REVIEW

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Resistant Hypertension and the Pivotal Role for Mineralocorticoid Receptor Antagonists: A Clinical Update 2016

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ABSTRACT

True resistant hypertension must be distinguished from apparent resistant hypertension, of which important causes include medication nonadherence, illicit drug use, and alcoholism. Ambulatory blood pressure monitoring should be considered to rule out white coat hypertension. The pathogenesis is multifactorial, but the 2 pivotal factors include volume excess and the myriad effects of aldosterone. Aldosterone increases vascular tone because of endothelial dysfunction and enhances the pressor response to catecholamines. It also plays a crucial role in vascular remodeling of small and large arteries. Aldosterone also promotes collagen synthesis, which leads to increased arterial stiffness and elevation of blood pressure. Because aldosterone has been demonstrated to modulate baroreflex resetting, in cases of severe hypertension, there would be fewer compensatory mechanisms available to offset the blood pressure elevation.
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KEYWORDS: Aldosterone; Carotid baroreceptor stimulation; Mineralocorticoid receptor antagonists; Renal nerve denervation; Resistant hypertension; Spironolactone

Resistant hypertension is a common medical disorder encountered by all clinicians. Demographic trends, including the aging of our adult population and the increasing prevalence of obesity, indicate that resistant hypertension will become even more common. The past few years have witnessed increased clinical and investigative attention to this disease entity that informs an appropriate clinical management.[1,2]

Moreover, clinical studies have focused increasingly on the overriding importance of aldosterone and mineralocorticoid signaling in the pathogenesis and maintenance of resistant hypertension.[3-6] This review will focus on the clinical features of resistant hypertension and consider the importance of several risk factors undergoing reappraisal and clinical investigation, as well as the pivotal pathogenic role of aldosterone in both promoting and sustaining resistant hypertension.

DEFINITION

Resistant hypertension is defined as failure to attain the goal blood pressure of <140/90 mm Hg despite adherence to 3 different antihypertensive medications at reasonable dosages, one of which must be a diuretic.[1,7] For patients with diabetes or renal failure (defined as a serum creatinine >1.5 mg/dL or 133 μmol/L and/or proteinuria >300 mg in 24 hours), the definition is modified as a failure to reach a goal blood pressure of <135/85 mm Hg with the stated criteria.

SCOPE OF THE PROBLEM

Increased Cardiovascular/Renal Morbidity and Mortality

Hypertension is a major independent risk factor for cardiovascular disease and mortality, and patients with resistant

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hypertension represent a more severe subset with an even greater increased cardiovascular risk compared with patients without resistant hypertension.[8] Compared with patients with controlled hypertension, patients with resistant hypertension develop greater target end-organ damage, including increased left ventricular hypertrophy, retinal changes, and microalbuminuria.[9] Consequently, these translate into an enhanced overall long-term cardiovascular risk.[10,11]

Inadequate Blood Pressure Control

Data from the National Health and Nutrition Examination Survey, 2011-2012 reported that the age-adjusted prevalence of hypertension among US adults aged 18 years or more was 29.1% in 2011-2012, similar to the prevalence in 2009-2010.[12] Among adults with hypertension, approximately 83% were aware of it, approximately 76% were taking medication to lower their blood pressure, but only 52% had controlled hypertension, and the control rates failed to increase from 2009-2010 to 2011-2012. The failure to control blood pressure exists across all socioeconomic and ethnic groups and is likely multifactorial, including sociologic factors, such as health care access; patient factors, such as lack of understanding and financial burden; and provider factors, such as prescribing inappropriate combinations of medications or inadequate dosages despite poorly controlled blood pressure.[13,14]

Of great importance, some studies suggest that the most common reason for poor blood pressure control is the failure of providers to prescribe optimal antihypertensive therapy and that rational titration of diuretics and increasing the number of blood pressure-lowering medications were the most likely interventions to achieve the target blood pressure.[15,16] Thus, truly resistant or difficult-to-control hypertension explains only a part of the huge public health problem of uncontrolled blood pressure. In all probability, the problem will be magnified after the publication of the results of the recent Systolic blood PRessure INterventional Trial (SPRINT), which provided evidence that in a large hypertensive population the target blood pressure of 120/80 mm Hg is more beneficial than 140/90 mm Hg.[17]

Causes of Resistant Hypertension

Table 1 lists the common causes of resistant hypertension. A large portion of patients have "apparent" resistant hypertension that must be distinguished from true resistant hypertension. Causes of "apparent resistant hypertension" include improper blood pressure measurements, pseudohypertension, medication nonadherence, and white coat hypertension.[1]

CLINICAL SIGNIFICANCE

- Volume excess and the myriad actions of aldosterone are pivotal factors in the pathogenesis of true resistant hypertension.
- Spironolactone is the most effective add-on drug for the treatment of resistant hypertension.
- The risk of mineralocorticoid receptor antagonist-induced hyperkalemia is increased in chronic kidney disease, diabetes mellitus, and elderly patients.
- Renal denervation system and carotid baroreceptor stimulation are not ready for clinical application for the treatment of resistant hypertension.

The Overriding Importance of Proper Technique for Blood Pressure Recording

Diagnosis of all forms of hypertension requires 2 or 3 separate elevated blood pressure readings that are documented with proper technique.[18] The patient should be seated for at least 5 minutes, and blood pressure should be measured with an appropriately sized cuff that encircles 80% of the arm. Blood pressure should be confirmed in both arms, with the arms supported at heart level.

Some patients exhibit pseudohypertension in which sclerotic arteries are incompressible and therefore have falsely elevated cuff blood pressures. Pseudohypertension can be distinguished from resistant hypertension by the Osler maneuver, in which the radial artery is still palpable after compression of the brachial artery with the blood pressure cuff.[19] Only an intra-arterial blood pressure can provide a true measurement of blood pressure in these patients.

Medication Nonadherence

Medication nonadherence or noncompliance is an extremely important cause of both "apparent" resistant hypertension and poorly controlled hypertension. Adherence is usually defined as taking the medication regimen correctly $\geq$80% of the time. The World Health Organization reports 7 estimates that at least 50% of hypertensive patients do not adhere to the prescribed medication regimen.[20] The term "noncompliance" is no longer favored because of its negative connotation that the patient is a passive recipient of the doctor's order; therefore, the preferred term is "nonadherence." Because the definition of resistant hypertension is contingent on patients adhering to their multidrug antihypertensive regimens, medication nonadherence does not constitute a cause of true resistant hypertension, but rather a form of apparent resistant hypertension, often due to multiple causes.

Clinical Relevance of Obstructive Sleep Apnea

Several studies have reported an extremely high prevalence of obstructive sleep apnea in patients with resistant hypertension.[21,22] Activation of the sympathetic nervous system