Compendium on the Pathophysiology and Treatment of Hypertension

Treatment of Resistant and Refractory Hypertension

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Abstract: **Resistant hypertension (RHTN) is defined as uncontrolled blood pressure despite the use of ≥3 antihypertensive agents of different classes, including a diuretic, usually thiazide-like, a long-acting calcium channel blocker, and a blocker of the renin- angiotensin system, either an ACE (angiotensin-converting enzyme) inhibitor or an ARB (angiotensin receptor blocker), at maximal or maximally tolerated doses. Antihypertensive medication nonadherence and the white coat effect, defined as elevated blood pressure when measured in clinic but controlled when measured outside of clinic, must be excluded to make the diagnosis. RHTN is a high-risk phenotype, leading to increased all-cause mortality and cardiovascular disease outcomes. Healthy lifestyle habits are associated with reduced cardiovascular risk in patients with RHTN. Aldosterone excess is common in patients with RHTN, and addition of spironolactone or amiloride to the standard 3-drug antihypertensive regimen is effective at getting the blood pressure to goal in most of these patients. Refractory hypertension is defined as uncontrolled blood pressure despite use of ≥5 antihypertensive agents of different classes, including a long-acting thiazide-like diuretic and an MR (mineralocorticoid receptor) antagonist, at maximal or maximally tolerated doses. Fluid retention, mediated largely by aldosterone excess, is the predominant mechanism underlying RHTN, while patients with refractory hypertension typically exhibit increased sympathetic nervous system activity. (*Circ Res*. 2019;124:1061-1070. DOI: 10.1161/CIRCRESAHA.118.312156.)**

Key Words: chlorthalidone ■ goals ■ humans ■ hyperaldosteronism ■ spironolactone

Resistant hypertension (RHTN) is defined as high blood pressure (BP) in a hypertensive patient that remains above goal despite use of ≥3 antihypertensive agents of different classes, typically including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system, either an ACE (angiotensin-converting enzyme) inhibitor or an ARB (angiotensin receptor blocker), and a diuretic, given at maximal or maximally tolerated doses.[1–3] The definition also includes BP that is controlled on ≥4 antihypertensive medications, controlled RHTN. The diagnosis of RHTN requires exclusion of common causes of pseudoresistance, which include improper BP measurement technique, which usually results in falsely elevated readings; white coat RHTN, defined as uncontrolled office BP but controlled out-of-office BP in a patient on ≥3 antihypertensive agents; undertreatment, including clinical inertia, which is the failure to establish appropriate BP targets and escalate treatment to achieve treatment goals; and medication nonadherence. The term apparent treatment RHTN is used to indicate patients diagnosed as having RHTN based on the number of prescribed medications and the office BP but in whom pseudoresistance cannot be excluded, that is, when medication dose, adherence, or out-of-office BP values are not documented.[1] These definitions are summarized in the Table.

The term RHTN has been used to identify patients with difficult-to-treat hypertension who might benefit from special diagnostic or therapeutic procedures or referral to a hypertension specialist. Observational studies and clinical trials of antihypertensive treatment have shown that patients with RHTN are at increased risk of cardiovascular disease (CVD) compared with patients with more easily controlled hypertension,[4] as well as higher risk of incident cardiovascular events, even after effective BP control is achieved.[5–9] This definition has also been useful for identifying patients with RHTN in a standardized fashion for research purposes, particularly in standardizing enrollment criteria worldwide for clinical trials of evolving treatment strategies for RHTN, including novel device-based approaches.[10–12]

Pseudoresistance

Most uncontrolled hypertension is not truly resistant to medical treatment but results from factors that lead to or maintain elevated BP readings independent of prescribed pharmacological treatment, termed pseudoresistance. The most common causes of pseudo-RHTN are inaccurate BP measurement, resulting in falsely elevated readings, the white coat effect, where in-office BP is persistently elevated but out-of-office BP is at goal, undertreatment, including clinical inertia, and medication nonadherence (Figure 1). Identification of factors that contribute to pseudoresistance is important in preventing costly and potentially risky diagnostic evaluations of patients who are not truly resistant to treatment, and avoiding inappropriate intensification of treatment, which can be costly and potentially increases the risk of adverse events.

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Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blocker
BP	blood pressure
CAD	coronary artery disease
CPAP	continuous positive airway pressure
CRIC	Chronic Renal Insufficiency Cohort
CVD	cardiovascular disease
INVEST	International Verapamil SR-Trandolapril Study
MR	mineralocorticoid receptor
OSA	obstructive sleep apnea
PATHWAY-2	Prevention and Treatment of Hypertension With Algorithm Based Therapy
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RfHTN	refractory hypertension
RHTN	resistant hypertension

Use of poor BP measurement technique is common in routine clinical settings, often resulting in inaccurate BP values. Some of the most common errors are not letting the patient rest in a quiet area, measuring the BP while the patient is standing or supine, engaging the patient in conversation during the BP measurement process, use of a BP cuff that is too small, placing the cuff over clothing, and introduction of operator biases through use of nonautomated devices. These errors often result in falsely elevated BP readings and have been shown to be particularly common in patients with presumed uncontrolled RHTN.

In a prospective evaluation performed in our hypertension referral clinic, Bhatt et al[13] compared BP measurements made routinely during the triage process with BP measurements made in the same patients by trained clinicians. The latter measurements used an automated oscillometric device BpTRU (VSM Med Tech, Ltd, Coquitlam, Canada). A total of 130 consecutive patients referred for suspected uncontrolled RHTN were included in the analysis. After having their triage BP measured, patients were seated in a quiet room, a correctly sized cuff was placed directly over the brachial artery of their nondominant arm, and then were left unattended for 3 to 5 minutes. Six serial, automated, unattended measurements were obtained, and the last 5 were averaged for the final reading. BP values obtained during the triage process were consistently higher compared with the unattended BP values obtained by the trained clinicians. The systolic and diastolic BP measurements were ≤33/21 mm Hg higher in the triage setting versus the standardized assessment, with a median difference of 23/13 mm Hg. Overall, 33% of the patients would have been misdiagnosed as having uncontrolled RHTN based solely on the triage assessments. These findings suggest that approximately one-third of patients referred to a hypertension specialty clinic may be falsely misidentified as having uncontrolled RHTN based on routine clinic BP measurements, highlighting the need for standardized, automated-based BP measurements to confirm true RHTN.

White coat RHTN is another common cause of pseudotreatment resistance. De la Sierra et al[14] determined the prevalence of white coat RHTN among >8200 patients with apparent RHTN included in the Spanish Ambulatory Blood Pressure Monitoring Registry. Overall, 62.5% were classified as having true RHTN, based on having sustained uncontrolled hypertension both in clinic and during 24-hour ambulatory BP monitoring, whereas the remaining 37.5% were identified as having white coat RHTN. These findings clearly indicate that a prominent white coat effect is common in patients with suspected uncontrolled RHTN, and accurate out-of-office assessment of BP, ideally with ambulatory BP monitoring, is essential to confirm true RHTN. A study by Muxfeldt et al[15] further highlighted the need for continued out-of-office BP monitoring of patients with white coat RHTN. Among 198 patients with white coat RHTN whose ambulatory BP monitoring was repeated 18 months later, ≈50% had persistence of their white coat effect, but 50% had been reclassified as having true sustained RHTN. These studies indicate that out-of-office BP assessments are necessary to exclude a white coat effect to confirm true RHTN

Table. Definitions of Terms

RHTN	BP that remains elevated above goal in spite of the concurrent use of ≥3 antihypertensive agents of different classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system and a diuretic, administered at maximal or maximally tolerated doses, and requires exclusion of common causes of pseudoresistance.
Pseudoresistance	Factors that can cause a falsely elevated BP in a patient on ≥3 antihypertensive agents, such as improper BP measurement technique, white coat RHTN, undertreatment, clinical inertia, and medication nonadherence.
Clinical inertia	The failure to establish appropriate targets and escalate treatment to achieve treatment goals.
Controlled resistant hypertension	BP that is controlled on ≥4 antihypertensive medications at maximal or maximally tolerated doses.
Apparent treatment-resistant hypertension	Term used when medication dose, adherence, or out-of-office BP is not documented or accounted for, and pseudoresistance cannot be excluded in a patient on ≥3 antihypertensive agents.
White coat resistant hypertension	Term used when office BP is uncontrolled but out-of-office BP monitoring shows controlled SBP and DBP values in a patient on ≥3 antihypertensive agents.
Refractory hypertension	BP that remains uncontrolled on maximal or near-maximal therapy, which is the use of ≥5 antihypertensive agents of different classes, including a long-acting thiazide-like diuretic (such as chlorthalidone) and spironolactone.

BP indicates blood pressure; DBP, diastolic blood pressure; RHTN, resistant hypertension; and SBP, systolic blood pressure.

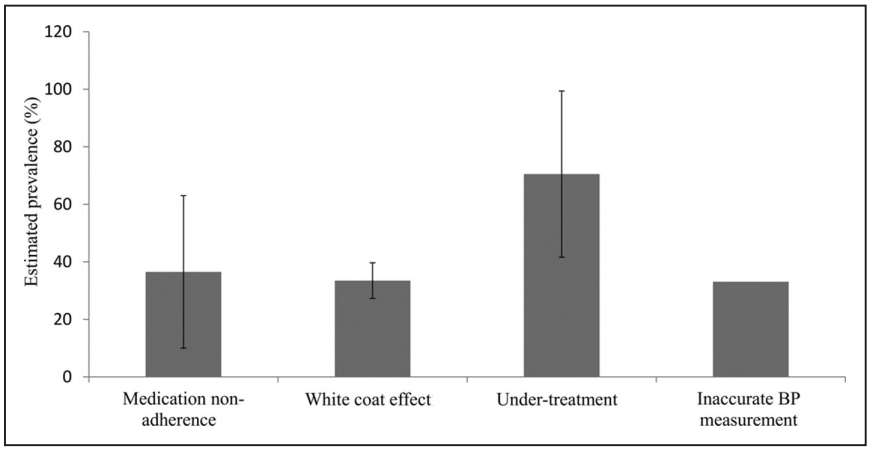

Figure 1. Estimated prevalence of common causes of pseudotreatment resistance. BP indicates blood pressure. Adapted from Bhatt et al[13] with permission. Copyright ©2016, Elsevier.

and avoid unnecessary treatment in those with pseudo-RHTN. These findings also emphasize that continued surveillance of out-of-office BP levels is necessary because many patients with white coat RHTN may develop true RHTN and will require intensification of antihypertensive treatment.

Undertreatment of hypertension, including lack of appropriate treatment intensification in uncontrolled patients, termed clinical inertia, is common and becomes more prevalent as the number of prescribed medications increases.[16] Egan et al[17] identified >44 000 patients who were enrolled in community-based practices in the Southeastern United States as having apparent uncontrolled RHTN using electronic medical records. Of these, only 15% had been prescribed an optimal antihypertensive regimen, defined as a diuretic and ≥2 additional antihypertensive agents at ≥50% of the recommended maximum dose for treating hypertension. Among patients receiving an optimal treatment regimen, including a diuretic, the mean number of prescribed medications was 4.2 in those whose BP remained uncontrolled versus 4.9 agents in those with controlled BP. These findings provide evidence that clinical inertia contributes importantly to lack of BP control in usual clinical practice.

Another common cause of pseudoresistance is poor medication adherence. Jung et al[18] assessed adherence with prescribed antihypertensive regimens by measuring antihypertensive drug or drug metabolite levels in urine samples from patients referred to a hypertension specialty clinic for uncontrolled RHTN. After excluding patients whose BP was controlled with optimization of therapy or who had white coat RHTN or secondary causes of hypertension, the 76 patients thought to have true RHTN were tested. Based on the presence of detectable urinary drug or drug metabolite levels, only 36 (47%) of these patients were adherent with all prescribed agents, whereas 40 (53%) were considered nonadherent. Twelve of the 40 nonadherent patients were taking none of their prescribed antihypertensive medications based on the complete absence of detectable urinary drug or metabolites, and the majority of those considered partially adherent were taking less than half of the prescribed medications. Other studies based on measurement of serum or urinary drug levels confirmed poor medication adherence levels in patients with apparent RHTN.[19,20]

It is well established that as the number of the prescribed medications increases and as the dosing schedule becomes increasingly complex, adherence with prescribed regimens declines.[16] Accordingly, treatment of RHTN is often complicated by worsening adherence as therapy is intensified. A major challenge in the management of these patients is accurate assessment of medication adherence. Clinician impression is often incorrect, and self-reported adherence is often overstated. Increased use of electronic medical records allows for better monitoring of prescription refill rates, but having a medication refilled, especially if done automatically through a mail order service, does not ensure adequate adherence. Observed pill ingestion to document lack of adequate BP response is not likely viable for most clinics, given space and staffing constraints. Commercial laboratories are increasingly offering standardized testing of blood and urine for the presence of prescribed medications and their metabolites, but issues of patient consent and lack of insurance coverage for the testing need to be resolved to allow for routine clinical use.

Prognosis

RHTN is a high-risk phenotype of hypertension. Uncontrolled BP is the single most important modifiable risk factor for cardiovascular morbidity and mortality worldwide.[21] Patients with RHTN typically have long histories of severe BP elevation, predisposing them to higher cardiovascular risk than treated hypertensive patients with controlled BP. A retrospective cohort study performed by Daugherty et al[5] in 2 integrated health plans examined the CVD outcomes of patients with incident hypertension who went on to develop RHTN. They found that patients who developed RHTN are more likely to experience clinical outcomes of death, myocardial infarction, heart failure, stroke, or chronic kidney disease (CKD) compared with treated hypertensive patients with controlled BP (18% versus 13.5%; $P<0.001$; hazard ratio, 1.47; 95% CI, 1.33–1.62) during a mean 3.8 years follow-up. In another retrospective analysis of >400 000 persons, patients with RHTN had increased risk of developing end-stage renal disease, ischemic heart disease, heart failure, stroke, or death compared with treated hypertensive patients with controlled BP (multivariable adjusted hazard ratios of 1.32 [95% CI, 1.27–1.37], 1.24 [95% CI, 1.20–1.28], 1.46 [95% CI, 1.40–1.52], 1.14 [95% CI, 1.10–1.19], and 1.06 [95% CI, 1.03–1.08], respectively).[7]

Patients with RHTN also have a higher prevalence of comorbid conditions, including diabetes mellitus (48% versus 30% in hypertensive patients with controlled BP), CKD (45% versus 24%), ischemic heart disease (41% versus 22%), and

cerebrovascular disease (16% versus 9%), which greatly increase the risk of clinical events.[7] In the CRIC (Chronic Renal Insufficiency Cohort), a multicenter, prospective, observational study of risk factors for progression of CKD, patients with CKD, but not on dialysis, and RHTN had a higher risk of a composite outcome of myocardial infarction, stroke, peripheral arterial disease, congestive heart failure, and all-cause mortality than hypertensive patients with CKD and controlled BP, even when the BP was at goal.[22] In hypertensive patients with coronary artery disease (CAD), the presence of RHTN is associated with a higher risk of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke compared with treated hypertensive patients with controlled BP.[8] In another study of patients with CAD, the risk of death and morbidity was increased by as much as 64% to 73% in patients with RHTN compared with treated hypertensive patients with controlled BP.[23] Women with RHTN and signs and symptoms of myocardial ischemia had worse outcomes, including an increased risk of death, than treated hypertensive women with controlled BP.[9] Further, the mortality risk persisted for at least 10 years from the determination of treatment-resistant status, regardless of the presence of obstructive CAD.[9]

It is uncertain whether the increased cardiovascular risk seen in RHTN is related solely to the persistent BP elevation per se or whether specific pathophysiologic factors are involved. The high CVD burden in RHTN results from an interplay of multiple processes, for example, increased renin-angiotensin system and sympathetic nervous system activity, hyperaldosteronism, and increased arterial stiffness, that have been associated with increased cardiovascular risk. In a post hoc analysis of the INVEST (International Verapamil SR-Trandolapril Study), a prospective, randomized, open-label, blinded end point trial that compared clinical outcomes in 22 576 participants with CAD and hypertension who were randomly assigned to a calcium channel blocker–based or β-blocker–based antihypertensive treatment strategy, there was no difference in outcomes between patients with uncontrolled RHTN versus those with controlled RHTN, despite a difference in mean BP of ≈27/10 mm Hg between the 2 groups.[8] Further, it has been shown that patients who are prescribed a greater number of antihypertensive medications have increased cardiovascular risk independent of BP level.[24] The Reduction of Atherothrombosis for Continued Health Registry followed people ≥45 years of age with ≥3 risk factors for atherosclerosis and with established CAD, CVD, or peripheral artery disease prospectively for 4 years.[24] Participants in Reduction of Atherothrombosis for Continued Health with RHTN on 4 antihypertensive agents had a 15% higher risk of the primary end point, a composite of cardiovascular death, myocardial infarction, or stroke at 4 years, when compared with treated hypertensive patients with controlled BP (20.1% versus 13.9%; hazard ratio, 1.15; 95% CI, 1.06–1.24; P=0.0004). Participants on ≥5 agents were at even higher risk compared with those with controlled BP; 20% higher hazard of the primary end point (21.3% versus 14.7%; hazard ratio, 1.20; 95% CI, 1.01–1.43; P=0.036). In the REGARDS study (Reasons for Geographic and Racial Differences in Stroke), differences in BP control among patients with RHTN were not associated with differences in stroke or mortality.[25] Further, BP lowering may confer less improvement in the cardiovascular risk profile of patients with RHTN than in hypertensive patients without RHTN.[26] Collectively, these studies provide evidence that the presence of RHTN, more than the level of the BP alone, is an important predictor of cardiovascular risk in patients with hypertension.

The prognosis of patients with RHTN may be improved with lifestyle modification. Healthy lifestyle factors, including having a normal waist circumference, engaging in physical activity ≥4× per week, nonsmoking, moderate alcohol consumption, high Dietary Approaches to Stop Hypertension diet score, and low sodium-to-potassium intake ratio; all of which are recommended for all patients with hypertension, are associated with a lower risk for cardiovascular events and mortality among individuals with RHTN.[27] In particular, nonsmokers and those who engage in physical activity ≥4× per week had the lowest associated risk for cardiovascular events during a mean follow-up of 4.5 years.

Pharmacological Treatment

Initial 3-Drug Regimens

Pharmacological therapy of RHTN is based on use of effective combinations of ≥3 antihypertensive medications. While particular combinations have to be individualized based on patients' comorbidities, prior medication intolerances, and financial considerations, the initial 3-drug regimen should be standardized as much as possible to include a renin-angiotensin system blocker, specifically an ACE inhibitor or ARB, a long-acting calcium channel blocker, most commonly amlodipine, and a long-acting thiazide-like diuretic, preferably chlorthalidone or indapamide. The standard 3-drug regimen of ACE inhibitor/ARB, amlodipine, and chlorthalidone combines classes of agents with complementary mechanisms of action that have been shown to be effective both individually and in combination in lowering BP and in preventing CVD and death. All of the recommended agents are available as generics and in long-acting formulations and are generally well tolerated. These particular agents have the advantage of being available in various dual or triple pill combinations, allowing for simplified regimens, reduction in pill burden, and sometimes lesser out-of-pocket, including copayment, costs. The standardized triple-drug combination of a renin-angiotensin system blocker, amlodipine, and a thiazide-like diuretic was used as baseline therapy in multiple studies of RHTN, including the PATHWAY-2 study (Prevention and Treatment of Hypertension With Algorithm Based Therapy), which demonstrated the superiority of spironolactone when added as a fourth drug.[28] The benefit of adding spironolactone to combinations of pills other than an ACE inhibitor or ARB, amlodipine, and chlorthalidone or indapamide has not been systematically determined. In addition, this particular triple combination continues to be widely used as the standard baseline therapy for ongoing clinical trials assessing the efficacy and tolerability of potential new pharmacological therapies for treatment of RHTN, as well as the multiple studies evaluating new device-based therapies for RHTN. Widespread use of the triple combination in prior and ongoing studies assessing novel treatment strategies for RHTN provides important clinical validation of the 3-drug regimen in terms of clinical benefit, including ease of use.

ACE inhibitors and ARBs play important roles in the treatment of patients with RHTN because of their efficacy and tolerability, as well as the prevention and management of common comorbidities, such as diabetes mellitus, heart failure, and CKD. Both ACE inhibitors and ARBs reduce the rate of incident diabetes mellitus by ≈20% to 30% compared with other classes of antihypertensive drugs.[29,30] Further, ACE inhibitors and ARBs are indicated for the management of patients with CKD and heart failure, which are common comorbidities in patients with RHTN.[31–33]

A long-acting thiazide-like diuretic, specifically chlorthalidone, if available, is recommended over hydrochlorothiazide (HCTZ) given its superior efficacy and clear benefit demonstrated in multiple outcome studies of hypertension.[4,34–36] Although the efficacy of chlorthalidone has not been prospectively compared with HCTZ in patients with well-characterized RHTN, some reports demonstrate that substituting chlorthalidone for HCTZ in patients uncontrolled on multiple-drug combinations provides further BP reduction and improves overall control rates.[37] The superiority of chlorthalidone over HCTZ to reduce BP, particularly nighttime BP, is likely related to its longer half-life. However, chlorthalidone use is more frequently associated with adverse metabolic effects, particularly hypokalemia and hyponatremia, compared with HCTZ. These adverse effects can be severe enough to require withdrawal of chlorthalidone, and it is important to monitor electrolytes regularly when prescribing chlorthalidone.

Fixed-dose combinations of ACE inhibitors or ARBs, amlodipine, and HCTZ are widely available, allowing for simplification of dosing, reduction in pill number, and possibly less cost, advantages which are well known to improve medication adherence. Combinations with chlorthalidone are less common but should be used preferentially if available and affordable for the patient.

Use of Spironolactone as the Fourth Agent for Treating RHTN

A large body of literature demonstrates that aldosterone excess is a common cause of RHTN.[38–42] Multiple studies indicate that true, classical primary aldosteronism is present in ≈20% of patients with confirmed RHTN. More importantly, lesser degrees of aldosterone excess that do not fulfill strict criteria for classical primary aldosteronism may contribute to resistance to commonly used antihypertensive medications.[43] This aldosterone excess is related to being overweight or obese, common comorbidities in patients with RHTN.[44] There is a positive relationship between weight gain and aldosterone levels in both women and men, but this effect is more pronounced in men (Figure 2).[44] This finding suggests that accumulation of excess abdominal adiposity, more characteristic of men, may either directly release aldosterone or indirectly stimulate the release of aldosterone secretagogues. Such a possibility is consistent with cell culture studies suggesting that adipocytes, particularly abdominal adipocytes, are hormonally active and release agents that stimulate the secretion of aldosterone from isolated zona glomerulosa cells.[45,46]

Given that excess aldosterone is a common cause of antihypertensive treatment resistance, it is not surprising that MR (mineralocorticoid receptor) antagonists, which block the action of aldosterone on MRs, are especially effective for treatment of RHTN.[47–51] Three MR antagonists, spironolactone, eplerenone, and canrenone (not available in the United States), are available for the treatment of hypertension, and spironolactone is the most studied in RHTN. Spironolactone is the most effective fourth medication for treating RHTN in patients already on treatment with triple regimens that include an ACE inhibitor or ARB, amlodipine, and a thiazide-like diuretic.[28] Early studies that assessed the add-on benefit of spironolactone as the fourth drug for treating RHTN demonstrated substantial antihypertensive benefit, with mean BP reductions often exceeding 20/10 mm Hg.[49,50] These studies typically had important limitations, including open-label assessments of medication use, lack of an active comparator, failure to confirm true RHTN, and inclusion of small numbers of patients. Nonetheless, they were critical in showing consistent benefit of spironolactone for treatment of hypertension uncontrolled on multiple-drug regimens.

The landmark PATHWAY-2 study demonstrated a major benefit of spironolactone in treating patients with RHTN

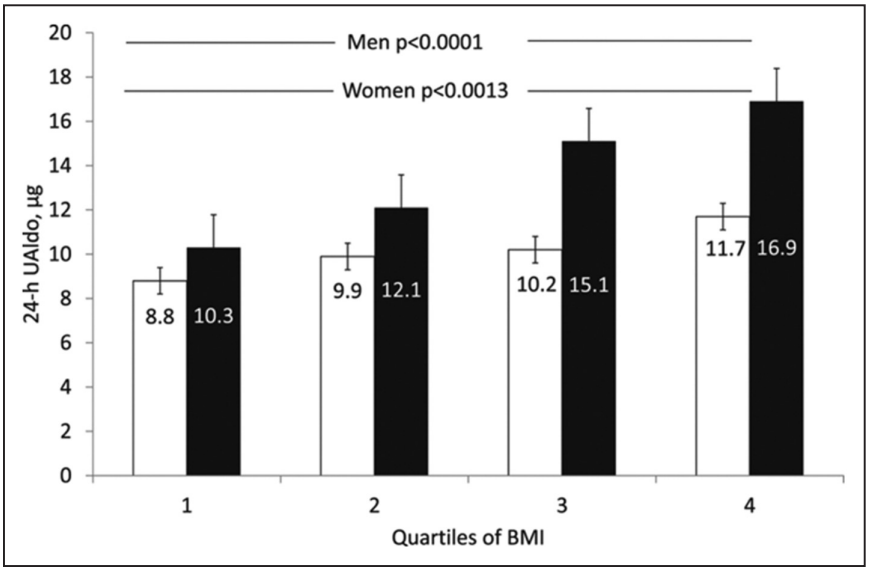

Figure 2. Mean 24-h urinary aldosterone (UAldo) levels to quartiles of body mass index (BMI) in men (black columns) and women (white columns) with resistant hypertension. Adapted from Dudenbostel et al[44] with permission. Copyright ©2016, the American Heart Association.

uncontrolled on a standardized 3-drug regimen of an ACE inhibitor or ARB, amlodipine, and the thiazide-like diuretic indapamide.[28] PATHWAY-2 was a double-blind, 4-way crossover study that compared 3 months of treatment with spironolactone 25 to 50 mg daily to the β-blocker bisoprolol 5 to 10 mg, the α-blocker doxazosin 5 to 10 mg, or placebo as add-on therapy for RHTN. True RHTN was confirmed after home BP remained uncontrolled following observed ingestion of maximum tolerated doses of the standardized triple-drug regimen. Adherence during the study was monitored by pill counts and by measurement of serum ACE activity. PATHWAY-2 showed that spironolactone was superior to placebo and the 2 active comparators for reducing BP in patients with uncontrolled RHTN. On average, spironolactone reduced home systolic BP by 8.70 mm Hg more than placebo, 4.48 mm Hg more than bisoprolol, and 4.03 mm Hg more than doxazosin ($P<0.0001$). The percentage of patients whose BP was controlled was 58.0% for spironolactone compared with 23.9% for placebo, 43.3% for bisoprolol, and 41.5% for doxazosin ($P<0.001$ for all groups).

Spironolactone was well tolerated in those PATHWAY-2 study participants who had normal renal function (estimated glomerular filtration rate, >45 mL/min, and mean estimated glomerular filtration rate, 91.1 mL/min). Overall, there was no difference in the occurrence of adverse events between treatments, including adverse events that might be expected to limit spironolactone use, such as gynecomastia or hyperkalemia. Six of the 285 patients (2%) receiving spironolactone developed a serum potassium level >6.0 mmol/L on a single occasion. No gynecomastia was reported during the study, but study participants had only 3 months of exposure to spironolactone. Similarly, in our experience, the risk of spironolactone-induced hyperkalemia is low in patients with normal renal function, particularly if they are already receiving chlorthalidone, which promotes potassium excretion. However, risk of hyperkalemia increases with declining renal function.

PATHWAY-2 provided 2 additional findings that are clinically important. First, it clearly demonstrated an additional BP-lowering effect of titrating spironolactone dosage ≤50 mg. Prior studies assessing the benefit of spironolactone for treating RHTN were generally limited to the 25-mg dose. In PATHWAY-2, spironolactone was titrated to 50 mg and at week 12 produced greater BP reductions than the other treatments after titration to higher doses (−3.86 [CI, −5.28 to −2.45] versus −0.88 mm Hg [CI, −2.32 to 0.56] for doxazosin, −1.49 mm Hg [CI, −2.94 to −0.04] for bisoprolol, and −0.68 mm Hg [CI, −2.10 to 0.75] for placebo; $P<0.0001$). The other important finding was the enhanced benefit of spironolactone in patients with suppressed renin levels. Although spironolactone reduced BP in patients at all renin levels, there was a strong inverse relation between baseline renin levels and the magnitude of BP reduction, with patients with the lowest renin levels exceeding on average 20 mm Hg reduction in home systolic BP. This level of BP reduction is extraordinary, especially in patients already treated with 3 other classes of agents, and in being predicted by a routine biochemical assessment.

Pathogenesis of RHTN: Role of Aldosterone-Induced Fluid Retention

PATHWAY-2 included several substudies designed to prospectively explore the pathogenesis of RHTN.[52] The first substudy showed that the baseline aldosterone-renin ratio and baseline renin level strongly predicted the BP response to spironolactone, whereas the baseline aldosterone level only weakly predicted the BP response (Figure 3). In contrast, the BP responses to the β-blocker and the α-blocker were unrelated to the baseline aldosterone-renin ratio. The second substudy demonstrated that the antihypertensive effect of spironolactone was associated with a significant reduction in thoracic fluid content—an index of fluid retention. In contrast, β-blockade had no significant effect on thoracic fluid content, whereas β-blockade increased it. The 3 add-on agents were associated with similar small reductions in vascular resistance.

Given that the aldosterone-renin ratio is strong index of volume status, with suppressed renin and a corresponding high aldosterone-renin ratio indicating excess volume retention, the PATHWAY-2 substudy findings indicate that RHTN is attributable in large part to excess fluid retention mediated by aldosterone excess. The benefit of spironolactone in patients with RHTN is thus related to reversal of aldosterone-induced fluid retention. These results are consistent with prior findings of increased intravascular fluid retention evidenced by high natriuretic peptide levels and increased intracardiac volumes measured by magnetic resonance imaging in patients

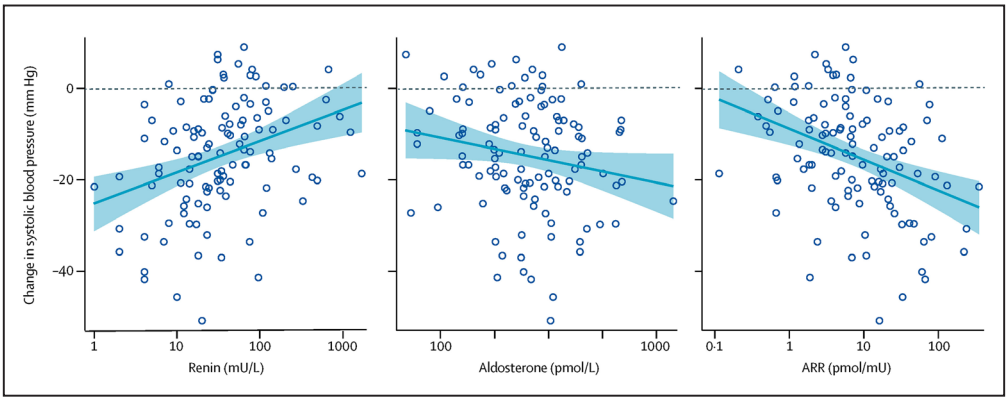

Figure 3. Relation between baseline plasma renin, aldosterone, and the serum aldosterone and renin concentration (ARR) ratio and the home systolic blood pressure response to spironolactone in the PATHWAY-2 study (Prevention and Treatment of Hypertension With Algorithm Based Therapy). Adapted from Williams et al.[52] Copyright ©2018, The Authors. Published by Elsevier Ltd (https://creativecommons.org/licenses/by/4.0/).

with RHTN.[53] In addition, a study of salt sensitivity in patients with RHTN has demonstrated that the excess fluid retention characteristic of these patients can be overcome by dietary sodium restriction.[54] The prior study results, combined with the PATHWAY-2 findings, strongly implicate inappropriate fluid retention secondary to high dietary sodium intake and aldosterone excess as an important mediator of antihypertensive treatment resistance that is best overcome by the natriuretic and diuretic effects of spironolactone in patients with RHTN.

The third substudy of PATHWAY-2 assessed the antihypertensive effect of amiloride as an alternative to spironolactone.[52] This was an open-label assessment performed after completion of the double-blind, randomized main study protocol, in which participants who were willing to continue in the study were crossed-over from spironolactone to amiloride for 6 to 12 weeks. In these 146 subjects, amiloride 10 to 20 mg daily reduced home systolic BP by 20.4 mm Hg—an effect comparable with the 18.3-mm Hg reduction induced by spironolactone, suggesting that amiloride can be as effective as spironolactone as a fourth medication in treating RHTN. The amiloride substudy lacked the scientific rigor of the main protocol because of its open-label design and the lower number of participants. Nevertheless, it does provide compelling support for preferential use of amiloride as an alternative to spironolactone, if the latter is not tolerated, in patients with RHTN.

Overall, PATHWAY-2 and its substudies provide clinically important guidance on how to treat RHTN. The study clearly establishes spironolactone as the most appropriate fourth medication for treating RHTN uncontrolled on a standardized triple combination of an ACE inhibitor or ARB, amlodipine, and a long-acting thiazide-like diuretic (chlorthalidone or indapamide). Additional findings demonstrate an effective dose range for spironolactone ≤50 mg daily and support use of amiloride as an effective alternative if spironolactone is not tolerated. From a mechanistic standpoint, the findings are important in providing compelling evidence that treatment resistance to the most commonly used classes of antihypertensive agents is broadly attributable to inappropriate volume retention secondary to aldosterone excess, even at low levels. This effect is clearly reflected in the large BP reduction induced by MR blockade and predicted by suppressed renin levels. This mechanistic insight highlights the need to overcome underlying fluid retention in patients with RHTN through a treatment strategy based on effective dietary sodium restriction and combined use of thiazide-like diuretics and MR antagonists. Eplerenone, which is more selective for the MR, has also been shown in small studies to be effective in treating patients with RHTN[49] and may be considered when adverse effects, such as gynecomastia or vaginal bleeding, are noted with spironolactone therapy.

Nonpharmacological Therapies

A large body of literature demonstrates consistent benefit of dietary sodium restriction on BP reduction in patients with hypertension.[55] This benefit may be greater in patients with RHTN, given the broad role that aldosterone-induced sodium and fluid retention play in contributing to development of RHTN. Such large benefit was suggested in a small study that compared extreme dietary sodium restriction (50 mEq/d) for 7 days to high dietary sodium intake (250 mEq/d) in crossover evaluation of 12 patients with confirmed RHTN.[54] The low compared with the high sodium intake induced a substantial reduction in BP, reducing 24-hour ambulatory BP monitoring by 20.1/9.8 mm Hg. While the study was limited by the small number of subjects, the findings suggest that some patients with RHTN may be especially salt-sensitive and may have large BP benefit with intensive sodium restriction, consistent with the well-recognized role that aldosterone plays in the pathogenesis of RHTN.

Lifestyle changes known to provide antihypertensive effects in the general hypertensive population, such as weight loss and regular exercise, have not been adequately evaluated in patients with RHTN. Such interventions clearly provide overall cardiovascular and metabolic benefits, and likely will provide BP reductions in RHTN patients similar to or greater than those seen in the general hypertensive population, and so should be recommended.

Obstructive sleep apnea (OSA) is especially common in patients with RHTN, with observational studies suggesting prevalence rates as high as 90%, especially in men.[56,57] Studies link this high prevalence of OSA to the aldosterone excess that is common in patients with RHTN.[58–60] Antihypertensive treatment resistance and OSA are hypothesized to share a common mechanism, in that aldosterone promotes intravascular fluid retention, thus increasing BP and accumulation of fluid in the parapharyngeal region, promoting increases in upper airway resistance and thereby worsening OSA severity.[60] Such an mechanistic effect is supported by studies demonstrating that spironolactone reduces the severity of OSA by about 50% in patients with RHTN.[60–62]

Use of continuous positive airway pressure (CPAP) to treat OSA tends to induce relatively modest decreases in BP in patients with RHTN, as well as in the general population of patients with hypertension. In a rigorous comparison of CPAP use to no treatment in 194 subjects with RHTN, CPAP reduced 24-hour diastolic BP by 3.2 mm Hg and had no significant effect on 24-hour systolic BP overall.[63] However, CPAP use was <4 hours per night in 28% of the participants. Among those who used CPAP >4 hours per night, CPAP significantly reduced 24-hour systolic and diastolic BP by 4.4 and 4.1 mm Hg, respectively. The benefit was especially prominent at night, with 7.7 and 4.1 mm Hg reductions in systolic and diastolic BP, respectively. Importantly, there was a significant positive correlation between CPAP use and BP reduction: patients fully adherent with CPAP (>8 hours/night) manifested a reduction in 24-hour systolic BP >10 mm Hg. Overall, studies indicate that OSA is common in patients with RHTN, and so these patients should be screened intensively for OSA and, when present, should be treated with CPAP. The BP benefit of CPAP in patients with RHTN and OSA rivals that of adding another BP medication in fully adherent patients.

Refractory Hypertension

Refractory hypertension (RfHTN) is a proposed phenotype of antihypertensive treatment failure in which BP remains uncontrolled on maximal or near-maximal therapy.[64–66] The current definition of RfHTN is based on failure to control BP with use of ≥5 antihypertensive agents of different classes, including a long-acting thiazide-like diuretic, such as chlorthalidone

and spironolactone. Observational studies of patients with uncontrolled RHTN who were referred to our hypertension clinic and who were managed by 2 hypertension specialists, with continued titration and optimization of antihypertensive therapy, suggest that RfHTN is rare, affecting <5% of patients.[64] Patients with RfHTN, identified after routine clinical follow-up of ≥3 visits for ≥6 months, had uncontrolled BP in spite of being adherent to a regimen of >5 classes of antihypertensive agents, including chlorthalidone 25 mg daily and MR antagonists (spironolactone, 25 mg daily, or eplerenone, 50 mg BID) without evidence of underlying secondary causes of hypertension.[64] Risk factors for RfHTN, including black race, obesity, diabetes mellitus, and CKD overlap with those for RHTN. However, patients with RfHTN tend to be younger and more often women than those with RHTN. Not surprisingly, given their long history of poorly controlled, often severe hypertension, patients with RfHTN frequently manifest target organ damage, including left ventricular hypertrophy and heart failure with preserved left ventricular ejection fraction.[65–67]

The patients with RfHTN in our study underwent transthoracic impedance cardiography to measure thoracic fluid content and systemic vascular resistance, as well as assessment of pulse wave velocity—a measure of arterial stiffness. Indirect evidence suggests that antihypertensive treatment failure in RfHTN, as opposed to the much larger category of patients with RHTN, may not be secondary to persistent excess fluid retention, but instead is likely neurogenic in pathogenesis, and attributable to heightened sympathetic outflow. This potentially important mechanistic distinction is based on persistently higher heart rates, greater vascular stiffness as indexed by pulse wave velocity, and greater 24-hour excretion of urinary norepinephrine typical of patients with RfHTN compared with patients with controlled RHTN.[68] In contrast, indices of volume status, including renin activity, aldosterone levels, urinary sodium excretion, natriuretic peptide levels, and intracardiac volumes, are similar or lower in patients with RfHTN compared with patients with controlled RHTN, suggesting that persistent fluid retention does not contribute to their antihypertensive treatment failure.[65,68] These findings suggest that with use of effective doses of chlorthalidone and spironolactone, any underlying fluid retention is largely overcome, and the continued failure to control BP in patients with RfHTN is attributable to other causes, particularly excess sympathetic outflow.

Effective treatment for RfHTN, by definition, remains unavailable. By having RfHTN, these patients have failed all or nearly all available classes of antihypertensive agents. Apparent normalization of volume status with use of chlorthalidone and spironolactone fails to control BP in patients with RfHTN, suggesting that further intensification of diuretic therapy is unlikely to be effective. Based on the evidence implicating heightened sympathetic tone as an important mediator of the treatment failure, sympatholytic agents should be beneficial, but use of effective doses of currently available agents that inhibit sympathetic output, such as clonidine, is often precluded by intolerable adverse effects. Accordingly, effective management of RfHTN may be dependent on development of more effective and better tolerated sympatholytic compounds, or perhaps use of evolving, but still unproven device-based strategies, such as renal denervation or carotid sinus activation.

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