Update on Diagnosis and Treatment of Resistant Hypertension

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Resistant hypertension is an increasingly common medical problem, and patients with this condition are at a high risk of cardiovascular events. The prevalence of resistant hypertension is unknown, but data from clinical trials suggest that 20% to 30% of hypertensive individuals may be resistant to antihypertensive treatment. The evaluation of these patients is focused on identifying true resistant hypertension and contributing and secondary causes of hypertension, including hyperaldosteronism, obstructive sleep apnea, chronic kidney disease, renal artery stenosis, and pheochromocytoma. Treatment includes removal of contributing factors, appropriate management of secondary causes, and use of effective multidrug regimens. More established approaches, such as low dietary salt and mineralocorticoid receptor blockers, and new technologies, such as carotid stimulation and renal denervation, have been used in the management of patients with resistant hypertension.

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INTRODUCTION

Resistant hypertension is defined as a blood pressure (BP) that remains above goal in spite of use of 3 antihypertensive medications prescribed at optimal dose amounts. According to the Scientific Statement for Diagnosis and Treatment of Resistant Hypertension published by the American Heart Association in 2009, one of the three agents should ideally be a diuretic.[1] Hypertensive patients whose BP is controlled on 4 or more antihypertensive medications and patients who have uncontrolled BP on regimens of 3 drugs from other classes and who do not tolerate diuretics are also considered to have resistant hypertension.

The prevalence of resistant hypertension is unknown, but data from clinical trials suggest that 20% to 30% of hypertensive individuals may be resistant to antihypertensive treatment.[2,3] For example, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 34% of participants remained with uncontrolled BP despite an average of 2 antihypertensive medications after approximately 5 years of follow-up.[2] At the end of the ALLHAT, 27% of participants were controlled on 3 or more medications, and overall, 49% of participants were controlled on 1 or 2 medications. This means that approximately 50% of participants needed 3 or more BP medications. However, the real prevalence of resistant hypertension may be underestimated in the ALLHAT, because patients with a history of difficult-to-treat hypertension (defined as 2 or more medications to achieve a BP lower than 160/100 mm Hg) were excluded from the study.

Factors that predispose to antihypertensive treatment resistance include population characteristics, such as increased life expectancy, higher obesity rates, and decreased physical activity, as well as provider characteristics, including inadequate attention to systolic BP elevations and the more aggressive BP goals recommended by guidelines. Furthermore, contributing factors (Table 1) and secondary causes of hypertension are more likely to present in patients with resistant hypertension (Table 2). All patients confirmed to have resistant hypertension should be therefore investigated for these secondary causes and, when possible, referred to an appropriate specialist.[1]

Table 1. Contributing Factors and Secondary Causes of Resistant Hypertension

Contributing Factors
Volume expansion
Excess sodium intake
Volume retention secondary to chronic kidney disease
Inadequate diuretic therapy
Obesity
Exogenous substances
Nonsteroidal anti-inflammatory agents
Oral contraceptives
Alcohol
Corticosteroids
Anabolic steroids
Sympathomimetic agents (nasal decongestants, diet pills, and cocaine)
Caffeine
Cyclosporine
Erythropoietin
Chemotherapeutic agents
Antidepressants

Table 2. Secondary Causes of Hypertension

Secondary Causes
Primary aldosteronism
Obstructive sleep apnea
Chronic kidney disease
Renal artery stenosis
Pheochromocytoma
Central nervous system tumors
Coarctation of the aorta
Thyroid diseases

The impact of treatment of resistant hypertension on cardiovascular morbidity and mortality has not been specifically addressed. Furthermore, there are few high-quality data comparing cardiovascular risk in patients with resistant hypertension with those in whom hypertension is more easily controlled. However, because cardiovascular risk increases linearly and progressively with BP levels and that lowering of BP reduce cardiovascular and renal morbidity and mortality,[4] it is reasonable to conclude that patients with resistant hypertension are likely to have a higher risk and benefit from antihypertensive treatment.

In the present article we discuss the assessment and treatment approaches that have been specifically tested in patients with confirmed resistant hypertension.

PSEUDORESISTANCE

Pseudoresistance is defined as factitious lack of BP control caused by inaccurate measurement of BP, inappropriate drug choices or doses, nonadherence to prescribed therapy, or the "white-coat" effect. Pseudoresistance should be ruled out in patients with uncontrolled BP. Identification of pseudoresistance avoids overtreatment and excessive and expensive evaluation.[5]

White-coat effect and poor adherence to prescribed medications are common causes of uncontrolled hypertension. White-coat effect is the difference between office BP and ambulatory or home BP measurements and can be calculated as the mean office BP minus mean daytime ambulatory BP. Ambulatory and home BP monitoring are important methods to evaluate patients with uncontrolled BP and to assess true treatment resistance in clinical practice. Poor adherence to prescribed medications is a common cause of uncontrolled hypertension. High cost of treatment, poor relations between doctor and patient, complex medical regimens, and adverse effects of medical therapy are additional causes of poor adherence (Figure 1).[6]

Clinical inertia, defined as the provider's failure to increase therapy when the treatment goal is not reached, is a major contributor to suboptimal medical treatment and results in uncontrolled hypertension.[7] Common causes of clinical inertia include lack of knowledge of treatment guidelines, underestimation of cardiovascular risk, and the use of spurious reasons to avoid intensification

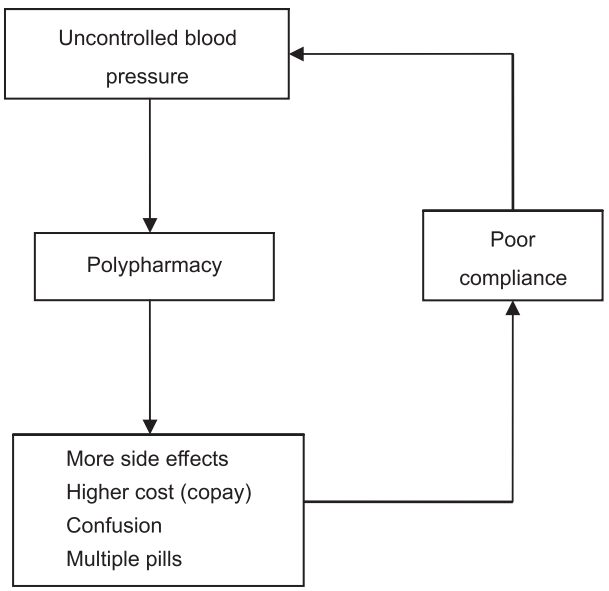

Figure 1. Consequences of poor adherence.

of therapy, eg, physician perception (without patient input) that the patient will not accept more medications.

SECONDARY HYPERTENSION

The prevalence of secondary hypertension is higher in patients with resistant hypertension than in the general hypertensive population. The most common secondary causes of resistant hypertension are primary aldosteronism (PA), chronic kidney disease, renal artery stenosis, and obstructive sleep apnea (OSA). The prevalence of secondary hypertension increases with age, mainly due to increases in the risk of developing chronic kidney disease, OSA, and renal artery stenosis.

Primary Aldosteronism

Primary aldosteronism is the most common cause of secondary hypertension and is a frequent contributor to treatment resistance. The prevalence of PA is greater than previously thought, partially because hypokalemia and adrenal tumors are no longer necessary criteria for the diagnosis of PA. In fact, a substantial proportion of patients with PA have normal potassium.[8] Multiple studies have confirmed a prevalence of PA of approximately 10% among general hypertensive patients, and the prevalence is positively correlated with the severity of BP.[9] Among untreated patients, the prevalence of PA increases with increasing severity of the hypertension, from 2% in patients with stage 1 hypertension to 8% in those with stage 2 hypertension and 13% in those with stage 3 hypertension.[10]

The prevalence of PA is even higher in patients with resistant hypertension, approaching 17% to 22% in multiple studies (Figure 2).[11-14] For example, in a prospective study 18 of 88 patients (20%) with resistant hypertension referred to the University of Alabama at Birmingham were diagnosed with PA based on a suppressed plasma renin activity (< 1.0 ng/mL/h) and a high 24-hour urinary aldosterone excretion (> 12 µg/24 h) during high dietary sodium intake (> 200 mEq/24 h).[11] The prevalence of PA was similar in African-American and white patients. Because of its high prevalence in this patient group, all patients with resistant hypertension, even those with normal potassium levels, should be evaluated for PA.

We have shown that patients with resistant hypertension are characterized by higher aldosterone

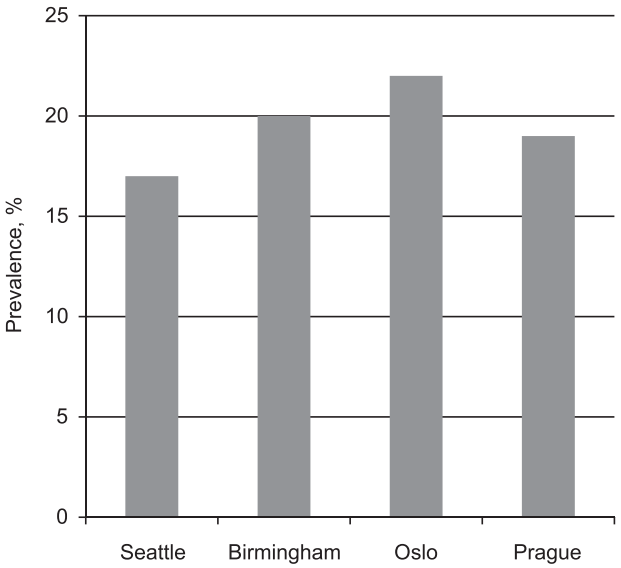

Figure 2. Prevalence of primary aldosteronism among patients with resistant hypertension in multiples studies of Birmingham,[11] Seattle,[12] Oslo,[13] and Prague.[14]

levels. In a cross-sectional analysis, 279 consecutive patients with resistant hypertension were compared to 53 controls (with normotension or hypertension controlled on 2 antihypertensive medications and less).[15] Plasma aldosterone, aldosterone-renin ratio, and 24-hour urinary aldosterone were significantly higher in patients with resistant hypertension than in controls. Patients with resistant hypertension had lower levels of plasma renin activity and higher levels of brain and atrial natriuretic peptides compared to controls, providing the evidence that intravascular fluid retention plays an important role in hypertension resistant to treatment. It is of note that 85% of patients with resistant hypertension were on recommended doses of thiazide diuretics.

Aldosterone-renin ratio is considered the most reliable test for screening of PA, but false-positive and false-negative results may occur depending on posture, time of the day, salt intake, plasma potassium, and concurrent medications.[16] Medications such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) can mask the diagnosis of PA by causing false-negatively low aldosterone-renin ratios. However, although interfering medications should be ideally stopped before screening for PA, the risk of stopping medications in patients with resistant hypertension needs to be carefully assessed in order to avoid loss of hypertension control. If

aldosterone-renin ratio is positive, PA has to be confirmed by fludrocortisone suppression test, oral sodium loading, and saline infusion testing or captopril challenge test.[17] After confirmation of PA, lateralization of the source of the excessive aldosterone secretion demonstrated by adrenal vein sampling is critical to guide the management of PA. Unilateral adrenalectomy usually has a major beneficial effect in patients with confirmed PA and lateralization of aldosterone overproduction to one adrenal on adrenal venous sampling, not only on hypertension control, but also on quality of life, reduction in risk of cardiovascular and renal target organ damage and risk of events.[17-20]

Obstructive Sleep Apnea

Obstructive sleep apnea, which is defined as preserved and increased respiratory effort despite partial or complete occlusion of the upper airway, is a strong and independent risk factor for the presence and future development of hypertension and cardiovascular diseases.[21-25] Cross-sectional studies indicate that the severity of OSA is related to BP and that hypertension occurring in individuals with OSA is more likely to be severe and resistant to treatment.[21,25,26] In 42 patients with resistant hypertension referred to a university center, Logan and colleagues found that 83% of participants had unsuspected OSA (apnea-hypopnea index [AHI] $\geq$ 10/h).[27] The prevalence and severity were significantly higher in men than in women with resistant hypertension. Furthermore, studies have shown that OSA and hyperaldosteronism, both highly prevalent in patients with resistant hypertension, are related and may interact on a pathophysiologic basis.[28-30]

Chronic Kidney Disease

Chronic kidney disease is not only a common cause of resistant hypertension, but also a consequence of poor BP control over time. Fluid retention, excessive activation of the renin-angiotensin-aldosterone system (RAAS) and concomitant medicines are related to treatment resistance in patients with impaired kidney function.[31]

Albuminuria and glomerular filtration rate should be assessed in all patients with resistant hypertension. Because increases in the serum creatinine occurs in a late stage of kidney disease, glomerular filtration rate should be estimated by the use of the Modification of Diet in Renal Disease (MDRD) Study or Cockcroft-Gault equation.[32] Dietary salt reduction plays an important role in order to reduce volume expansion in patients with chronic kidney disease. Loop diuretics effectively reduce volume and facilitate BP control in patients with a creatinine clearance lower than 30 mL/min. Blockade of the RAAS in patients with impaired kidney function reduces cardiovacular risk, improves BP control, and reduces proteinuria and progression to end-stage renal disease.[33] Angiotensin-converting enzyme inhibitors and ARBs are indicated in patients with mild to severe chronic kidney disease, particularly in the presence of microalbominuria or macroalbuminuria. Reductions in the glomerular filtration rate can occur after starting ACE inhibitors or ARBs. These changes are usually limited and transitory and are not an indication for cessation of therapy.

Renal Artery Stenosis

Renovascular disease is commonly found among patients with resistant hypertension and multiple risk factors.[34,35] Stenotic lesions are largely secondary to atherosclerosis (90%), and their prevalence increases with age.[36] Renal artery stenosis is more common in patients with extrarenal atherosclerotic disease.[36] Fibromuscular dysplasia is present in approximately 10% of cases of renal artery stenosis and are more frequent in young women. Fibromuscular dysplasia is successfully treated with balloon angioplasty.[37]

Patients with resistant hypertension and known atherosclerotic disease, declining kidney function, or a history of flash pulmonary edema have an increased likelihood of atherosclerotic renal arterial disease. These patients have to be evaluated with renal artery Doppler ultrasonography, renal nuclear medicine scan, computed tomography scan, or magnetic resonance angiography of the renal arteries. The choice of treatment for atherosclerotic renal lesions is controversial due to a lack of strong evidence in favor of either medical treatment or revascularization for BP control and preservation of kidney function.[38,39] The renal venous-renin ratio study is the only diagnostic procedure able to determine renin production of each kidney separately and can be of considerable assistance in treatment decision making. It predicts improvement of hypertension after nephrectomy

in patients suspected of having unilateral renal renin hypersecretion associated with ipsilateral marked or complete loss of kidney function.[40-42]

Pheochromocytoma

Although the prevalence of pheochromocytoma in general hypertensive population is low (0.1% to 0.6%),[43,44] the diagnosis and treatment are extremely important due to difficult-to-control hypertension, the possibility of precipitating hypertensive crisis if the tumor is stimulated, and the possibility that the tumor could be malignant.[45] The clinical presentation of pheochromocytoma is widely variable, but the triad of headache, palpitations, and sweating are the most common findings.[46] All patients with resistant hypertension and symptoms typical of pheochromocytoma should be screened. Plasma free metanephrines are the best screening test for pheochromocytoma, with high sensitivity (99%) and specificity (89%).[47] Surgical removal of the tumor is the appropriate treatment.

TREATMENT

Salt Reduction

Sodium causes target organ-damage not only through hemodynamic mechanisms, ie, BP, but also through nonhemodynamic mechanisms. Dietary salt intake induces a complex series of events in the endothelium that appear to be independent of BP and the RAAS.[48]

Observational studies and clinical trials performed in general and hypertensive populations indicate that a high dietary salt intake is associated with higher BP. For example, in the INTERSALT study, a multinational evaluation that included more than 10 000 normotensive and hypertensive participants from 52 populations, differences in dietary sodium ingestion of 100 mmol per day were associated with differences in systolic BP of approximately 2.2 mm Hg after adjustment for age, sex, potassium excretion, body mass index, and alcohol intake.[49] The positive relation between salt ingestion and level of BP appeared to be stronger in patients with hypertension. Meta-analyses have suggested that low-salt intervention in hypertensive patients decreases systolic and diastolic BP by 3.7 mm Hg to 7.0 mm Hg and 0.9 mm Hg to 2.5 mm Hg, respectively.[50-52]

Although the effects of reducing dietary sodium intake on BP levels have been evaluated in the general hypertensive population, few studies have examined the role of dietary salt in patients with resistant hypertension per se. In one study, 16 patients with "refractory" hypertension, defined as uncontrolled BP on maximum doses of at least 1 diuretic and 1 sympatholytic agent, were treated with extreme dietary salt restriction (10 mmol of sodium per day) in combination with intense diuretic therapy (either hydrochlorothiazide 100 mg or furosemide 80 mg to 200 mg daily) after ceasing other antihypertensive therapy.[53] Systolic and diastolic BP decreased on average by 21 mm Hg and 7 mm Hg, respectively. However, this study had limited practical implications, because the definition of refractory hypertension differs from the current definition and such extreme sodium restriction (< 1.0 g of salt) would be almost impossible in the real life without home delivery of specially prepared meals. Furthermore, the study did not assess the effects of low-salt diet in combination with other antihypertensive therapies.

More recently, we published the results of a 4-week randomized cross-over study which included 12 patients with resistant hypertension.[54] Participants were on an average of 3.4 ± 0.5 medications, and all the patients were on a thiazide diuretic (hydrochlorothiazide, 25 mg/d) and an ACE inhibitor or an ARB. Participants were randomized to low- or high-salt diet for 1 week and crossed over to the opposite diet for 1 week after 2 weeks of wash out. Patients remained on the same antihypertensive treatment throughout the study. The low-salt meals were designed by nutritionists on individual basis in order to provide 50 mmol of sodium per day (2.8 g of salt). During the high-salt diet, patients received more than 250 mmol/d of sodium (14.3 g of salt). Adherence to diet was confirmed by measurement of 24-hour urinary sodium excretion. The mean office systolic and diastolic BP reduced by 22.7/9.1 mm Hg during low- compared to high-salt diets. Low-salt diet decreased daytime, nighttime, and 24-hour systolic and diastolic BP to a similar degree to office BP, when compared to high-salt ingestion. The effect of low-salt diet on ambulatory BP was persistent throughout the 24-hour period (Figure 3). The BP reduction achieved during the low-salt ingestion was estimated as being equivalent to adding 2 antihypertensive medications.[55] Considering BP reductions that have been observed in our

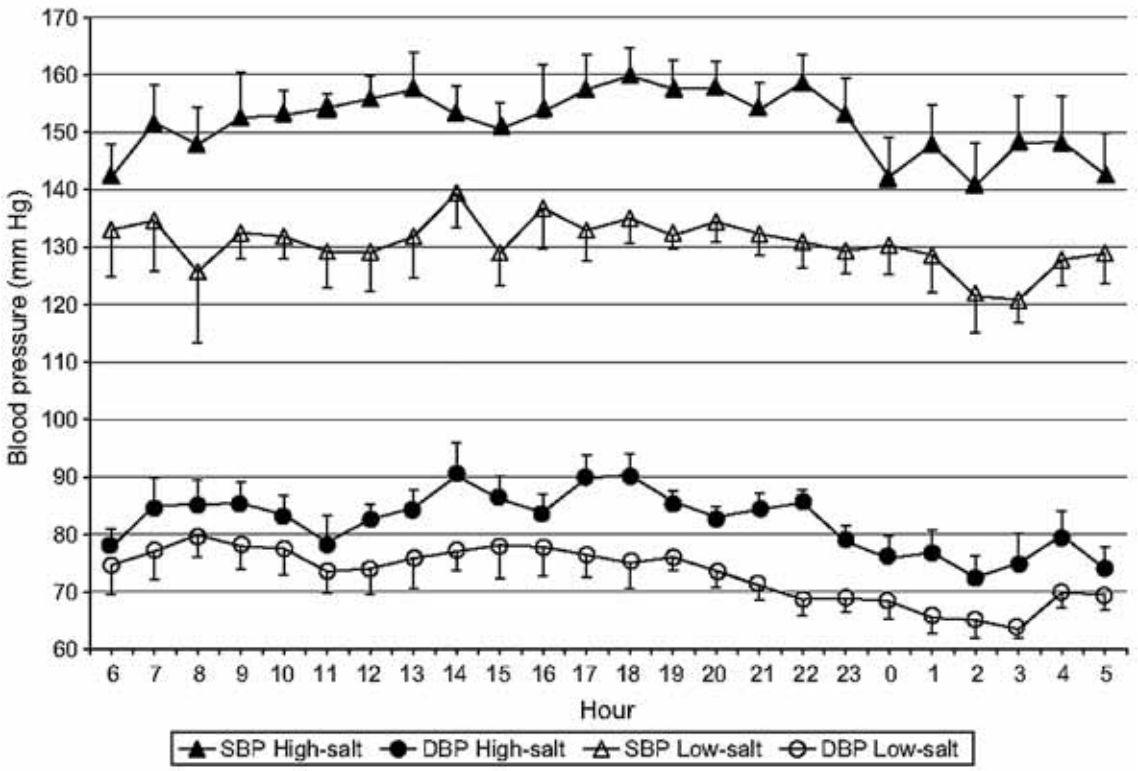

Figure 3. Comparison of 24-hour ambulatory blood pressure values during low- and high-salt diet. Data are presented as mean ± standard error. Adapted from a study published in 2009 by Pimenta and colleagues.[54]

study compared to clinical trials with unselected and untreated hypertensive subjects, our study suggested that patients with resistant hypertension are particularly salt sensitive.[55]

In our study, plasma renin activity increased and brain natriuretic peptide, body weight, and creatinine clearance decreased significantly with low-salt compared to high-salt diet, suggesting intravascular fluid retention with high-salt diet. It is of note that intravascular fluid retention was observed in spite of the use of conventional diuretic therapy (hydrochlorothiazide, 25 mg/d).

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP), which is used for treatment of OSA, has minimal BP effect.[56-58] However, CPAP treatment seems to have greater antihypertensive effect in patients with more severe hypertension. For example, in a retrospective study, effects of CPAP therapy on BP were assessed in patients with OSA (AHI > 5 events per hour) and hypertension.[59] After 1 year of follow-up, treatment with CPAP significantly reduced mean arterial pressure in patients with resistant hypertension, but not in patients with controlled hypertension. In a different study, 64 patients with resistant hypertension and OSA (AHI > 15 events per hour) were randomized to treatment with CPAP added to conventional medical treatment or conventional treatment alone for 3 months.[60] Reduction in 24-hour diastolic BP was significantly greater in patients with confirmed resistant hypertension (office BP > 140/90 mm Hg and 24-hour BP > 125/80 mm Hg) treated with CPAP compared to those treated with conventional treatment (-4.9 ± 6.4 versus 0.1 ± 7.3 mm Hg, P = .03). Reductions in daytime diastolic, 24-hour diastolic and systolic BP were also significantly greater among patients who used CPAP more than 5.8 hours per night. These results suggest that OSA should be investigated in patients with resistant hypertension, and CPAP therapy is recommended for those with OSA. However, more studies are necessary to confirm the CPAP effects on BP reduction.

Aldosterone Receptor Blockers

The addition of low doses of mineralocorticoid

receptor blockers to the current treatment effectively reduces BP in patients with resistant hypertension (Figure 4).[61-67] In a prospective study, patients with resistant hypertension received spironolactone (12.5 mg/d to 25 mg/d) in addition to their current treatment which included an ACE inhibitor or ARB and a diuretic.[63] Systolic and diastolic BP reduced by 25 mm Hg and 12 mm Hg, respectively, after 6 months of treatment. There was a similar BP reduction in patients with compared to those without PA. Furthermore, BP reduction was not predicted by baseline plasma aldosterone or renin levels or by 24-hour urinary aldosterone, and BP reduction was similar in African-American and white participants. In the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT), 1411 participants who finished the study and BP had uncontrolled on 3 antihypertensive agents received spironolactone (mean dose, 25 mg) as a fourth drug.[64] Systolic and diastolic BP reduced by 21.9 mm Hg and 9.5 mm Hg, respectively, after an average of 1.3 years, independently of age, sex, smoking, and diabetes status.

The above results raised the question whether the dual blockade of the RAAS with spironolactone in combination with an ACE or ARB is more effective than dual blockade with an ACE inhibitor and an ARB. In a prospective open-label crossover study, 42 patients with true resistant hypertension (determined by ambulatory BP monitoring) received an ACE inhibitor for 12 weeks in addition to their treatment, if they were already being treated with an ARB, or an ARB, if they were being treated with an ACE inhibitor.[68] After 4 weeks of washout without the added RAAS blocker, patients received spironolactone, 25 mg, for 12 weeks in addition to their current treatment. Spironolactone was increased to 50 mg after 4 weeks if necessary. The combination of an ACE inhibitor with an ARB reduced office BP by 12.9/2.2 mm Hg and 24-hour BP by 7.1/3.4 mm Hg. In contrast, the addition of spironolactone reduced office and 24-hour BP by 32.2/10.9 mm Hg and 20.8/8.8 mm Hg, respectively. The study not only showed the small BP effect of combining ACE inhibitor and ARB, but also confirmed that spironolactone should be considered in all patients with uncontrolled hypertension on three or more antihypertensive agents.[69]

Spironolactone, in addition to the lowering BP effect, seems to reduce the severity of OSA in patients with resistant hypertension. In a prospective open-label study, 12 patients with resistant hypertension and OSA, defined as AHI of 15 events per hour or higher, had spironolactone added to their current antihypertensive treatment for 8 weeks when polysomnography was repeated.[70] Apnea-hypopnea index, hypoxic index, weight, and clinical and ambulatory BP significantly reduced, and plasma renin activity significantly increased after treatment. These results support the concept that aldosterone-mediated chronic fluid retention may influence severity of OSA.

Eplerenone, a more selective mineralocorticoid receptor blocker, also effectively reduces BP in patients with resistant hypertension. In an open-

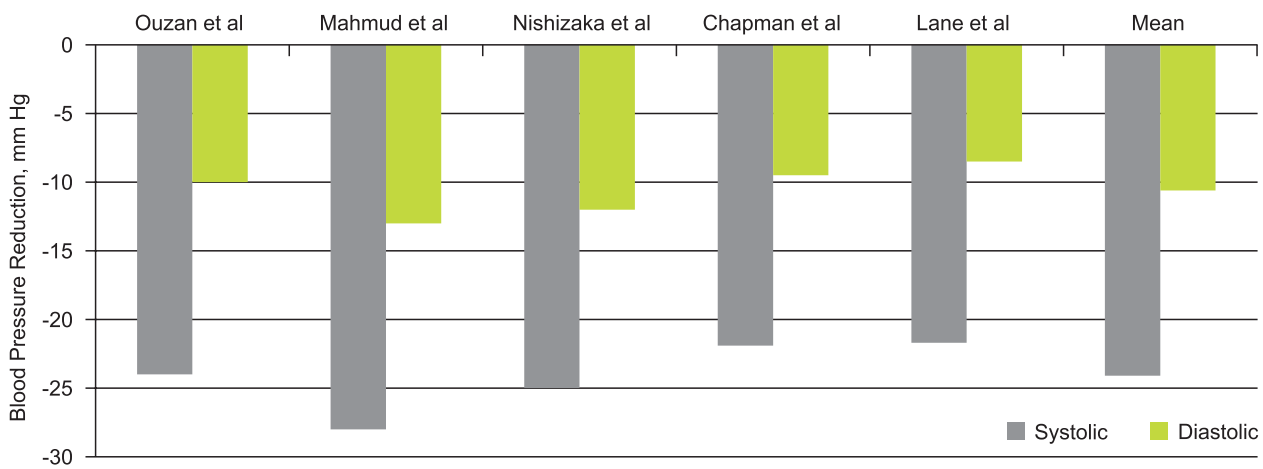

Figure 4. Spironolactone-induced blood pressure reductions observed in studies of patients with resistant hypertension.[61-64,66] Adapted from a review published in 2007 by Pimenta and colleagues.[65]

label non-placebo-controlled study, 52 patients with resistant hypertension received 50 mg to 100 mg of eplerenone daily for 12 weeks.[71] Eplerenone reduced clinic and 24-hour BP by 17.6/7.9 mm Hg and 12.2/6.0 mm Hg, respectively. Similar to the studies with spironolactone, BP reductions were weakly related to baseline serum aldosterone and unrelated to plasma renin activity, age, gender, or race.

Spironolactone at the studied doses (12.5 mg to 50 mg) is usually well tolerated even in combination with ACE inhibitors or ARBs. Serum potassium and creatinine levels should be monitored in patients treated with mineralocorticoid receptor antagonists. Potassium supplementation or salt substitutes that contain potassium should be discontinued or reduced in patients who are started on these agents. Spironolactone-associated hyperkalemia is uncommon in patients with normal kidney function, but risk of hyperkalemia is increased in older patients, in patients receiving ACE inhibitors or ARBs and/or non-steroidal anti-inflammatory drugs, and in patients with chronic kidney disease or diabetes mellitus. In these higher-risk patients, spironolactone can be started at 12.5 mg daily.

Breast tenderness with or without gynecomastia, occurs in less than 10% of men who take spironolactone, 25 mg daily, and its occurrence increases sharply with higher doses.[63,64] The more selective mineralocorticoid receptor antagonist eplerenone has lower affinity for progesterone and androgen receptors and is better tolerated than spironolactone.[72]

Amiloride, which antagonizes aldosterone action by blocking the epithelial sodium channel, has been demonstrated to effectively reduce BP in patients with aldosterone-related hypertension. However, there is less experience using it to specifically treat resistant hypertension.[13,73] Like direct mineralocorticoid receptor antagonists, there is a risk of hyperkalemia.

FUTURE PERSPECTIVES

Endothelin Receptor Blockers

Endothelin, which has been recognized as a potent vasoconstrictor factor, modulates cardiovascular function, and stimulation of endothelin receptors in the vascular system produces marked sustained hypertension.[74] Furthermore, endothelin administration results in renal vasoconstriction associated to a decrease in sodium excretion.[75] The endothelin receptor type A is widely expressed and is the main receptor of the endothelin system in the vascular smooth muscle.[76] Because plasma endothelin levels have been related to severity of hypertension, endothelin antagonists have been tested in patients with resistant hypertension.

A randomized double-blinded placebo-controlled trial (DORADO) tested darusentan, a selective endothelin type A receptor antagonist, in 379 patients with resistant hypertension who were receiving at least 3 antihypertensive medications including a diuretic.[77] Participants received placebo or darusentan, 50 mg, 100 mg, or 300 mg, for 14 weeks. Clinic systolic and diastolic BP were reduced by 9 ± 14 mm Hg and 5 ± 8 mm Hg, 17 ± 15 mm Hg and 10 ± 9 mm Hg, 18 ± 16 mm Hg and 10 ± 9 mm Hg, and 18 ± 18 mm Hg and 11 ± 10 mm Hg with placebo and darusentan at doses of 50 mg, 100 mg, and 300 mg, respectively ($P < .001$ for all the three darusentan doses compared to placebo). There were no significant differences between darusentan dose groups. In a different study, patients with resistant hypertension who had been treated with at least 3 antihypertensive agents, including a diuretic, were randomly assigned to receive darusentan, central α2-agonist guanfacine or placebo for 14 weeks.[78] Office systolic BP reduction with darusentan was significantly greater than that with guanfacine (15 ± 14 mm Hg versus 12 ± 13 mm Hg, $P < .05$), but not greater with placebo (14 ± 14 mm Hg). However, 24-hour systolic BP reduction with darusentan (9 ± 12 mm Hg) was significantly higher than that with guanfacine (4 ± 12 mm Hg) or placebo (2 ± 12 mm Hg). In both studies, adverse effects related to fluid retention occurred in approximately 30% of patients treated with darusentan despite the use of diuretics.[77,78] One study reported modest increases in serum creatinine and decreases in estimated glomerular filtration rate with 100 mg and 300 mg of darusentan.[77]

The endothelin type A receptor antagonist darusentan seems to be effective in the treatment of resistant hypertension, but volume retention and exacerbation of heart failure, in spite of diuretic use, occur in almost one-third of patients. More data on BP, as well as hypertension-related target-organ damage and cardiovascular events, and more safety data are needed before endothelin type A

receptor antagonist can be employed in the routine treatment of patients with resistant hypertension.

Baroreflex Activation

The carotid sinus is an important modulator of autonomic tone and regulates BP. The brain receives signals from the baroreceptors through afferent nerves, which subsequently reduces sympathetic outflow and BP. Clinical and experimental studies have demonstrated that electrical stimulation of carotid artery reduces BP.[79-83] However, electrical carotid sinus nerve stimulation in humans did present some limitations such as reduced long-term effect, unknown amount of stimulation required and size of the device, and orthostatic hypotension. Also, the development of new and effective antihypertensive medications prevented the development of new devices for some time.

A new implantable pulse generator, which is implanted in the chest similarly to a pacemaker, has been tested in patients with resistant hypertension. This device has leads that tunnel subcutaneously and are bilaterally attached to the carotid sinuses. In a nonrandomized prospective feasibility study designed to assess safety and efficacy of the pulse generator, 45 patients with resistant hypertension with baseline mean BP of 179/105 mm Hg on a median of 5 antihypertensive medications, received the device.[84] Only 37, 26, and 17 patients completed the 3-month, 1-year, and 2-year follow-up, respectively. For these time points, office BP was reduced by 21/12 mm Hg, 30/20 mm Hg, and 33/22 mm Hg, respectively. The mean 24-hour ambulatory BP was reduced by 6/4 mm Hg, 13/8 mm Hg, and 24/13 mm Hg for the same periods. One patient died 6 days after operation due to angioneurotic edema before device activation. Other serious adverse events included preoperative stroke, infection, generator dislocation, tongue paresis (likely due to hypoglossal nerve injury), and moderate pulmonary edema. Complications related to surgery are the major limitations to carotid stimulation despite overall good results. Furthermore, BP responses to baroreflex activation are largely variable with some patients not demonstrating any BP reduction at all.

Renal Denervation

The sympathetic nervous system is an important contributory mechanism in both acute and chronic BP pressure elevation. Radical surgical procedures, such as thoracic, abdominal, or pelvic sympathectomy, effectively reduced BP in patients with malignant hypertension. However, these procedures were associated with high rates of short-term and long-term complications.[85-88] Surgical renal denervation effectively reduces BP, which suggests that the sympathetic outflow to the kidneys is activated in patients with essential hypertension and other diseases that present with sympathetic system overactivity, such as congestive heart failure.[89,90]

These findings have stimulated novel treatments such as percutaneous catheter-based radiofrequency ablation of the afferent and efferent renal nerves, which lie in the wall of the renal artery.[91] In a safety and proof-of-principle study, 45 patients with resistant hypertension underwent renal sympathetic denervation through percutaneous radiofrequency ablation. Office BP was reduced by 14/10 mm Hg, 21/10 mm Hg, 22/1 mm Hg, 24/11 mm Hg, and 27/17 mm Hg after 1, 3, 6, 9, and 12 months of follow-up, respectively. Renal noradrenaline spillover was measured in 10 patients and was reduced by a mean of 47%. Periprocedure complications included renal artery dissection related to the catheter placement before delivery of radiofrequency energy in 1 patient and development of pseudo-aneurism of the femoral artery in another patient. Renal angiography was repeated 14 to 18 days after renal sympathetic ablation in 14 patients and showed no evidence of renal artery stenosis. Magnetic resonance imaging performed after 6 months in 14 patients showed a nonobstructive lesion in an untreated location in 1 patient.[91]

In the Simplicity HTN-2 Trial, 106 patients with resistant hypertension (baseline BP of 178/97 mm Hg on 5.2 antihypertensive medications) were randomized to renal denervation or medical treatment.[92] Change to baseline doses of antihypertensive medications were not allowed in any of the groups, unless judged medically necessary due to signs and symptoms related to BP elevation. Clinic BP reduced by 32/12 mm Hg ($P < .001$ both for systolic and diastolic) 6 months after renal denervation and by 1/0 mm Hg in the control group. Ambulatory BP monitoring data was available for 32 patients and showed a 24-hour BP reduction of 11/7 mm Hg.

Renal sympathetic denervation through percutaneous radiofrequency is a potentially major new addition to the range of treatment for patients with poorly controlled hypertension. Furthermore, these studies have provided interesting new information and opened up new avenues of exploration regarding the role of renal sympathetic activity in BP regulation and the development of essential hypertension. Further studies are needed to address the long-term effects of renal denervation and its safety and effectiveness in other disease states such as congestive heart failure.

CONCLUSIONS

Resistant hypertension is an increasingly common medical problem and patients with this condition are at a high risk of cardiovascular events. Because secondary hypertension may be the underlying cause of resistant hypertension, and sometimes a specific and definite treatment is available, a thorough investigation is mandatory in patients with resistant hypertension. However, in the majority of these patients, an underlying cause cannot be found. More established approaches, such as low dietary salt and mineralocorticoid receptor blockers are indicated for these patients. New technologies, such as carotid stimulation and renal denervation, may be used in the near future in the management of patients with resistant hypertension.

CONFLICT OF INTEREST

None declared.

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