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Characterization and Treatment of Resistant Hypertension

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Abstract

Resistant hypertension is a common medical problem and carries a significantly increased risk of end organ damage and cardiovascular events as compared with more easily controlled hypertension. Resistant hypertension is most often related to isolated systolic hypertension and is characterized by aldosterone excess and increased intravascular volume. Its diagnosis requires the exclusion of pseudoresistance. The etiology of resistant hypertension is almost always multifactorial and common reversible contributing factors need to be identified and addressed. Secondary causes of hypertension such as primary aldosteronism, parenchymal and vascular kidney disease, and obstructive sleep apnea require investigation and effective treatment if present. Therapy for resistant hypertension should be based on use of rational drug class combinations at optimal doses with particular attention to adequate diuretic use. The addition of an aldosterone antagonist may further improve blood pressure control.

Keywords

resistant hypertension; blood pressure; pseudoresistance

Introduction

Resistant hypertension (RH) is defined by a failure to achieve goal blood pressure (BP) despite appropriate adherence to a three antihypertensive drug regimen [1]. It is advised but not strictly required that one of the three agents is a diuretic and all agents are prescribed at optimal doses [1]. Target BP is <140/90 mmHg except for those with diabetes and chronic kidney disease (CKD) where the goal is <130/80 mmHg [2]. By this definition, subjects who achieve adequate BP control with optimal doses of 4 or more antihypertensive medications are considered to have RH. Uncontrolled BP includes both RH and pseudoresistance where lack of BP control may be due to poor BP technique, poor adherence, white-coat effect, or inadequate treatment regimen. In this article we provide an overview of the prevalence, prognosis, patient characteristics, associated life-style factors, diagnostic evaluation, and treatment of RH.

Prevalence

The exact prevalence of RH is unknown. Data from cross-sectional and hypertension outcome studies where adherence to treatment is closely monitored, medications are provided at no charge and their titration is required per protocol, have suggested that RH is common, involving 20–35% of study participants. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), that enrolled more than 33,000 subjects 55 years old or older with hypertension and another cardiovascular risk factor, 34% of participants had above goal BP on an average of 2 medications and 51% of participants required 3 or more BP

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medications [3]. In the International Verapamil-Trandolapril Study (INVEST), where more than 22,500 subjects with hypertension and known cardiovascular disease were enrolled, 29% had BP above goal and 50% required 3 or more BP medications [4]. The prevalence of RH is expected to increase due to increased life expectancy and prevalence of factors commonly associated with RH such as obesity, diabetes, and CKD.

Prognosis

Subjects with RH are at greater risk of target-organ damage such as left ventricular hypertrophy (LVH), carotid intima-media thickening, carotid plaques, advanced retinal involvement, and albuminuria than those with more easily controlled blood pressure [5]. They have increased risk of cardiovascular events, most likely due to the long term history of poorly controlled BP and the common association of RH with diabetes, CKD, and obstructive sleep apnea (OSA) [6]. Ambulatory BP is a strong independent predictor of cardiovascular morbidity and mortality in RH [7]. Ambulatory systolic BP (SBP) and diastolic BP (DBP) are superior to pulse pressure (PP) as predictors, while nighttime BP is superior to daytime BP; and, surprisingly, office BP lacks prognostic value in RH [7]. The non-dipping pattern is also an important independent predictor of unfavorable cardiovascular outcomes in RH subjects [8]. The extent of cardiovascular risk reduction by successfully treating RH is unknown. However, the benefits of RH treatment are undoubtedly substantial as suggested by the early Veteran Administration cooperative studies where a 96% reduction in cardiovascular events was achieved over 18 months with the use of three-drug antihypertensive regimens versus placebo in subjects with DBP between 115 and 129 mm Hg [9].

Patient characteristics

Factors associated with RH include isolated systolic hypertension (HTN), older age, aldosterone excess, increased intravascular volume, CKD, diabetes mellitus, obesity, black race, female sex, and living in the Southeastern United States [1]. Most subjects with RH have isolated systolic HTN as shown in a sub-analysis of the Framingham Heart Study where 90% of those treated for hypertension had their DBP <90 mmHg while just 49% had their SBP <140 mmHg [10]. This difficulty in controlling SBP versus DBP worsens with aging [3]. Subjects with RH have higher plasma and urinary aldosterone levels than those with more easily controlled HTN suggesting a potentially greater role of aldosterone in causing RH than just in subjects with primary aldosteronism [11]. Higher atrial and brain natriuretic peptide levels seen in subjects with RH and without CKD as compared to controls suggest persistent fluid retention, which occurs despite conventional diuretic use in RH [11].

Evaluation

The evaluation of subjects with RH should aim to: distinguish true resistance from pseudoresistance; identify the factors potentially contributing to RH; identify the causes of RH with a high suspicion for secondary causes of HTN; document the degree of target organ damage; and to look for other cardiovascular risk factors. Laboratory testing of patients with RH should include serum creatinine, electrolytes, glucose, uric acid, lipids, thyroid stimulating hormone (TSH), urinalysis with evaluation for microalbuminuria, and a paired, morning plasma aldosterone concentration (PAC) and plasma renin activity (PRA) to screen for primary aldosteronism (PA), the most common secondary form of HTN. PAC/PRA (ARR) ratio >20 (with aldosterone measured in ng/dL and PRA in ng/mL/hr) is suggestive of PA but further evaluation is needed to confirm the diagnosis due to its poor positive prognostic value. A ARR <20 reliably excludes PA due to its high negative predictive value [12]. A 24-hr urine collection is recommended to confirm the diagnosis of PA and also gives useful information about the dietary sodium intake and creatinine clearance. Adrenal imaging should be done only after

biochemical confirmation of hormonal excess. If imaging is suggestive of a tumor, it should be followed by adrenal vein sampling (AVS) to identify lateralization of aldosterone secretion consistent with an unilateral aldosterone-producing adenoma (APA) that is potentially amenable to adrenalectomy [12].

Pseudoresistance

Careful assessment of pseudoresistance avoids overtreatment and further expensive evaluations. BP should be measured after a patient has been seated quietly in a chair with his/her back supported for five minutes, with his/her arm supported at heart level, his/her legs uncrossed, and with a properly sized cuff. The BP cuff should be placed on a bare arm to avoid any constricting action of clothing. BP should be measured in both arms and the arm with higher pressures should be used for future readings. Supine and upright BPs should be measured to detect orthostatic changes. If the cuff is too narrow or short, readings may be erroneously as high as 5–15 mmHg in the case of SBP [13]. The presence of heavily calcified or atherosclerotic arteries that cannot be fully compressed, may lead to an overestimation of intra-arterial BP in older patients. Subject should not have smoked a cigarette in the 15–30 minutes preceding the evaluation since smoking can increase SBP of up to 5–20 mmHg [13]. It is generally recommended that coffee should be avoided although the increase in SBP following a cup of caffeinated coffee is limited to 1–2 mmHg [13].

Poor adherence to antihypertensive therapy is an important cause of uncontrolled BP with approximately 40% of patients with newly diagnosed HTN discontinuing their antihypertensive medications during the first year of treatment [1]. The use of multiple medications and their frequent changes make adherence worse. Adherence is improved by the use of less expensive agents, with low side effect rate and once-daily dosing regimen, patient education, frequent clinic visits and by patients recording their BP at home [1]. Poor adherence is less common among patients seen by specialists versus primary care physicians.

The white-coat effect, characterized by clinic BP persistently elevated with normal or consistently lower out-of-office BP, affects 20 to 30% of the subjects with RH [1]. As in the general antihypertensive population, these subjects have less severe target organ damage and are at less cardiovascular risk compared with subjects with persistent RH during ambulatory monitoring [14]. White-coat HTN should be suspected if home BP levels reported by the patient are significantly lower than clinic BP, no target organ damage is present, and hypotension symptoms are reported despite elevated clinic BP. A 24-hour ambulatory BP measurement (ABPM) should be used to diagnose white coat effect and if that is present, the use of home BP values should be used to guide therapy.

Inadequate treatment regimen was the single most common cause of RH in a study evaluating 91consecutive patients seen in a referral center [15]. This is most often due to lack of administration of more effective medications and inadequate diuretic therapy. Clinical inertia defined as a conscious reluctance by physicians to adequately treat elevated BP, contributes to this [16].

Lifestyle factors

Dietary salt

Excessive dietary sodium is common in subjects with RH and may directly increase BP and/or blunt the antihypertensive effects of most agents including diuretics, angiotensin-converting enzyme inhibitors (ACE-Is), and angiotensin receptors blockers (ARBs). Elderly, African-Americans, diabetics, and subjects with CKD appear to be at increased risk of salt sensitivity [17]. Salt restriction should be recommended to all subjects with RH and assessment of 24-

hour urine sodium excretion should be use to assess adherence to it with a goal of <100 mEq/24 hours (equivalent to 2.4 grams sodium or 6 grams sodium chloride intake) [2].

Alcohol consumption

Heavy alcohol ingestion is associated with increased BP and increased risk of BP being uncontrolled. This could be due to its physiologic effects and/or worsened adherence. In a small prospective study, cessation of heavy alcohol ingestion led to a reduction in 24-hr ambulatory SBP and DBP of 7.2 and 6.6 mmHg, respectively. Patients with RH should have their alcohol intake limited to ≤ 1 ounce ethanol/day [1].

Obesity

Obesity is common in subjects with RH. There is a direct correlation between BMI and blood pressure with each 10% increase in body weight associated with 6.5 mmHg increase in SBP and between BMI and number of prescribed antihypertensive medications [18,19]. In ALLHAT, obese subjects were achieving BP goal less than non obese subjects despite receiving more antihypertensive medications [3]. Activation of the renin-angiotensin-aldosterone system (RAAS) and of the sympathetic nervous system with sodium retention, OSA, and insulin resistance play an important role in the obesity-associated HTN [1]. Weight reduction should be recommended to all overweight subjects with RH.

Drug-related causes

Multiple pharmacological agents can increase BP and contribute to BP resistance to treatment (Table 1). These include nonsteroidal anti-inflammatory drugs (NSAIDs), sympathomimetic agents such as decongestants and weight loss pills, amphetamine-like stimulants, chemotherapeutic agents, immunosuppressants such as corticosteroids and calcineurin inhibitors, oral contraceptive pills, erythropoietin stimulating agents, licorice, and over-the-counter dietary and herbal compounds [1]. There is a wide variation in the hypertensive effect of these agents with a minority of subjects being extremely sensitive to their effects. Their withdrawal should be attempted if possible. NSAIDs impair natriuresis, cause fluid retention, and may induce acute renal failure in subjects with dehydration, CKD, elderly, and diabetics where renal dysfunction can be unrecognized. NSAIDs can also blunt the effects of most antihypertensive medications. Similar effects have been shown with selective cyclooxygenase-2 (COX-2) inhibitors and appear to be mediated by their inhibition of renal prostaglandin production [1].

Secondary causes

Secondary causes of HTN account for approximately 20% of subjects referred to a HTN specialty clinic for evaluation of RH (Table 2). Primary aldosteronism (PA) is the leading cause. Older subjects are at more risk of having secondary HTN because of an increased prevalence of OSA, CKD, renal vascular disease, and PA.

Primary aldosteronism

The prevalence of PA increases according to the severity of HTN, affecting 13% of subjects with BP >180/110 mmHg [20]. Approximately 20% of the subjects with RH were diagnosed to have PA based on a suppressed plasma renin activity and elevated 24-hour urine aldosterone excretion (>12 μg) in spite of dietary sodium loading in a hypertension referral clinic at the University of Alabama at Birmingham [21]. Experimental and clinical data have shown that aldosterone excess is associated with inflammation and fibrosis, evidence of intravascular volume expansion, increased risk of target organ damage and of cardiovascular events. Hypokalemia is usually a late manifestation of the disease occurring after HTN has developed

and should not be used to screen for PA; in our experience, 50% of subjects with RH and PA have normal serum potassium levels. PA secondary to APA responds well to resection of primary adenoma, often allowing for titration or even complete withdrawal of antihypertensives and potassium supplements while idiopathic PA is not amenable to surgical correction. In this case, long term use of aldosterone antagonists (spironolactone, eplerenone or amiloride) is the recommended treatment.

Chronic kidney disease

The presence of HTN increases linearly as the glomerular filtration rate (GFR) declines. CKD, usually resulting from diabetic nephropathy or hypertensive nephrosclerosis, is a common contributing factor to RH and also a strong predictor of failure to achieve BP goal [22]. Mechanisms involved in the pathogenesis of RH in subjects with CKD include: sodium retention, increased RAAS activity, increase sympathetic nervous system activity, and vasoconstriction secondary to hyperparathyroidism. Hypertension may also be exacerbated by the use of erythropoiesis stimulating agents in advanced CKD. RH subjects should have their GFR estimated by creatinine clearance and/or the use of Modification of Diet in Renal Disease (MDRD) Study equation, since serum creatinine is an unreliable marker of CKD, especially in the elderly [23]. They should also be assessed for the presence of albuminuria. Blockade of the RAAS slows the progression of CKD to end-stage renal disease (ESRD), reduces proteinuria and the cardiovascular risk in these patients [24].

Renal artery stenosis

Although RAS is common in hypertensive subjects undergoing cardiac catheterization with an incidence of significant lesions of 20%, it is unknown what role these lesions play in causing HTN since they may be found also in normotensive subjects. Atherosclerosis accounts for 90% of the cases of renal artery stenosis (RAS). Elderly, smokers, subjects with known atherosclerotic disease are at increased risk of atherosclerotic RAS that usually presents with an exacerbation of previously controlled HTN. Flash pulmonary edema with acute renal failure after being started on an angiotensin-converting enzyme inhibitor (ACE-I), angiotensin II receptor blocker (ARB), or diuretic should raise the suspicion of bilateral RAS. Randomized clinical studies have not shown strong evidence of a benefit of surgical or endovascular revascularization versus medical management in term of improvement of renal function or BP control in these subjects, although some were able to reduce the number of antihypertensive agents after revascularization. The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, a NIH-funded study to evaluate percutaneous intervention with stenting plus medical therapy versus medical therapy alone should provide important information about long-term cardiovascular and renal outcomes in atherosclerotic RAS. In the meanwhile, revascularization may be considered in cases of RH taking into account a significant BP reduction is not assured and the potential complications of the procedure such as puncture site hematoma, renal artery thrombosis or perforation, acute renal failure due to atheroembolic disease that is usually irreversible or radiocontrast agent that is usually reversible. Fibromuscular dysplasia is a non-inflammatory, non-atherosclerotic disorder that accounts for 10% of the cases of RAS. Young women are usually affected and revascularization is successful in curing or improving HTN in most of the cases. Screening for RAS is not recommended unless the plan is to intervene if a significant stenotic lesion is found. Duplex ultrasound, magnetic resonance angiography (MRA), or computed tomography angiography (CTA) are used to screen for renovascular disease and their choice should be based upon institutional expertise and patient factors such as CKD.

Obstructive sleep apnea

A significant direct correlation exists between severity of OSA and resistance to pharmacologic treatment of HTN [25,26]. OSA is very common in subjects with RH where it is more severe in men than women. Unsuspected OSA (apnea-hypopnea index ≥ 10/hour) was diagnosed in 83% of 41 consecutive subjects with RH [27]. How OSA contributes to HTN is not fully understood. Increased sympathetic nervous system activity secondary to intermittent hypoxemia and increased upper airway resistance play a major contributing role as well as RAAS activation, endothelial dysfunction, and oxidative stress. A strong correlation exists between severity of OSA and aldosterone excess in subjects with RH but not in normotensive or controlled hypertensive subjects [28]. It is unclear if aldosterone excess is cause or consequence of untreated OSA. The polysomnography (PSG) is the standard criterion to diagnose and assess severity of OSA. Treatment of OSA by continuous positive airway pressure (CPAP) minimally reduced blood pressure in most published reports with the greatest benefit seen in those with more severe RH [29].

Pheocromocytoma

Pheocromocytoma is a rare cause of RH and accounts for 0.1 to 0.6% of subjects in a general ambulatory population. However its diagnosis and treatment are very important due to the possibility of malignancy [1]. It should be suspected in subjects with labile HTN and headache, palpitations or diaphoresis although its clinical presentation is extremely variable. Assessment of plasma free metanephrines is the preferred screening test with a sensitivity of 99% and a specificity of 89% [30]. Surgical removal is the appropriate treatment.

Cushing's syndrome

RH is common in Cushing's syndrome where severe HTN has been described in 17% of the subjects. Target organ damage is more severe in Cushing's syndrome than in primary HTN. Excessive stimulation of nonselective mineralocorticoid receptor by cortisol, OSA, diabetes, obesity, and insulin resistance contribute to HTN in these subjects [1]. The most effective BP pharmacological therapy for Cushing's syndrome is the use of an aldosterone antagonist (spironolactone or eplerenone). Surgical removal of a cortisol or adrenocorticotropic (ACTH) tumor reduces BP.

Treatment of RH

RH has almost always multifactorial in etiology. Its treatment needs to be directed at identifying and reversing lifestyle factors contributing to RH; identifying and discontinuing, if possible, medications that can contribute to RH; diagnosing and treating secondary causes of HTN; and use of effective multidrug regimens to control BP. Low salt diet, regular exercise, weight loss, moderation of alcohol intake, and quitting smoking should be routinely encouraged. Antihypertensive agents should be prescribed at their maximum tolerated dose. Subjects whose BP remains above goal despite three or more antihypertensive medications should be referred to a hypertensive specialist. HTN specialists in a university HTN clinic, were able to achieve a BP <140/90 mmHg in 53% of subjects referred for evaluation of RH [31]. Recent data showing that bedtime dosing of antihypertensive medications was able to significantly reduce BP with greater benefit on nocturnal than diurnal HTN and to restore the non-dipping pattern in RH subjects, suggests that the use of at least one antihypertensive medication at bedtime is indicated, although this may reduce patients' adherence [32]. The efficacy of specific 3 or more drug combinations has not been evaluated in subjects with RH and the current recommendations are based largely on physiological principles, clinical experience, and patient characteristics (age, concomitant diseases). We often use an ACE-I (or ARB) in combination with a dihydropyridine calcium channel blocker such as amlodipine due to their better cardiovascular outcome in high risk patients and efficacy in controlling BP [33]. Since most

of the subjects with RH have volume expansion due to excessive dietary sodium and/or sodium retention, we also prefer the use of a long acting diuretic. We prefer chlorthalidone to hydrochlorothiazide due to its greater 24-hour ambulatory BP reduction and its demonstrated outcome benefits [34,35]. A loop diuretic is preferred to a thiazide diuretic if CKD is severe (eGFR <30–40 ml/min/1.73 sqm) or if a potent vasodilator is used. Furosemide and bumetanide are relatively short-acting and should be prescribed at least twice daily since intermittent natriuresis with once-daily administration may lead to reactive sodium retention mediated by increases in the RAAS with subsequent inadequate BP control. Hyponatremia, hypokalemia, hyperglycemia, and hyperuricemia should be periodically monitored for in patients on diuretic therapy. If BP is still not at goal, the next step is adding a fourth agent and we typically use an aldosterone antagonist unless there is concomitant CKD (eGFR <50–60 ml/min/1.73 sqm). Spironolactone (12.5 to 50 mg daily) decreased SBP by an additional 25 mmHg and DBP by 12 mmHg, without racial differences, in subjects with RH already treated with at least an ACEI or ARB and a diuretic [36] and its effect was independent of serum aldosterone and renin levels. Amiloride is another potassium-sparing diuretic that is effective in reducing BP in subjects with RH [37]. Both spironolactone and amiloride were well tolerated and hyperkalemia was uncommon in patients with normal renal function. However, the risk of hyperkalemia is significantly higher in elderly subjects with CKD and/or diabetes who besides an ACE-I and/or ARB may also regularly take a β-blocker or an NSAID. In these subjects, NSAIDS should be discontinued, spironolactone should be started at 12.5 mg daily and serum potassium and creatinine should be closely monitored; subjects should also be educated to avoid food or supplements rich in potassium. In case the BP is still above target, we prefer combined α-β blockers such as labetalol or carvedilol to pure β-blockers due to their suggested better BP control [38]. If β blockers are contraindicated, peripheral α-blockers may be considered: a recent retrospective study showed that doxazosin at a mean dose of 4 mg/day further decreased SBP by 16 mmHg and DBP by 7 mmHg in subjects with RH [39]. Vasodilators such as hydralazine or minoxidil and centrally acting agents such as clonidine and methyldopa may be effective but are associated with common side effects and lack of positive outcome data [2]. In particular, with minoxidil, concomitant β-blockers and loop diuretics are needed to counteract resultant reflex tachycardia and fluid retention. We do not combine an ACEI with an ARB since the combination does not significantly reduce BP or cardiovascular events as compared to individual agents and can also lead to worse renal outcome and hyperkalemia [40–42]. The ACEI/ARB combination should be limited to subjects with severe proteinuria under the care of a nephrologist. We also do not combine a renin inhibitor (aliskiren) with an ACEI or ARB since this does not generally provide substantive additional BP reduction [43]. Ongoing phase III trials are evaluating the anti-hypertensive effects of endothelin-receptor antagonists (ERAs) in RH. Cathether-based ablation of renal sympathetic nerves might be considered in the future for those subjects whose BP is persistently refractory to maximal medical treatment; this technique was safe and resulted in further decrease in SBP by 27 mmHg and DBP by 17 mmHg twelve months after the procedure in 45 subjects with RH [44]. Its efficacy and safety need however to be confirmed in randomized control studies as well as for interventions aimed to electrically activate the carotid baroflex system through a surgically implantable device [45].

Conclusions

RH is a common medical problem and its prevalence is expected to increase. RH is most often related to poorly controlled SBP. Its diagnosis requires first the use of good BP techniques to confirm the BP elevation. Other forms of pseudoresistance need to be excluded. Its etiology is almost always multifactorial and common reversible contributing factors need to be identified. The most common secondary causes of RH are PA, CKD, RAS, and OSA. Pharmacologic treatment of RH should be based on the maximum tolerated doses of multiple agents one of

which, if possible, should be a long-acting diuretic to control volume overload. The addition of an aldosterone antagonist may further improve the BP control.

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Table 1

Exogenous Substances that Can Contribute to Resistant Hypertension

Nonsteroidal antinflammatory agents including
Selective COX-2 inhibitors
Sympathomimetic agents (decongestants, weight loss pills, cocaine)
Stimulants (methylphenidate, amphetamine, modafinil)
Oral contraceptives
Calcineurin inhibitors
Steroids
Erythropoietin
Tricyclic antidepressant
Licorice
Alcohol
Herbal compounds (ephedra or ma huang)

Table 2

Secondary Causes of Resistant Hypertension

Common Causes
Primary aldosteronism
Renal artery stenosis
Chronic kidney disease
Obstructive sleep apnea
Rare Causes
Pheochromocytoma
Cushing's disease
Coartation of Aorta
Intracranial tumor
Carcinoid syndrome
Hyperparathyroidism
Hypo/hyperthyroidism