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Resistant Hypertension: Mineralocorticoid Receptor Antagonist or Renal Denervation?

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Resistant hypertension (RH) is defined as blood pressure (BP) that remains above goal in spite of optimal doses of three antihypertensive agents of different classes, one ideally a diuretic (1). Patients achieving BP control with the addition of a fourth antihypertensive agent also meet the definition of RH. Thus, the population with apparent RH includes hypertensive patients that are both controlled (4 drugs) and uncontrolled (3 drugs) using office BP measurements. The paper by Rosa *et al.* (2) in the current issue of *Hypertension* addresses this important clinical problem.

The definition of apparent RH does not distinguish patients with true RH from those with pseudo-RH, including individuals with elevated office BP due to “white coat” hypertension, inaccurate BP measurement due to faulty technique, or lack of adherence to the prescribed antihypertensive regimen (1,3,4). When pseudo-resistance has been excluded by 24h-ambulatory BP monitoring (ABPM), appropriate office BP measurement technique and confirmation of medication adherence, the diagnosis of true RH can be endorsed. The prevalence of apparent RH has been estimated as approximately 10-15% of the treated hypertensive population, but only approximately 50% of these patients can be classified as having true RH as defined above (3-5). The diagnosis of RH carries an unfavorable prognosis. Patients with uncontrolled true RH are at high risk for end-stage renal disease, ischemic heart disease, congestive heart failure, cerebrovascular accident, cardiovascular events and death compared with those with controlled RH and pseudo-RH (6).

The pathophysiology of RH is poorly understood. Inappropriate sodium and fluid retention, as evidenced by elevated brain natriuretic peptide (BNP) levels, suppressed plasma renin activity and responsiveness of BP to dietary sodium restriction or diuretic therapy, has been repeatedly demonstrated in RH (1,3,4). In addition, there is evidence for excessive aldosterone secretion, including high plasma aldosterone levels, albeit not as high as in patients with primary aldosteronism, and BP responsiveness to mineralocorticoid receptor antagonists (1,3,4). A small subset (2.7%) of RH, requiring 5 classes of antihypertensive agents for BP control, has recently been termed “refractory hypertension” (7). These patients may have different pathophysiologic mechanisms for treatment failure, especially excessive sympathetic output as evidenced by greater urinary 24h normetanephrine levels, greater

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arterial stiffness, higher heart rate, lower heart rate variability, and higher systemic vascular resistance than patients with controlled RH (7).

The treatment of RH has traditionally addressed the known mechanisms of treatment failure. Because many patients with RH have clinical evidence of volume expansion, switching from a standard thiazide diuretic to longer acting chlorthalidone or, if renal function is compromised, to a long-acting loop diuretic (eg. torsemide) may be effective (1,3,4). In patients who are unresponsive to these changes or have suppressed plasma renin activity or salt-sensitivity of BP, mineralocorticoid receptor antagonists (spironolactone or eplerenone) may reduce BP to goal (1,3,4).

While several uncontrolled trials had shown that low-dose spironolactone (25 mg daily) substantially lowers BP in RH, evidence from randomized clinical trials was necessary to establish efficacy and safety. This was accomplished in several recent trials. The Addition of Spironolactone in Patients with Resistant Arterial Hypertension (ASPIRANT) and ASPIRANT-EXT trials indicated that spironolactone markedly improves BP control in RH (8). The results of this trial were recently confirmed and extended by the spironolactone versus placebo, bisoprolol and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2) trial, a 12-month randomized, double-blind, placebo-controlled trial (9). This trial demonstrated unequivocally that spironolactone is superior to other antihypertensive agents including β -adrenergic blocker (bisoprolol) and α_1 -adrenergic receptor antagonist (doxazosin) in the treatment of RH (9). Importantly, spironolactone was superior to the other comparators despite existing baseline diuretic therapy, suggesting that the main pathophysiologic mechanism preventing the effectiveness of antihypertensive therapy to achieve goal is indeed sodium and volume expansion. PATHWAY-2 also challenged the widely held belief that RH cannot be adequately treated with existing drug therapies (9).

Endovascular renal denervation with radiofrequency ablation has emerged as a new invasive treatment for patients with RH. The initial randomized trials provided evidence of efficacy to lower BP to goal and the safety of the procedure. However, the Simplicity HTN-3 trial (the first prospective, randomized, sham-controlled, double-blinded study of renal denervation in RH) was unable to demonstrate the efficacy of this procedure (10). However, the recent DENERHTN open-label randomized controlled trial demonstrated that renal denervation plus standardized stepped-care antihypertensive treatment does decrease ambulatory BP more than medical therapy alone in RH (11). Differences in these results may be attributable, among other factors, to differences in the location of renal artery lesion placement.

On this background of uncertainty concerning the efficacy of renal denervation, Rosa *et al.* (2) report the 12-month results of the PRAGUE-15 trial in which the efficacy and safety of pharmacologic therapy including addition of spironolactone or renal denervation was studied in randomized fashion in patients with RH. The results demonstrate that renal denervation is not superior to intensified pharmacological therapy. Importantly, the results of the per-protocol analysis showed significantly greater reduction of 24h systolic BP in

patients in whom spironolactone was added to and continued in the pharmacological regimen compared with renal denervation.

This study has a number of strengths: use of 24-hour ABPM to exclude white coat hypertension and monitor results of therapy, rigorous exclusion of secondary hypertension and validation of adherence to pharmacological treatment, assuring that the study population had true RH. A potential weakness of the study, as pointed out by the authors, is that 24-27% of the patients were already taking spironolactone at baseline prior to randomization. Spironolactone was simply continued in these patients. Thus, 24 of patients randomized to renal denervation were still taking spironolactone at 12 months, whereas there was a 32% increase in spironolactone-takers in the pharmacological treatment group. Because spironolactone was being taken at baseline and continued in such a large number of patients in both groups, the results could have been biased. Another weakness is the small number of patients, particularly in the per-protocol pharmacological group. Notwithstanding, these results show that an intensified medical regimen, including spironolactone, is at least as effective in lowering BP as renal denervation, which should not constitute a routine therapeutic approach in RH.

These results, as well as those of the PATHWAY-2 trial and other available evidence, currently suggest the following approach to the treatment of RH (Figure). In patients with apparent RH according to the American Heart Association definition (1), the major causes of pseudo-RH, including white coat hypertension (preferably using ABPM), faulty BP measurement technique and non-adherence with the prescribed pharmacological regimen, must be excluded. If so, the patient has true RH, and every effort should be made to identify and reverse contributing lifestyle factors, discontinue or minimize interfering substances and exclude secondary causes of hypertension (1). Since volume expansion is the usual pathophysiologic mechanism of RH in spite of background diuretic therapy, patients should be switched from a thiazide diuretic to chlorthalidone or, if renal insufficiency is present, to a long-acting loop diuretic. As well, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) should be added. If the BP goal is not achieved, adherence should be reassessed and, if optimal, renal denervation may be considered as a last resort. However, results from randomized clinical outcomes trials are needed before renal denervation can be accepted with confidence.

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Figure.

Schematic diagram of the management of resistant hypertension (RH) based on the present study (2) and other available evidence. Questions in the trapezoids represent decision points in management. Abbreviations: WCH – white coat hypertension; BPM – blood pressure measurement; BP – blood pressure; MR – mineralocorticoid receptor.