothelial growth factor) pathway have emerged as inducers of hypertension.[225–227] As an example, hypertension frequently developed in patients receiving treatment with VEGF inhibitors.[228] Multiple mechanisms are proposed, including a reduction of nitric oxide and prostacyclin bioavailability, an increase of systemic vascular resistance, and vascular stiffness, which has been observed in animals treated with tyrosine kinase inhibitors of VEGF.[229–237]

Cocaine

Tachycardia and BP elevation are common clinical manifestations of cocaine use.[238] BP elevation is caused by increased central sympathetic outflow and blockade of neuronal norepinephrine reuptake, resulting in neurotransmitter accumulation in the synaptic cleft with resulting intense sympathetic activation.[239]

Amphetamines

Amphetamines increase norepinephrine production, augmenting sympathetic nervous system activation. The complications of amphetamines are comparable to those of cocaine and include hypertension and tachycardia.[240] Methylphenidate has been implicated in the development of hypertension in children treated for attention deficit disorder.[241] Mescaline has effects very similar to those of amphetamines and can increase BP.[240]

Antidepressants

Monoamine oxidase inhibitors may lead to severely elevated BP in individuals who consume foods containing tyramine.[242,243] Although the drugs themselves can exacerbate hypertension by increasing the half-life of norepinephrine at sympathetic nerve terminals, the effect is often magnified when amine precursors are also consumed.[243] Tranylcypromine is the most likely of the agents to raise BP compared with moclobemide and brofaromine.[244,245] Tricyclic antidepressants have been found to increase BP in patients with panic disorders.[246] Likewise, dose-dependent increases in BP have been reported in patients receiving therapeutic doses of venlafaxine.[247] Severe hypertension has also been identified in patients treated with antidepressants such as fluoxetine.[248]

Sleep Disorders and Pseudopheochromocytoma

Sleep Deprivation and Pseudopheochromocytoma

Contributing causes of RH are sleep disorders and a related problem called pseudopheochromocytoma. The term, which originated in 1999, describes a pheochromocytoma-like syndrome. Once true pheochromocytoma is excluded, one should consider pseudopheochromocytoma, a syndrome characterized by the presence of paroxysmal hypertension with 3 distinct features: abrupt elevation of BP, equally abrupt onset of distressful physical symptoms, and absence of reported fear or panic at the onset of attacks.[249] The original description involved patients with a history of emotional trauma from an event that they had denied; many improved with antidepressant therapy, β-blockers, and counseling. Since that report, there have been numerous case reports of pseudopheochromocytoma with a recent update summarizing the syndrome.[250]

A related problem in many people with pseudopheochromocytoma is poor sleep quality. Poor sleep quality, if long term, yields the same symptomology of paroxysmal hypertension and elevated BP, especially during the afternoon and evening hours. Poor sleep quality is not the result of just OSA but a host of sleep disorders, including restless leg syndrome and insomnia of various causes.[251] Many times, these different sleep disorders coexist and prevent the patient from achieving proper sleep.

The mechanism of poor sleep quality contributing to elevated BP and paroxysmal bouts of very high BP relates to activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone system.[252–255] Sympathetic activity is also increased in sleep deprivation, restless leg syndrome, and OSA.[252–254] To further support this in RH, data from a post hoc analysis of the SYMPLICITY HTN-3 trial evaluated the effect of renal denervation versus sham control on office and ambulatory (including nocturnal) SBP in patients with OSA. Compared with sham control, renal denervation reduced the 6-month office SBP in subjects with OSA.[56]

Patients without OSA who suffer from sleep deprivation, defined as less than a minimum of 6 hours of uninterrupted sleep, also have increased sympathetic activity. In this case, it is a consequence of reduced time in non–rapid eye movement or slow-wave sleep that also affects the nocturnal dip in BP.[252] This supports the hypothesis that disturbed non–rapid eye movement sleep quantity or quality is a mechanism by which sleep deprivation or restless leg syndrome leads to an increase in sympathetic tone.

SBP, diastolic BP, and heart rate increase the day after a sleep-deprived night compared with the day after a normal sleep; urinary excretion of norepinephrine is also increased.[56,253–256] In addition, BP, heart rate, and peripheral vascular resistance progressively decrease in non–rapid eye movement sleep. Thus, any deterioration in sleep quality or quantity may be associated with an increase in nocturnal BP, which could contribute to the development of poor hypertension control.

In contrast to reduced sleep time and quality, the increase in sympathetic activity associated with OSA is a function of intermittent hypoxia; the short-term rise in BP parallels the severity of oxygen desaturation at night.[256,257] Indeed, increased sympathetic activity is seen in both animal models subjected exclusively to intermittent hypoxia[258] and healthy human volunteers exposed to intermittent hypoxia in a "tent."[259] Respiratory event–related intermittent hypoxia is caused not only by overactivity of the adrenergic system but also by the renin-angiotensin system, as further supported by a meta-analysis.[255] It is also important to note that OSA-associated hypertension is only slightly reduced by continuous positive airway pressure (CPAP) treatment.[260] Nevertheless, addressing sleep disorders or sleep habits is relevant when considering the risk of either developing or controlling preexistent hypertension.

Poor BP control is strongly associated with OSA, especially in those patients with an apnea/hypopnea index of at least 30 events per hour.[261] Correction of sleep apnea with CPAP reduces BP in those who are adherent; however, because the SBP reduction is only from 2 to 5 mm Hg, adjunctive medications are almost always needed.[260] Use of ARBs and some β-blockers,[262] as well as central α-agonists such as clonidine or guanfacine, a longer-acting agent with comparable activity, at bedtime improves BP control.[263] Failure to achieve a sufficient amount of time in the deep stages of sleep increases the risk of developing hypertension.

The relationship between self-reported sleep duration and prevalent hypertension follows a U-shaped association with the nadir of the U being between 7 and 8 hours of uninterrupted sleep per night.[256,264,265] As sleep time is either reduced or increased from this range, there is higher prevalence of hypertension.[56,266] Moreover, sleep duration of <5 hours is associated with incident hypertension in subjects <60 years of age, whereas sleep duration of >9 hours per night is associated with incident hypertension in subjects >60 years. These early observations have been further confirmed with larger, more recent studies and meta-analyses.[256,264,267,268]

In summary, sleep quality and duration are critically important in the control of BP in RH. Clinicians should ask frequently about sleep quality and duration because they clearly affect BP control by activating both the sympathetic and renin-angiotensin systems and will further mitigate against controlling BP in RH. Many of these patients will have elevated heart rate disproportionate to their BP, a clinical clue that may be related to sleep quality.[269,270] In this setting, reinstating proper sleep patterns is critical, as is using agents that block the systems involved in the problem. Note that if the patient is receiving diuretics and is not adherent to a low-sodium diet, this will produce nocturnal micturition and result in interrupted sleep. Moreover, diuretics increase sympathetic tone; spironolactone blunts this activation, but ARBs do not.[271]

Obstructive Sleep Apnea

OSA is extremely common in patients with RH, with prevalence rates as high as 70% to 90%, and when present, OSA is often severe.[272–277] The high occurrence of OSA in patients with RH has been attributed to increased fluid retention and accompanying upper airway edema, as suggested by studies positively relating the presence and severity of OSA to aldosterone excess and high dietary sodium intake.[47,49,277–279] The role of aldosterone in promoting OSA is additionally supported by studies demonstrating that mineralocorticoid receptor antagonists reduce the severity of OSA in patients with RH.[280–282] Other studies implicate excessive accumulation of fluid centrally, including in the neck, as an important contributor to OSA severity in patients with RH by demonstrating increased shifting of fluid from the lower extremities into the upper body during supine sleep.[283] This central accumulation of fluid has been shown to contribute to upper airway edema with associated increases in upper airway resistance, thereby worsening OSA.[284,285] This effect is blunted by intensification of diuretic therapy, including the use of spironolactone.[286]

Treatment of patients with OSA and RH with CPAP induces significant but generally modest reductions in BP. In a randomized evaluation of treatment of moderate to severe OSA with CPAP versus no CPAP in patients with RH, treatment with CPAP reduced mean 24-hour SBP and diastolic BP by 3.1 and 3.2 mm Hg, respectively.[287] The treatment effect, however, was larger with increasing CPAP adherence. When analyzed separately, patients using CPAP at least 4 hours per night had reductions in 24-hour SBP and diastolic BP of 4.4 and 4.1 mm Hg, respectively, and reductions in nocturnal SBP and diastolic BP of 7.1 and 4.1 mm Hg, respectively.[287] However, a well-conducted randomized controlled trial recently demonstrated that CPAP plus usual care, compared with usual care alone, did not prevent CVD events in patients with moderate to severe OSA and established CVD.[288]

Routine evaluation by polysomnography is not indicated for all patients with RH. However, given the high prevalence of often severe OSA in patients with RH and the potential benefit of CPAP to enhance BP control, clinicians should vigorously screen such patients for symptoms of OSA (loud snoring, frequent nocturnal arousals, witnessed apnea, and excessive daytime sleepiness) and have a low threshold for referral for definitive evaluation and treatment.

Secondary Hypertension: Diagnosis and Management

Primary Aldosteronism

Primary aldosteronism is defined as a group of disorders in which aldosterone production is inappropriately high, relatively autonomous, and independent of the renin-angiotensin system and in which aldosterone secretion is not suppressed by sodium loading.[289] The disorder includes hypertension caused by volume expansion and sympathetic nervous system activation, hypokalemia, metabolic alkalosis, and advanced cardiovascular and renal disease. Because of the toxic effects of aldosterone on heart and blood vessels, primary aldosteronism is accompanied by a major increase in CVD and events compared with those observed in primary hypertension, including stroke (4.2-fold), myocardial infarction (6.5-fold), and atrial fibrillation (12.1-fold).[290] Primary aldosteronism is also associated with left ventricular hypertrophy, diastolic dysfunction and heart failure, large artery stiffness, oxidative stress, widespread tissue inflammation and fibrosis, and increased resistance vessel remodeling compared with primary hypertension.[291–293]

The majority of studies indicate that primary aldosteronism is a particularly common cause of RH. Observational studies from many different countries have demonstrated a prevalence rate of primary aldosteronism of ≈20% in patients with confirmed RH.[57,160,294–296] This relatively high prevalence contrasts with the ≈8% overall prevalence of primary aldosteronism in primary hypertension.[289] However, the prevalence of confirmed primary aldosteronism among 1656 hypertensive Chinese patients with RH was only 7.1%, indicating significant variation in prevalence in different populations.[297] When considering the frequency of primary aldosteronism, it is important not simply to accept a positive plasma aldosterone:renin ratio as diagnostic of the disease but to confirm the results of this screening test with 1 of 4 recommended confirmatory tests.[289] In the Chinese study, saline infusion was performed in all patients to confirm the diagnosis.[297]

Given the relatively high prevalence of primary aldosteronism in patients with RH, all such patients should be screened.[289] Screening for primary aldosteronism should be conducted with the ratio of plasma aldosterone concentration to PRA (aldosterone/renin ratio [ARR]) from a blood sample obtained in the morning with the patient in a seated position for at least 30 minutes before sampling.[289,298] A positive screening test requires an ARR of >30 or >20 if plasma aldosterone concentration is ≥16 ng/dL.[289] The validity of the screening test depends critically on appropriate preparation of the patient before the test. Hypokalemia, which reduces aldosterone secretion, should be corrected with oral K^+ supplements before testing. Pharmacological agents that markedly affect plasma ARR (spironolactone, eplerenone, and high-dose amiloride) should be withdrawn at least 1 month before testing.[289] It is also important to recognize that antihypertensive medications other than spironolactone, eplerenone, and amiloride can alter screening test results. For example, β-adrenergic receptor blockers, central α_2-receptor agonists, and renin inhibitors suppress PRA, and ACE inhibitors, ARBs, non–potassium-sparing diuretics, and dihydropyridine CCBs increase PRA, thus altering plasma ARR values. If the initial screening test results are not convincing, these medications can be selectively withdrawn for at least 2 weeks while BP is controlled with other agents that do not influence the renin-angiotensin-aldosterone system such as slow-release verapamil, hydralazine, or an α_1-adrenergic receptor antagonist (prazosin, doxazosin, or terazosin).[289]

If the screening test for primary aldosteronism is positive, the patient is usually referred for further evaluation to an endocrinologist or hypertension specialist. Further steps include administration of a confirmatory test (saline suppression test, oral salt-loading test, captopril test, or fludrocortisone suppression test). If primary aldosteronism is confirmed with one of these tests, subtype classification is usually performed with adrenal venous sampling. Patients with unilateral disease (50%; aldosterone-producing adenoma or, much less frequently, unilateral hyperplasia) respond to unilateral laparoscopic adrenalectomy with complete cure (≈50%) or improvement (≈50%) in BP control. Patients with bilateral disease (idiopathic hyperaldosteronism) usually have marked improvement in hypertension control with spironolactone or eplerenone.[289]

Renal Parenchymal Disease

CKD is both a cause and a complication of poorly controlled hypertension. Reduced kidney function results in impaired salt excretion, overactivation of the renin-angiotensin-aldosterone system, increased sympathetic nervous system activity, and altered medication efficacy. Treatment resistance in patients with CKD is undoubtedly related in large part to increased sodium and fluid retention and consequential intravascular volume expansion. An excess of total body salt and water limits the efficacy of antihypertensive medication classes that lack a natriuretic effect. In addition, salt may have a direct effect on the vasculature, hastening arteriosclerosis and blunting the vascular response to medication.

As the population ages, the prevalence of CKD is estimated to rise, and correspondingly, the number of individuals with RH will increase. From data from NHANES 1999 to 2010, the lifetime risk of developing (or "progressing to") moderate-stage CKD from normal baseline kidney function is 54% (age, 30–49 years), 52% (age, 50–64 years), and 42% (age ≥65 years).[299] An alternative simulation for a 30-year-old individual estimated a residual lifetime risk of 59.1% for estimated glomerular filtration rate (eGFR) <60 mL·min^{-1}·1.73 m^{-2}.[300] Although most of the CKD population will ultimately require antihypertensive drug therapy (30.2% with stage 1 CKD increasing to 78.9% with stage 4 CKD), achievement of current BP goals (≤130/80 mm Hg) declines with higher CKD stage from 49.5% at stage 1 to 30.2% at stage 4 (overall rate, 44.6%) despite greater use of antihypertensive medications. Even when a higher goal of ≤140/90 mm Hg was used, only 66.5% overall reached this target.[301]

Difficulty controlling BP in late stages of CKD was also seen in CRIC (Chronic Renal Insufficiency Cohort), in which 88% of participants had stage 3 or 4 CKD. Of the 86% with hypertension, 67% were controlled to <140/90 mm Hg and 46% were controlled to <130/80 mm Hg, with a higher prevalence of uncontrolled hypertension in those with lower

eGFR.[302,303] aTRH was present in 40% and was associated with higher cardiovascular event rates and mortality whether BP was uncontrolled (≥140/90 mm Hg) with 3 antihypertensive agents (52.5%) or controlled with ≥4 agents (47.5%).[19] aTRH was more common in patients with lower eGFR, including 22.3% with eGFR >60 mL·min⁻¹·1.73 m⁻², 39.4% with eGFR of 0 to 60 mL·min⁻¹·1.73 m⁻², and 54.2% in those with eGFR <30 mL·min⁻¹·1.73 m⁻². This trend was quantified as 14% higher odds of having aTRH for every 5–mL·min⁻¹·1.73 m⁻² decrease in eGFR (adjusted odds ratio, 1.14; 95% CI, 1.10–1.17). Doubling of proteinuria was associated with a higher likelihood of aTRH with an adjusted odds ratio of 1.28 (95% CI, 1.16–1.42). aTRH was common among CRIC participants, although 72% were receiving nephrology care.

Other data confirm that even when patients with CKD were followed up in nephrology clinics, <15% had their BP controlled to <130/80 mm Hg and <40% achieved a BP of <140/90 mm Hg despite the use of 3 different antihypertensive agents.[304] In ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), CKD as indicated by a serum creatinine of >1.5 mg/dL was a strong predictor of failure to achieve goal BP. Thus, patients with CKD and aTRH are at higher risk for CVD events and renal events (50% decrease in eGFR or incident end-stage renal disease) compared with patients with CKD without aTRH.[67]

Evaluation of the patient with CKD and RH includes consideration of other secondary causes that may coexist, including renal artery stenosis, primary aldosteronism, or other endocrine causes. Special attention should be focused on appropriate dietary sodium restriction because reduced salt intake may improve the efficacy of antihypertensive medications. Effective control generally requires a diuretic in the regimen with evolution to more potent agents, either thiazide-type agents at higher doses or loop diuretics, as renal function declines.

Renal Artery Stenosis

Hypertension accelerated or worsened by renal artery stenosis remains among the most common causes of RH, particularly in older age groups.[305] Among a series of 4494 patients referred to hypertension specialty clinics, 12.7% had secondary causes overall, of which 35% were associated with occlusive renovascular disease.[306] More recent series indicate that 24% of older subjects (mean age, 71 years) with RH have significant renal arterial disease.[307] Most cases are caused by atherosclerotic disease, but the syndrome of renovascular hypertension can result from other less common obstructive lesions, including a variety of fibromuscular dysplasias, renal artery dissection or infarction, Takayasu arteritis, radiation fibrosis, and renal artery obstruction from aortic endovascular stent grafts. Renal artery stenosis is recognized to produce a wide spectrum of manifestations ranging from an incidental, asymptomatic finding to accelerated hypertension and renal insufficiency. The latter often reflects disease progression.[308] Moderate degrees of renovascular hypertension most often can be managed with medical therapy, particularly with the use of agents that block the renin-angiotensin system (ACE inhibitors/ARBs), as several prospective randomized trials have demonstrated.[309,310] As a result, current practice has shifted to optimizing antihypertensive drug therapy as the primary treatment for patients with identified renal artery stenosis before embarking on complex imaging or interventional strategies. Most patients with renovascular disease tolerate ACE inhibitor or ARB therapy without adverse renal effects,[311] but a modest fraction (10%–20%) will develop an unacceptable rise in serum creatinine, particularly with volume depletion.[312] A subset of medically treated patients develop progressive disease syndromes with worsening hypertension, renal insufficiency, or circulatory congestion ("flash pulmonary edema"), which carry high mortality risks. Observational series have repeatedly demonstrated that BP control and mortality can be improved substantially after successful revascularization.[313,314] Post hoc analysis of the CORAL trial (Cardiovascular Outcomes With Renal Artery Lesions) data suggests a mortality benefit of revascularization compared with medical therapy for atherosclerotic renal artery stenosis in patients without proteinuria.[315]

Management of renal artery stenosis can be particularly challenging when bilateral lesions are present because there are considerable risks both with intervention and if intervention is not performed. Diagnosis of this disorder depends on clinical suspicion and consideration for arterial imaging for subjects with unexplained progressive hypertension or renal dysfunction. Duplex imaging to identify increased peak systolic velocity in the renal arteries is most commonly used, often with confirmation by computed tomography angiography or magnetic resonance angiography before invasive studies. Although initial treatment usually includes systematically advancing medical therapy, restoring main renal artery patency with endovascular stenting is also likely to reduce arterial BP, albeit with a residual requirement for antihypertensive drug therapy.[316] The most reliable predictor for effective BP reduction after revascularization remains a short duration of pressure elevation.

Medical treatment options for renal artery stenosis have been enhanced with the availability of effective blockade of the renin-angiotensin system and potent CCBs. Large data registries indicate that ACE inhibitor or ARB treatment in patients with identified renal artery stenosis confers a long-term mortality benefit.[317] Those individuals who experience a rise in creatinine during ACE inhibitor or ARB treatment usually tolerate restarting the medication after successful revascularization. The rise in serum creatinine during treatment in patients with renal artery stenosis or CKD is often transient and related to sluggish renal autoregulation when BP falls, with the fall being even greater if intravascular volume drops with diuretics or renin-angiotensin system blockers, which dilate the renal efferent more than the afferent arteriole. Patients failing antihypertensive drug therapy or those with bilateral renal artery disease with loss of renal function or episodes of pulmonary edema should be considered for revascularization.[318] Most patients with RH and atherosclerotic renal artery stenosis failing medical therapy can be treated with endovascular procedures such as stenting. Restenosis may develop in 15% to 24% of treated patients but may not always be associated with worsening hypertension or kidney function.[319] Surgical revascularization is reserved most often for subjects with complex anatomy or associated aortic disease.

Pheochromocytoma/Paraganglioma

The chromaffin cell tumors, pheochromocytoma (adrenal catecholamine producing, 90%) and paraganglioma (extra-adrenal, sympathetic/parasympathetic derived, 10%), are rare even in the hypertensive population, with a prevalence estimated at 0.01% to 0.2%. The prevalence is likely higher in patients referred for RH (eg, up to 4%).[320] Symptoms include paroxysmal hypertension (which may be sustained in up to 50% of those with high norepinephrine production or orthostatic in epinephrine-predominant tumors) associated with headache, palpitations, pallor, and piloerection ("cold sweat"). Given the high morbidity and mortality of not treating these tumors, the usual 3-year delay in diagnosis, and the fact that one-third are inherited, it is essential to consider the diagnosis in anyone referred for RH.

The screening test of choice for pheochromocytoma/paraganglioma is measurement of circulating catecholamine metabolites. Catechol *O*-methyl transferase releases normetanephrine and metanephrine from the tumors, measured as plasma free (sensitivity, 96%–100%; specificity, 89%–98%) or urinary fractionated (sensitivity, 86%–97%; specificity, 86%–95%) metanephrines.[321] Hypertensive patients frequently have elevated levels of catecholamine metabolites, especially in the presence of obesity and OSA and with the use of certain drugs such as tricyclic antidepressants. The levels are usually <4 times the upper limit of normal, but assessment should be repeated. If still elevated, they can be further evaluated as false positives by clonidine-suppression testing, with 100% specificity and 96% sensitivity of failure to reduce plasma metanephrines by 40%.[322]

Imaging should be pursued only after biochemical evidence for a pheochromocytoma has been obtained. The recent Endocrine Society guideline recommends starting with computed tomography, with magnetic resonance imaging as an alternative and metaiodobenzylguanidine scanning to further evaluate suspected metastatic disease.[323] Once the tumor has been confirmed, the patient should be prepared to undergo surgery by an experienced team (endocrinologist or hypertension specialist, surgeon, and anesthesiologist). Treatment with α-adrenergic blockade, a high-sodium diet, and fluid intake are recommended for at least a week before surgery to prevent intraoperative BP instability and to reverse volume contraction from pressure-natriuresis.[323] Postoperatively, patients should be followed up for the possibility of recurrence or metastasis, especially with the inherited forms.

Cushing Syndrome

Cushing syndrome is a relatively uncommon endocrine disorder caused by chronic excessive glucocorticoid exposure from endogenous or exogenous sources. This leads to a constellation of classic symptoms (mood disorders, menstrual irregularities, muscle weakness) and signs (weight gain, abdominal striae, hirsutism, dorsal and supraclavicular fat, fragile skin). Glucose abnormalities and hypertension are also common; thus, the disorder mimics a severe form of the metabolic syndrome. Although a variety of relatively small cohort studies suggest that high BP is highly prevalent (often exceeding 80%),[324,325] the overall frequency of hypertension, mild or severe, among patients with Cushing syndrome remains to be

accurately characterized. Since the earlier AHA statement,[2] there has also been little progress in better understanding the degree to which Cushing syndrome plays a role in RH. However, the available evidence does not support it as a common cause. In a recent study of 423 individuals with RH, a systematic evaluation for Cushing syndrome found no overt cases.[326] This suggests that although high BP (perhaps even severe forms) may be common among patients with Cushing syndrome, it is unlikely that it is prevalent in the overall population of patients with RH. This is likely principally a result of its rarity; however, the possibility should be recognized that some unknown percentage of patients with RH may be undiagnosed given the high prevalence of the metabolic syndrome, potentially masking occult disease.

Detailed guidelines on whom to screen, the diagnostic algorithm, and the treatment of patients with various forms of Cushing syndrome have been published.[327,328] Given the high risk for CVD events, the guidelines explicitly recognize the importance of aggressively treating hypertension.[328] Prior reviews outlining the underlying mechanisms of high BP in Cushing syndrome[324,325] suggest that blocking the mineralocorticoid actions of excess cortisol that increase renal sodium absorption with agents such as spironolactone or eplerenone is likely a sensible strategy. However, it is also recognized the hypercortisolism can promote hypertension through a variety of additional pathways (eg, activating the renin-angiotensin system, sensitizing the vasculature to catecholamines, and impairing endogenous nitric oxide bioavailability).[324,325] The optimal antihypertensive regimen in patients with Cushing syndrome therefore remains to be adequately described; there have been no randomized controlled trials in this area. Nevertheless, it is probable that excessive activation of mineralocorticoid receptors plays a prominent role and thus adequate diuretic therapy will likely prove to be a cornerstone of successful therapy. Further details on the overall treatment and surgical management of Cushing syndrome are provided in the recent guidelines.[328]

Coarctation of the Aorta

Patients with operated coarctation of the aorta are likely to have hypertension in adulthood and are at risk for premature CVD, including myocardial infarction, aortic aneurysm (ascending or descending), stroke, and heart failure.[329–331] Lifetime BP load is likely higher in patients with repaired coarctation compared with those with normal aortas because they have an exaggerated BP response to exercise. This response may also predict future hypertension.[332] All patients with a history of coarctation repair and hypertension should be evaluated for residual aortic arch obstruction with computed tomography angiography, particularly if a gradient between the right arm and leg is present and other sequelae of surgery such as descending aortic aneurysm are present.[331] If hypertension is resistant to treatment, surgical or catheter-based intervention should be considered if the risk/benefit ratio for the contemplated procedure is favorable. Because persistent hypertension may be secondary to increased sympathetic tone, β-blockers may be most useful for BP control.[333] Antihypertensive therapy typically also includes an ACE inhibitor or an ARB.

Other Causes of Secondary Hypertension

In addition to the above, other unusual/rare endocrine causes of secondary hypertension are included in Table 3.

Evaluation of RH

The evaluation of patients with RH should be directed toward confirmation of true treatment resistance, identification of causes contributing to resistance (including secondary causes of hypertension), and documentation of complications of the hypertensive disease process (see the evaluation algorithm in Figure 2). Assessment for treatment adherence and use of ABPM (or home BP monitoring if ABPM is unavailable) are needed to confirm RH. True RH usually has multiple causes, including excessive dietary salt intake, obesity, CKD, and OSA. Assessment for comorbidities and hypertensive complications is relevant because it will influence antihypertensive therapy in terms of the class of pharmacological agent selected and BP goals.[334]

Medical History

Documentation of the duration, severity, and behavior of the hypertension is important, along with adherence to medical appointments and antihypertensive treatment, clinical and adverse event responses to prior antihypertensive medications, and current prescription and over-the-counter medications that may elevate BP or interfere with antihypertensive drug effects. In the clinical setting, accurate medication adherence is not usually self-reported. Hence, clinicians must diplomatically inquire about how often patients might miss their medication doses per week, whether adverse effects might be playing a role in nonadherence, or whether patients have financial challenges affecting their ability to pay out-of-pocket expenses for their antihypertensive drugs.

The medical interview should also be directed toward identifying secondary causes of hypertension (for details, see the Secondary Hypertension: Diagnosis and Management section).

Physical Examination

The examination of patients with RH should be oriented toward ascertainment of target organ damage and possible secondary causes. BP should be measured as described previously. The presence of vascular disease, including in the retina, should be pursued with fundoscopic evaluation and careful examination of the quality of peripheral and carotid pulses and auscultation for bruits. Although not specific, abdominal bruits increase the possibility that obstructive renal artery disease exists. BP should be measured in both arms and in the thigh (in patients <30 years of age) if aortic occlusive disease or aortic coarctation is suspected. If the thigh SBP is >10 mm Hg lower than the arm SBP while the patient is supine, imaging studies for coarctation should be performed.[3] Hypercortisolism may be suspected in patients with obesity, diabetes mellitus, hypertension, depression, and bone loss accompanied by abdominal striae, "moon" facies, and intrascapular fat deposition.

Out-of-Office BP Monitoring

Disparities between in-office and out-of-office BP should be adjudicated.[334–339] Unattended automated office measurements, self-measurements (home or work), and ABPM have

Table 3.   Other Endocrine Causes of Secondary Hypertension

Disorder	Major Clinical Findings	Physical Examination	Screening Tests	Additional/Confirmatory Tests
Hypothyroidism	Dry skin; cold intolerance; constipation; hoarseness; weight gain	Delayed ankle reflex; periorbital puffiness; coarse skin; cold skin; slow movement; goiter	High TSH; low or normal fT4	
Hyperthyroidism	Warm, moist skin; heat intolerance; nervousness; tremulousness; insomnia; weight loss; diarrhea; proximal muscle weakness	Lid lag; fine tremor of the outstretched hands; warm, moist skin	Low TSH; high or normal fT4 and T3	Radioactive iodine uptake and scan
Hypercalcemia and primary hyperparathyroidism	Hypercalcemia	Usually none	Serum calcium	Serum parathyroid hormone
Congenital adrenal hyperplasia (excess DOC)	Hypertension and hypokalemia; virilization (11-β-OH deficiency); incomplete masculinization in males and primary amenorrhea in females (17-α-OH deficiency)	Signs of virilization (11β) or incomplete masculinization (17α)	Hypertension and hypokalemia with low or normal aldosterone and renin	11-β-OH: elevated DOC, 11-deoxycortisol and androgens; 17-α-OH: decreased androgens and estrogen; elevated DOC and corticosterone
Other mineralocorticoid excess syndromes caused by DOC	Early-onset hypertension, hypokalemia	Arrhythmias (with hypokalemia)	Low aldosterone and renin	DOC; urinary cortisol metabolites; genetic testing
Acromegaly	Acral features; enlarging shoe, glove, or hat size; headache; visual disturbances; diabetes mellitus	Acral features; large hands and feet; frontal bossing	Serum growth hormone ≥1 ng/mL during oral glucose load	Elevated age- and sex-matched IGF-1 level; MRI scan of the pituitary

DOC indicates deoxycorticosterone; fT4, free thyroxine; IGF-1, insulin-like growth factor-1; MRI, magnetic resonance imaging; OH, hydroxylase; T3, triiodothyronine; and TSH, thyroid-stimulating hormone.
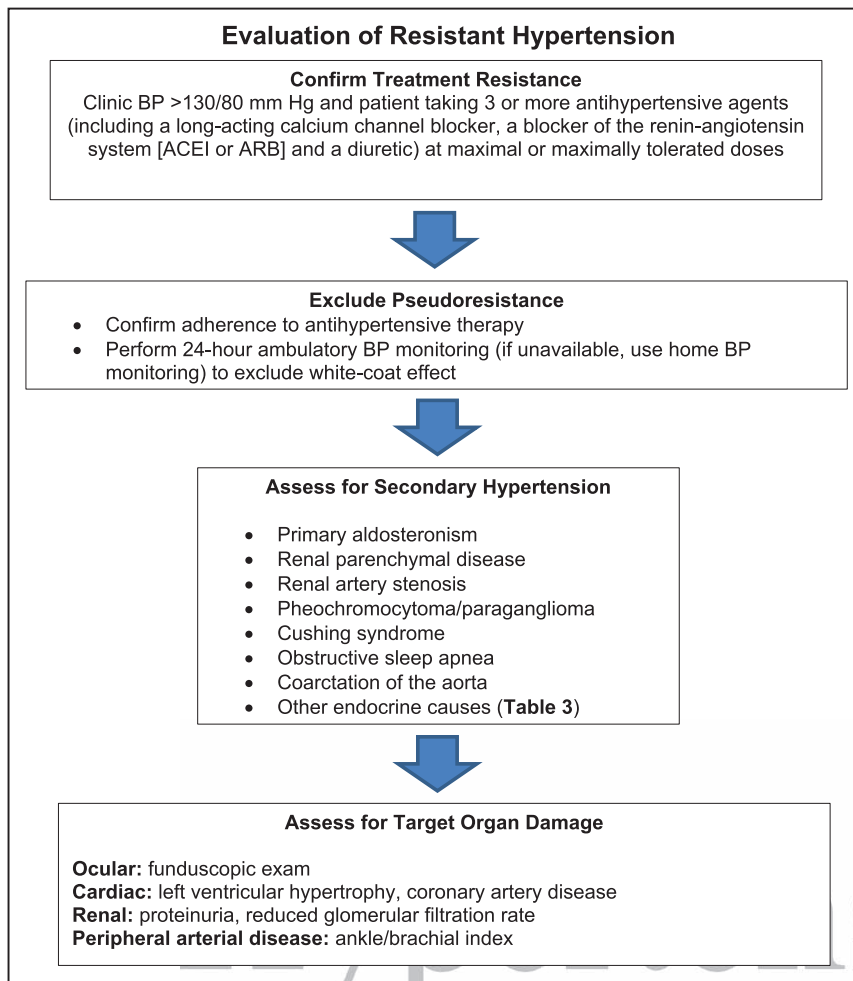
Evaluation of Resistant Hypertension

Confirm Treatment Resistance
Clinic BP >130/80 mm Hg and patient taking 3 or more antihypertensive agents (including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system [ACEI or ARB] and a diuretic) at maximal or maximally tolerated doses

Exclude Pseudoresistance
- Confirm adherence to antihypertensive therapy
- Perform 24-hour ambulatory BP monitoring (if unavailable, use home BP monitoring) to exclude white-coat effect

Assess for Secondary Hypertension

- Primary aldosteronism
- Renal parenchymal disease
- Renal artery stenosis
- Pheochromocytoma/paraganglioma
- Cushing syndrome
- Obstructive sleep apnea
- Coarctation of the aorta
- Other endocrine causes (**Table 3**)

Assess for Target Organ Damage

Ocular: funduscopic exam
Cardiac: left ventricular hypertrophy, coronary artery disease
Renal: proteinuria, reduced glomerular filtration rate
Peripheral arterial disease: ankle/brachial index

Figure 2. Algorithm depicting the evaluation of resistant hypertension. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and BP, blood pressure.

utility in determining whether there might be a white-coat effect that creates the appearance of treatment resistance. Of these methods, ABPM is the most objective and robust means to define the white-coat effect because it has been shown to be a stronger predictor of CVD morbidity and mortality than clinic measurements[340] and has received recommendations for use in the diagnosis of hypertension in both the United Kingdom and the United States.[1,341,342]

A white-coat effect (office BP above goal but ambulatory BP below goal) should be considered in patients with normal or lower self-measured BP, in those lacking target organ involvement (eg, retinopathy, CKD, left ventricular hypertrophy), and when there are symptoms of excessive antihypertensive therapy. If a white-coat effect is confirmed, out-of-office measurements (ambulatory or self-measured values if ABPM is not available) should be used to confirm the achievement of BP goals and to adjust drug therapy.[339,343]

Biochemical Evaluation

Laboratory examination of the patient with RH should include a basic metabolic profile (serum sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, and creatinine), urinalysis, and a paired morning plasma aldosterone and PRA to screen for primary aldosteronism. Interpretation of the ARR

is diminished in the setting of certain antihypertensive agents such as mineralocorticoid receptor antagonists (raise aldosterone levels) or direct renin inhibitors and β-adrenergic–blocking drugs (lower renin levels). The ratio is an effective screening test because it has a high negative predictive value for screening of primary aldosteronism.[344,345] The specificity for a high ARR is low as a result of the common occurrence of low-renin states (eg, volume expansion, dietary salt excess or sensitivity). A high ratio (> 20) when the serum aldosterone is >16 ng/dL and PRA is <0.6 ng/mL per hour is suggestive of primary aldosteronism, particularly in a patient taking an ACE inhibitor or ARB (these drugs elevate the PRA; hence, if renin is still suppressed, it increases the sensitivity of the ratio), but further assessments are required to confirm the diagnosis.

Measurement of plasma metanephrines or 24-hour urinary metanephrines is an effective screening test for patients in whom paraganglioma or pheochromocytoma is suspected.[346]

Noninvasive Imaging

Imaging for the evaluation of renal artery stenosis in patients with RH should be reserved for those with a high likelihood of renovascular disease: young patients in whom fibromuscular dysplasia could be present and older patients with a history of smoking or vascular disease who have increased risk for

atherosclerosis. Calculation of aortic and renal artery veloci-ties by duplex ultrasonography of the renal arteries is the usual initial test and is preferred over computerized tomography and magnetic resonance angiography as a screening tool, particu-larly when patients have CKD (eg, eGFR <60 mL·min^{-1}·1.73 m^{-2}). Direct renal arteriography in the absence of suspicious noninvasive imaging is not recommended. Abdominal imag-ing of the adrenal glands by high-resolution computerized tomography or magnetic resonance imaging is indicated only if there is biochemical evidence of hormonally active tumors (eg, elevated aldosterone, catecholamines, or cortisol).

Management of RH

An algorithm for managing RH is depicted in Figure 3.

Lifestyle Interventions

Weight Loss

Weight-reducing diets are well established to lower BP among patients with hypertension, by 4.5/3.2 mm Hg in the most recent meta-analysis.[347] On the other hand, the effect of pharmacologi-cally aided weight loss is mixed, with some medications show-ing modest benefits (eg, orlistat), whereas others (sibutramine) may even raise BP.[348] Although obesity clearly increases the risk for RH, trials demonstrating the efficacy of weight loss among these patients are lacking. Guidelines consistently promul-gate a healthy lifestyle (including caloric restriction), aiming for a >5% to –10% body weight loss among overweight and obese adults to help lower BP.[1,174] These same recommenda-tions should also apply to patients with RH (despite the lack of published studies among these patients), particularly in light of the fact that weight loss can lead to the successful withdrawal of medications, thereby easing hypertension control.[174,348] However, it is important to note that the long-term persistence of weight loss (>1 year) and the associated BP reduction are poorly described and warrant future investigation.

Dietary Salt Restriction

A reduced-sodium diet is well proven to decrease BP.[174,349] In a recent meta-analysis, an estimated 1-g (43.5-mmol) reduc-tion in daily sodium intake produces a 2.1– and 1.2–mm Hg decrease in SBP among hypertensive and normotensive patients, respectively.[349] In addition to hypertensives, other subgroups of individuals (eg, those with CKD[350] and obesity, blacks) are often more sensitive and can derive particularly robust benefits from sodium restriction.[153,155] In patients with RH, 2 recent small studies have demonstrated the efficacy of a reduced dietary sodium intake for BP lowering.[58,161] In 12 patients with true RH (taking 3.4±0.5 antihypertensive medi-cations), a low-sodium (50 mmol/d) versus a high-sodium (250 mmol/d) diet resulted in a profound reduction in aver-age office BP (−22.7/−9.1 mm Hg) over a 7-day period.[58] The low-sodium diet also led to significant reductions in daytime, nocturnal, and 24-hour BP levels (−20.1/−9.8 mm Hg). In a 6-week-long double-blind placebo-controlled crossover trial of 20 patients with stage 3 to 4 CKD, many of whom had RH (average, 3.2 ± 1.1 antihypertensive medications), a low-sodium (75 mmol/24-hour urine) versus a high-sodium (168 mmol/24-hour urine) diet significantly reduced 24-hour ambulatory BP (−9.7/−3.9 mm Hg).[161]

At present, debate remains about the optimal intake of sodium for the prevention of CVD morbidity and mortal-ity.[153–155,349] There is concern that a U-shaped relationship may exist, with the greatest risk reductions being achieved by following only moderate restriction in sodium intake of 173 to 217 mmol/d (4–5 g/d) despite the fact that BP continues to decrease in a linear fashion with even further reductions to <65 mmol/d (1.5 g/d).[349] It has been posited that sympathetic nervous system and renin-angiotensin system activation may counter the health benefits derived from the additional BP lowering at the lower range of sodium intake <130 mmol/d (3 g/d). AHA recommendations[155] have continued to promul-gate that an ideal daily sodium intake is <65 mmol/d (1.5 g/d), particularly among high-risk populations. Moreover, it is possible that the meta-analysis findings do not apply specifically to individuals with RH and that the additional BP lowering achieved through sodium restriction may off-set putative risks of achieving low levels of sodium intake. Evidence-based recommendations on the optimal sodium intake among patients with RH must await more definitive clinical trial data. For the time being, the available studies (albeit of short-term duration) support that sodium restric-tion, even to low levels <65 to 100 mmol/d (1.5–3.0 g/d), yields significant linear reductions in BP among patients with high BP[153–155,349] and RH.[58,161] Therefore, it seems pru-dent to continue to support the prior AHA recommendations for patients with RH[1] to reduce daily sodium intake to <100 mmol/d (2.3 g/d) and to consider more stringent restrictions to <65 mmol/d (1.5 g/d) on a case-by-case basis. Future trials testing the efficacy of this approach, particularly over longer-term durations (>6–12 months), are vital.

DASH Diet and Other Dietary Factors

A DASH-style eating pattern,[174,175] alcohol restriction to <10 g/d (women) and <20 g/d (men),[162–165] and a variety of other dietary modifications[174] can each yield significant reductions in BP among patients with hypertension. Diet intervention trials specifically among patients with RH are absent. In light of their safety and proven efficacy to lower BP in the general hypertensive population, patients with RH should follow the established dietary recommenda-tions promoted by the AHA[1,351] and American Society of Hypertension, as outlined in detail elsewhere.[174] Caution should be exercised in adopting a potassium-rich DASH diet in patients with more advanced (stage 4 and 5) CKD because these individuals are at risk for severe hyperkalemia and its consequences.

Exercise

Numerous clinical trials demonstrate that exercise can effec-tively lower BP, particularly among patients with preexisting hypertension.[352,353] In the largest meta-analysis to date, BP was lowered by 8.3/5.2 mm Hg over several weeks by a vari-ety of endurance (aerobic) exercise programs in patients with hypertension.[353] Moreover, dynamic resistance exercise was also shown to reduce BP by 1.8/3.2 mm Hg among hyperten-sive patients. As previously outlined, a treadmill walking exer-cise program in 1 study was safe and effective for lowering BP in patients with RH.[173] A recent small pilot study (n=16) also demonstrated that a water-based aerobic exercise program

Management of Resistant Hypertension

Step 1

| **Exclude other causes** of hypertension, including secondary causes, white-coat effect and medication nonadherence | + | **Ensure low sodium diet** (<2400 mg/d) **Maximize lifestyle interventions**: • ≥6 hours uninterrupted sleep • Overall dietary pattern • Weight loss • Exercise | + | **Optimize 3-drug regimen** Ensure adherence to 3 antihypertensive agents of different classes (RAS blocker, CCB, diuretic) at maximum or maximally tolerated doses. Diuretic type must be appropriate for kidney function. |

BP not at target

Step 2

Substitute optimally dosed thiazide-like diuretic: ie, chlorthalidone or indapamide* for the prior diuretic.

BP not at target

Step 3

Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone**

BP still not at target

Note: Steps 4-6 are suggestions on the basis of expert opinion only and these steps should be individualized.

Step 4

Check heart rate: unless <70 beats/min, **add β-blocker** (eg, metoprolol succinate, bisoprolol) or combined α-β-blocker (eg, labetalol, carvedilol). If β-blocker is contraindicated, consider central α-agonist (ie, clonidine patch weekly or guanfacine at bedtime). If these are not tolerated, consider once-daily diltiazem.

BP still not at target

Step 5

Add hydralazine*** 25 mg three times daily and titrate upward to max dose; in patients with congestive heart failure with reduced ejection fraction, hydralazine should be administered on background isosorbide mononitrate 30 mg daily (max dose 90 mg daily).

BP still not at target

Step 6

Substitute minoxidil***** 2.5 mg two to three times daily for hydralazine and titrate upward. If BP still not at target, consider referral to a hypertension specialist and/or for ongoing experimental studies— www.clinicaltrials.gov.
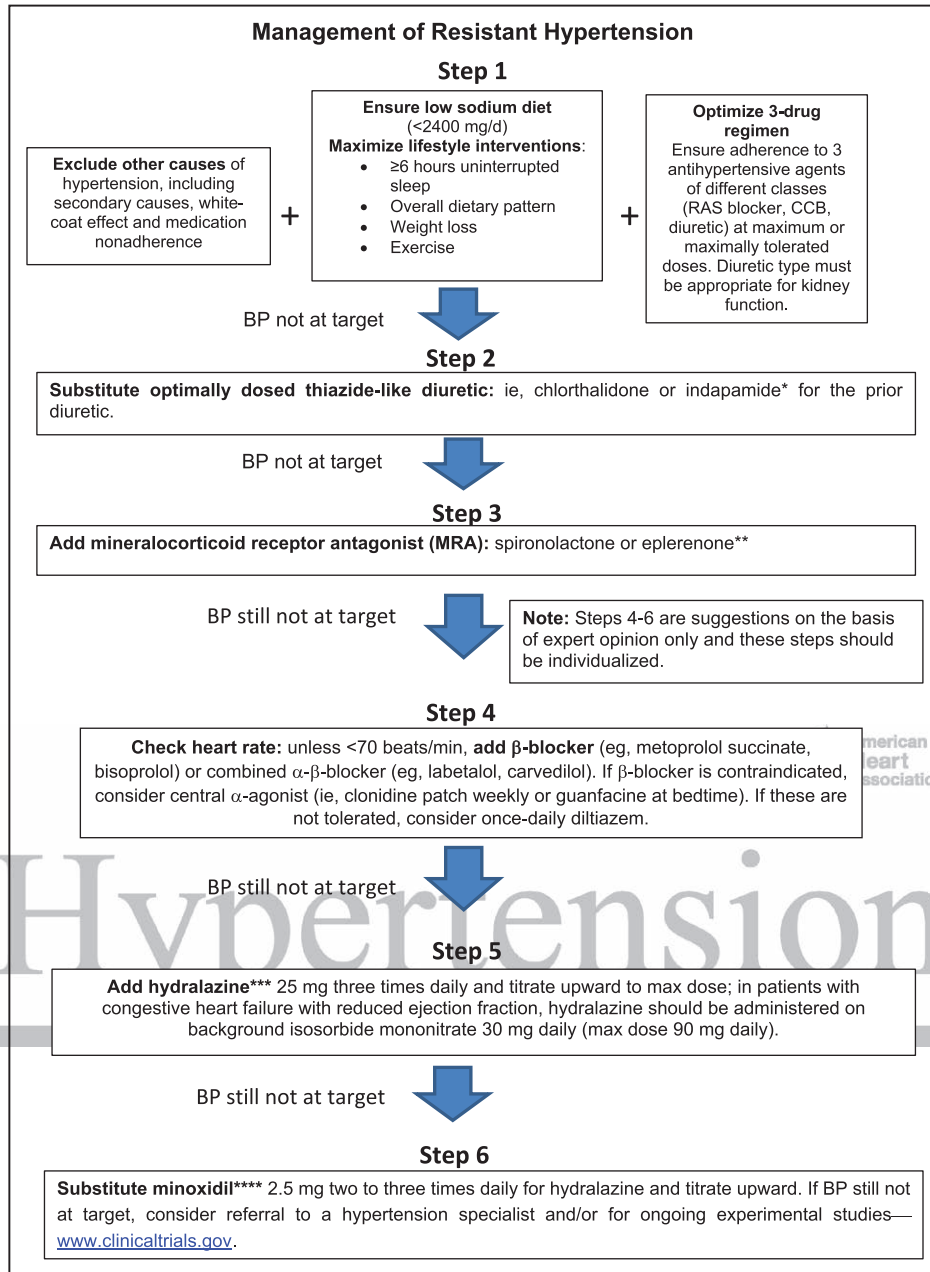
Figure 3. Algorithm depicting the management of resistant hypertension. BP indicates blood pressure; CCB, calcium channel blocker; and RAS, renin-angiotensin system. *These diuretics maintain efficacy down to estimated glomerular filtration rates (eGFRs) of 30 mL·min^{-1}·1.73 m^{-2}. **Use caution if eGFR is <30 mL·min^{-1}·1.73 m^{-2}. ***Requires concomitant use of a β-blocker and diuretic. ****Requires the concomitant use of a β-blocker and loop diuretic.

may be safe and effective for lowering BP in this population.[354] Although limited data are available, it seems appropriate that patients with RH should follow current exercise recommendations as promoted by numerous expert guidelines, including the 2017 American College of Cardiology/AHA guideline,[1] to reduce BP. In general, this involves ≥150 min/wk (in 3–5 sessions of 30–40 minutes) of moderate to intense aerobic activity, optimally supplemented with 2 to 3 sessions of light resistance training per week. Because RH is more common in obese and older adults, some may be unable to achieve moderate to intense aerobic activity. Low-intensity physical activity, 6 minutes hourly over an 8-hour period, in sedentary individuals lowered BP (14/8 mm Hg) and can improve metabolic syndrome

variables.[355–359] Moreover, evidence suggests that low-intensity physical activity may be similarly as effective as moderate to intense physical activity in preventing type 2 diabetes mellitus,[360] which is a concern in nondiabetic adults with RH.

Alternative Approaches

In a recent scientific statement from the AHA, the evidence supporting the BP-lowering efficacy of alternative approaches was reviewed.[361] Although many treatments had inadequate scientific support (eg, acupuncture, yoga), several modalities, including transcendental meditation, device-guided slow breathing, and isometric handgrip exercise, were felt to hold promise for clinical practice. More recent evidence continues to support the efficacy of isometric handgrip in particular. The

latest meta-analysis demonstrates that isometric handgrip, typically performed for 12 minutes 3 to 5 times per week, lowers BP by 5.2/3.9 mm Hg.[362] However, no trials among patients with RH have been performed. The usefulness of any alternative approach as an adjuvant to control BP in this population requires further investigation. Furthermore, the efficacy of intervening on other lifestyle factors that have been linked to high BP or RH, such as improving sleep quality and mitigating environmental triggers (eg, cold, noise, pollution), remains unknown.

A least 1 ongoing randomized clinical trial (TRIUMPH [Triple Pill vs Usual Care Management for Patients With Mild-to-Moderate Hypertension]) is investigating the effectiveness of an intense multifaceted lifestyle intervention program versus routine care in patients with RH.[363]

Pharmacological Treatment of RH

General Principles

Once all identifiable forms of hypertension, particularly endocrine causes, have been excluded and contributions from the white-coat effect (office BP at least 20/10 mm Hg higher than home or ABPM measurements) and masked uncontrolled hypertension (office BP measurements suggesting adequate BP control but out-of-office readings elevated above goal) are considered, therapeutic approaches for improved BP control in RH can begin. Three mechanistically complementary antihypertensive agents, commonly including a long-acting CCB, a blocker of the renin-angiotensin system (ACE inhibitor or ARB), and a diuretic, should already be prescribed and taken by the patient to ensure a proper diagnosis of RH (Figure 3, step 1). Hydrochlorothiazide does not induce a predictable natriuresis below an GFR of 45 mL·min^{-1}·1.73 m^{-2}, but chlorthalidone induces natriuresis down to an eGFR of 30 mL·min^{-1}·1.73 m^{-2}. Thiazide or thiazide-like diuretics are appropriate down to an eGFR of 25 to 30 mL·min^{-1}·1.73 m^{-2}.[364] Below this eGFR level or in hypoalbuminemic states (ie, serum albumin < 3.0 g/L), a long-acting loop diuretic such as torsemide should be used over shorter-acting agents such as bumetanide or furosemide.[365] These 3 separate pharmacological classes of antihypertensive agents must be given at maximally tolerated doses such as amlodipine 10 mg, chlorthalidone 25 mg, and one of the ACE inhibitors or ARBs at maximal dose.[366] Suboptimal medication regimens are common in patients with hypertension resistant to antihypertensive therapy.[21,60,367]

Specific Therapeutic Regimens

Because most cases of RH are linked to either volume excess, especially in CKD, or high sympathetic tone, establishment of the pathogenesis will optimally facilitate the choice of the fourth drug. In addition, ensuring that the most effective antihypertensive agent from certain pharmacological classes is selected is important when a fourth agent is added (Table 4).

Diuretic choices (Figure 3, step 2, and Table 4) are important because volume excess and failure to adhere to low-sodium diets are very common causes of RH. The diuretics with the greatest evidence base for reducing cardiovascular outcomes are the thiazide-like diuretics chlorthalidone and indapamide.[368,369] Comparative studies show an additional SBP

Table 4. Specific Clinical Issues Associated With Treatment Resistance*

Issue Associated With Treatment Resistance	Management Consideration(s)
Volume control, edema resolution	Thiazide→chlorthalidone→loop diuretic
Heart rate control inadequate	β-Blocker, α,β-blocker, verapamil, diltiazem
Renin and aldosterone levels low	Low-salt diet, avoid nighttime shift work, amiloride
Renin low, aldosterone normal to high normal	Mineralocorticoid receptor antagonist
Would split dosing of medications improve control?	Evaluate BP pattern according to home and ambulatory BP monitoring
Medication adherence questionable	Initiate indirect or direct methods to detect nonadherence; if nonadherence is documented (partial or complete), discuss frankly, nonjudgmentally with patient and family
Pattern of BP response to medications outside clinician visit times unknown	Identify meal effects on BP, duration of medication effect, relationship of BP to side effects using out-of-office BP monitoring
Sleep disordered breathing; significant anxiety associated with highly variable hypertension	Initiate nondrug strategies concurrently with or separately from antihypertensive drug therapy

BP indicates blood pressure.

*Modified from White et al[334] with permission from the American Society of Hypertension. Copyright © 2014, American Society of Hypertension.

reduction of 7 to 8 mm Hg simply by switching from hydrochlorothiazide to the same daily dose of chlorthalidone.[370–372]

Recent reports document the efficacy of mineralocorticoid receptor blockade (Figure 3, step 3, and Table 4) to improve BP in patients with RH.[373–377] In patients who are not overtly volume overloaded but who have evidence of low renin status or salt sensitivity of BP, mineralocorticoid receptor antagonists (spironolactone or eplerenone) are more successful than α- or β-blockers.[373,377] Spironolactone has the advantage of once-daily administration and can be initiated at doses of as little as 12.5 to 25 mg daily. However, the use of spironolactone as a fourth drug is limited by tolerability issues in some patients, including the development of hyperkalemia in those with CKD with an eGFR <45 mL·min^{-1}·1.73 m^{-2} or baseline serum potassium >4.5 mEq/L.[378] Approximately 70% of adults with RH are candidates for mineralocorticoid receptor antagonists based on eGFR and serum K$^+$, yet only a small fraction receive these effective agents.[379] With prolonged use at higher doses, gynecomastia and erectile dysfunction in men and menstrual irregularities in women may limit the use of spironolactone. In such cases, eplerenone may be used successfully.[380] Because of its shorter half-life compared with spironolactone, eplerenone should be administered twice daily for optimal effect.

The choice of ARB may also be important. Studies comparing various ARBs demonstrate clear advantages of certain agents in BP reduction over others. Specifically, 24-hour ABPM studies demonstrate that azilsartan medoximil provides

on average an additional 4 to 8 mm Hg further SBP reduction over other ARBs (eg, valsartan and olmesartan) or the ACE inhibitor ramipril.[381–383]

Dihydropyridine CCBs such as amlodipine and nifedipine extended release are the most studied in the setting of hypertension. Other drugs in this class such as nicardipine and isradipine are administered 2 or 3 times daily and do not lend themselves to optimal adherence in RH. Some data suggest that long-acting formulations of nifedipine may have slightly greater antihypertensive actions than amlodipine but are associated with more edema.[384–386] Nondihydropyridine CCBs such as verapamil also may be useful, but the evidence supporting their use in RH is limited.

Alteration of the dosing times (eg, to include a nocturnal dose) or using divided doses of drugs with half-lives of <12 to 15 hours may also improve BP control even when the drug theoretically has a pharmacodynamic effect of up to 24 hours in duration.[387,388] Dosing at night of certain agents, for example, guanfacine, also helps reduce adverse effects such as drowsiness and may aid in sleeping.

The choice of a fifth drug (to add) depends on sympathetic drive as assessed in part by heart rate (Figure 3, step 4). In 2 post hoc analyses from large outcome trials, patients with heart rates >80 bpm had higher mortality.[389,390] Thus, agents such as β-blockers or, if medically contraindicated, central α-2 agonists such as transdermal clonidine or guanfacine should be considered (Figure 3, step 4). Clonidine tablets should be avoided because of the need for frequent administration and the risk of rebound hypertension during periods of nonadherence and after discontinuation.

If BP is still not controlled with the above-described measures, the addition of hydralazine should be considered and combined with nitrates in cases of heart failure[391,392] (Figure 3, step 5). Nitrates are preferred in this setting because they help restore calcium (Ca^{2+}) cycling and cardiac contractile performance and control superoxide production in isolated cardiomyocytes.[393] Moreover, hydralazine reduces nitrate tolerance in this setting.[394] Note that hydralazine causes increased sympathetic tone and sodium avidity and therefore should be used in the presence of background appropriate diuretic and β-blocker therapy (Figure 3, step 5). Total daily doses of hydralazine should be <150 mg to avoid drug-induced systemic lupus erythematosus.

Lastly, minoxidil may be tried if hydralazine fails (Figure 3, step 6). Minoxidil is not well tolerated. It induces hirsutism, which in women can lead to discontinuation of the agent. Minoxidil must be given a minimum of twice daily and causes profound sodium avidity with fluid retention and increased sympathetic tone. Thus, a loop diuretic and β-blocker are required in virtually all cases. In this setting, however, minoxidil lowers BP effectively in most cases.[395]

Hypertension Specialist

The American Hypertension Specialists Certification Program has developed criteria for physicians to become Certified Hypertension Specialists (physicians only) and Certified Hypertension Clinicians (physicians and allied health providers). The requirements for both certification programs may be found at online.[396]

Hypertension specialists and clinicians have greater experience and knowledge managing the RH patient compared with most healthcare professionals. Retrospective studies have demonstrated improved BP control by hypertension specialists for patients referred for uncontrolled hypertension.[366,397] When BP control is not progressing the way the primary care provider thinks it should, the patient should be referred.

Device-Based Treatment of RH

Human sympathetic nervous system dysfunction plays an important role in the development and progression of hypertension, heart failure, and CKD.[398,399] In the 1940s, surgical sympathectomy demonstrated dramatic improvement in BP control and accompanying reduction in cardiac size, improved renal function, and a decrease in the rate of cerebrovascular events before the availability of antihypertensive drugs.[400] These successes were soon diminished by the occurrence of severe orthostatic hypotension, as well as erectile dysfunction and bowel and bladder incontinence, and the increasing availability of antihypertensive agents that eventually led to the general discontinuation of lumbar sympathectomy in clinical practice by the mid-1970s. Nevertheless, these early studies formed the basis for research on modern devices for the treatment of RH, the majority of which reduce sympathetic nervous system outflow.

Renal Nerve Ablation

Renal nerve ablation has been studied and used in clinical practice outside the United States for several years; hence, until recently, most data reported on its effects have come from centers in Australia and Europe. Early studies in this field were quite promising and showed large reductions of clinic BP in patients failing to be controlled with 4 or 5 antihypertensive drugs.[401,402] However, these studies were uncontrolled, and most did not study ambulatory BP as the primary end point. Later research showed that in uncontrolled studies, effect sizes using ABPM were much less (one-third) than the changes measured in the clinic setting.[403]

The first sham-controlled prospective randomized study in the field of renal ablation therapy, SYMPLICITY HTN-3, showed little to no effect of renal denervation therapy in a severely drug treatment–resistant population.[404] The failure of this most rigorously designed randomized sham-control study to meet the efficacy end points raised several methodological concerns, including alterations in patient behavior in adherence to their multidrug pharmacological regimens and inadequate denervation resulting from technical failure of the catheter, the interventional proceduralist, or both.[405]

The methodological concerns arising from SYMPLICITY HTN-3 have led to several new catheters and new trial designs to evaluate the efficacy of more extensive renal denervation. Several studies are ongoing, but there are no conclusions at present. Data from animal studies clearly document a reduction in norepinephrine spillover rate and lowering of BP with both radiofrequency and ultrasonic catheters to induce renal artery denervation. Post hoc analyses from SYMPLICITY HTN-3 suggest that BP fell in patients with more complete ablation compared with those with lesser degrees of renal

nerve ablation. In addition, the DENERHTN trial (Renal Denervation for Hypertension) recently demonstrated a statistically significant reduction in daytime ambulatory SBP (−5.9 mm Hg; *P*=0.03) in patients on 3 antihypertensive drugs randomized to renal denervation versus those on 4 antihypertensive drugs.[406] At present, renal denervation procedures to treat RH have been discontinued in most countries unless patients are in research programs.

More recent data from the SPYRAL HTN-OFF MED study using a different catheter providing more extensive renal denervation showed a significant reduction in BP.[407] However, the patients enrolled in this study did not have RH, and at best, this represents a proof-of-principle study demonstrating the role of the renal sympathetic nervous system in hypertension.

Carotid Baroreceptor Activation Therapy

Carotid baroreceptor activation therapy is a system that consists of baroreflex activation leads placed adjacent to the carotid sinus, an implantable pulse generator, and an external programming system. This modality electronically activates baroreceptors that signal the brain to orchestrate a multisystemic response for disorders associated with sympathetic overactivity such as hypertension, heart failure, and arrhythmias.[408,409] Consequences of carotid sinus stimulation include reduced sympathetic nervous system activity and enhanced vagal activity. Hence, the heart rate slows, allowing greater left ventricular filling time and reducing cardiac workload and energy demands. In addition, arterial dilation occurs, reducing cardiac afterload and improving renal blood flow, which augments natriuresis. The degree of stimulation can be titrated in ≈4-minute periods to meet individual patient hemodynamic requirements.

The first results from a large randomized trial in 322 participants with RH[410] failed to meet the primary end point of the trial, a composite of 5 individual efficacy and safety end points. However, the device was considered safe and efficacious long term in RH. This has led to refinements of the device and further research with single-sided catheters and a new Rheos system.[408]

The MobiusHD carotid bulb expansion device is a small endovascular implantable device that works by stretching the carotid artery at the bulb and activates baroreceptors to lower BP. Studies in Europe, CALM-FIM_EUR[411] (Controlling and Lowering Blood Pressure With the MOBIUSHD), which was completed, and in the United States, CALM-FIM_US,[412] which is ongoing, should provide results in 1 to 2 years. CALM-FIM_EUR has recently demonstrated in patients with RH that endovascular baroreflex amplification with the MobiusHD device substantially lowered BP with an acceptable safety profile.[413]

Devices on the Horizon for RH

In addition to renal nerve ablation therapy and baroreceptor activation therapy, other novel experimental devices are being explored for the treatment of RH with varying degrees of success and experience in patients. To date, most of the studies with these devices are uncontrolled and have small sample sizes. These include the central arteriovenous anastomosis

ROX coupler device,[414] the ReCor endovascular ultrasonic renal denervation device,[415] and median nerve stimulation that uses an electro-acupuncture technique to reduce sympathetic outflow.[416]

In conclusion, device therapy for RH is investigational at present. Future research and development is encouraged because novel devices that are effective may be applicable to patients who are refractory to drug therapy or who have difficulty tolerating efficacious drugs.[405]

Research Challenges and Needs

Knowledge of the prevalence of true RH that accounts for inaccurate BP measurement, white-coat effect, and medication nonadherence is urgently needed. Reducing the BP target in the general hypertensive population will no doubt increase the prevalence of RH. Coupled with the documentation of prevalence, the prognosis of RH needs to be reconfirmed. It is probable that the characteristics of patients with RH may change with refinement of the definition using lower BP thresholds. Better understanding of the optimal BP target for RH is needed.

The pathophysiology of RH is not always clear in individual patients and urgently needs elucidation. This includes environmental influences, especially the role of dietary salt intake and the salt sensitivity of BP.[417] Despite the sophisticated genetics technologies available today, the genetic basis for hypertension and RH continues to defy clear understanding. Except for the rare monogenetic causes, the pathophysiology of primary hypertension appears to be governed by a multiplicity of genes, each contributing only weak effects. Potential phenotypes to be explored by genetic analysis include RH at a young age, obesity-induced hypertension, salt-sensitive hypertension, and hypertension related to dysregulation of selected hormonal systems such as the renin-angiotensin-aldosterone system and the sympathetic nervous system. Identifying specific phenotypes of RH, which could be explored in greater depth for genetic contributions, would likely enhance our understanding of the origins of this complex disease process.

Once the prevalence of true RH is known, strategies for prevention should be considered. These might include earlier pharmacological treatment in the life course of those at high risk for RH and to prevent comorbidities that might make hypertension more difficult to treat such as vascular stiffening, arteriolar hypertrophy, and loss of renal function. Nonpharmacological strategies might include behavioral and sleep interventions.

Currently, the approach to BP control in RH has focused on the addition or substitution of drugs or drug classes based on meaningful pharmacological principles that are only partially successful in true RH. Future research should seek to improve personalized antihypertensive drug selection in patients with RH. For example, pharmacogenetics and pharmacogenomics are expected to provide a more rational and targeted approach to treatment. However, a prerequisite is to define in selected populations the role of genetic/genomic variation in BP responses to different pharmacological classes. This will take large well-controlled studies in which the participants are as well characterized phenotypically as

possible. In the meantime, the development of new classes of pharmacological agents will be important to improve the currently limited selection of drug alternatives in RH. It will also be important to broaden the approach to treatment to better ways of effecting long-term beneficial lifestyle change, detecting and reversing nonadherence, and using team-based care and telehealth to reduce BP. Alternative approaches such as improving sleep quality may also help reduce the prevalence of RH.

Several studies suggest that the benefits of BP control are less in patients with RH than those without RH. The reason for the lesser efficacy of hypertension control in RH is unclear but could be related to differences in the 24-hour BP profile (eg,

less nocturnal dipping or greater BP variability), differences in pathophysiological mechanisms, or greater degrees of subclinical target organ injury.

The role of device-based sympatholytic treatments, as with renal denervation and baroreceptor stimulation, awaits clarification. Although previously approved and used in different countries worldwide, validation of true benefit has not been confirmed in rigorous, double-blind comparisons with sham intervention. Such studies are ongoing with preliminary results expected in 2018. If independent benefit is confirmed, incorporation of device-based therapies into current treatment algorithms based on lifestyle and pharmacological therapies would be appropriate.

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*Modest.

†Significant.

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*Modest.

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