Review Paper

Resistant Hypertension: Prevalence and Evolving Concepts

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Guest Editor

Resistant hypertension is a common medical disorder. Although the exact incidence of resistant hypertension is not established, estimates derived from recent outcome studies including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Valsartan Antihypertensive Long-term Use Evaluation (VALUE), and Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) emphasize that this condition may be more common than previously thought. A major advance in our understanding of the pathogenesis and management of resistant hypertension is the recognition of the importance of aldosterone. Several investigators have postulated a direct role of aldosterone excess as an important mechanism for drug resistance in hypertension. The mechanisms whereby aldosterone elevates BP are complex. It was previously thought that aldosterone produced hypertension primarily by promoting sodium retention with consequent hypervolemia. Recent studies of the effects of aldosterone on vascular smooth muscle have, however, delineated several extrarenal mechanisms whereby aldosterone produces hypertension—primarily by its direct vasoconstrictor effects and by altering vascular compliance. Consequently, aldosterone blockade constitutes an effective intervention for treating resistant hypertension. (J Clin Hypertens. 2007;9(1 suppl 1):2–6) ©2007 *Le Jacq*

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Resistant hypertension is a common medical disorder encountered by all clinicians. As our adult population ages and as obesity becomes more prevalent, resistant hypertension will probably become even more common. The past few years have witnessed increased clinical and investigative attention to this disease entity. Clinical studies, moreover, have focused increasingly on the importance of aldosterone in the pathogenesis of resistant hypertension. This overview will focus on the prevalence of resistant hypertension and consider the importance of several risk factors undergoing reappraisal and clinical investigation, as well as potential pathogenetic mechanisms of aldosterone in resistant hypertension.

DEFINITION

Resistant hypertension is defined as the failure to reach goal blood pressure (BP) despite adherence to appropriate treatment with full doses of at least 3 antihypertensive medications, including a diuretic.[1] Goal BP is defined as ≤140/90 mm Hg in the general population or ≤130/80 mm Hg in patients with diabetes or renal disease (serum creatinine >1.5 mg/dL in men or >1.3 mg/dL in women, or urinary protein excretion >300 mg over a 24-hour period).[1]

In Europe, guidelines issued by the European Society of Hypertension/European Society of Cardiology (ESH/ESC) define resistant hypertension as occurring when lifestyle measures and a combination of at least 3 drugs in adequate doses have failed to lower systolic and diastolic BP sufficiently.[2]

The traditional definition (the first mentioned above) has been reproduced frequently in many medical texts, and appears to be sacrosanct. Careful consideration of this traditional definition, however, raises several objections and drawbacks that may confound attempts to establish this diagnosis.

In the following paragraphs, I will review the major concerns.

First, the term "full doses" is problematic. In reality, many clinicians don't prescribe full doses of common antihypertensive agents because the dose-response relationship on BP is relatively flat with most antihypertensive agents. As an example, a patient who is treated with lisinopril 40 mg/d will not conform to the definition of resistant hypertension because full doses of the angiotensin-converting enzyme inhibitor were not prescribed. Of note, the ESH/ESC guidelines use the term "adequate doses" rather than "full doses." The term "adequate" is also problematic because it is vague and subject to different interpretations.

A second problem is use of the phrase "failure to reach goal BP." As an example, if the patient is receiving 4 or 5 different drugs and is "controlled at goal," that patient would not be diagnosed as having resistant hypertension.

A third objection is the obligatory use of a diuretic. Volume management is an important aspect of treatment in many patients with resistant hypertension and, consequently, a diuretic should constitute a mainstay of antihypertensive therapy. Unfortunately, for many reasons (including misinformation) many patients are not treated with a diuretic. If a patient's BP is uncontrolled on 4 or 5 different drugs but one of them is not a diuretic, this would not conform to the traditional definition of resistant hypertension. Of interest, the ESH/ESC guidelines require "at least 3 drugs," but do not specify that one must be a diuretic.

These considerations suggest that the drafters of future guidelines may wish to reconsider and possibly revise the current definition of resistant hypertension.

PREVALENCE

The exact prevalence of resistant hypertension is unknown; our current information is derived from observational and hypertension outcome studies. Cross-sectional analyses including the most recent National Health and Nutrition Examination Survey (NHANES) indicate that poorly controlled hypertension is quite common.[1] As an example, among patients with diabetes being treated for hypertension, only 25% were controlled to a BP <130/85 mm Hg.[3] Uncontrolled hypertension, however, is not the same as resistant hypertension, because of several confounders such as undertreatment and poor adherence.

A better estimate of the prevalence of treatment-resistant hypertension is currently provided by hypertensive outcome studies. In such studies, drug selection and dose titration are mandated per protocol to achieve goal BP and adherence is closely monitored. In this regard, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[4,5] provides a valuable body of data from which to derive a reliable estimate of the prevalence of resistant hypertension, as this trial included more than 33,000 subjects with an average follow-up of approximately 5 years.

Table. Common Clinical Characteristics of Patients With Resistant Hypertension

Obesity
Diabetes
Chronic kidney disease
Black race
Female sex
Left ventricular hypertrophy

In ALLHAT, after 5 years of follow-up, 34% of subjects remained uncontrolled (BP >140/90 mm Hg) on an average of 2 medications, with 27% of subjects receiving 3 or more medications.[5] At the end of the study, approximately 8% of ALLHAT subjects were prescribed 4 or more medications. These numbers probably underestimate the prevalence of resistant hypertension in ALLHAT. If we add the number of subjects on 3 medications but whose BP remained elevated (ie, patients who possibly should have been titrated to 4 medications) to the 8% who were receiving 4 or more medications, this might give a better estimate of the occurrence of resistant hypertension. Approximately 15% of the entire cohort could be classified as having resistant hypertension.

Data from other recent clinical trials are consistent with ALLHAT in demonstrating a high degree of uncontrolled hypertension despite use of appropriate multidrug regimens. In the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial,[6] hypertensive persons at least 55 years of age and with at least 1 cardiovascular risk factor other than hypertension were randomized to either controlled-onset extended-release verapamil, atenolol, or hydrochlorothiazide. Other agents were added in stepwise fashion as needed for BP control. At the end of the study, 33% of subjects remained uncontrolled (BP >140/90 mm Hg), with 18% of subjects being treated with 3 or more medications. In the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) study,[7] hypertensive persons at least 50 years of age with multiple cardiovascular risk factors were randomized to valsartan

or amlodipine with hydrochlorothiazide and other agents being added to lower BP to <140/90 mm Hg. At 30 months of follow-up, 40% of subjects failed to achieve goal BP. Among the 15% of subjects receiving 3 or more drugs, BP remained elevated in 61%. In summary, although the exact incidence of resistant hypertension is not precisely known, these estimates, derived from recent outcome studies, emphasize that this condition is a common clinical problem.

CLINICAL FEATURES

Reviews have traditionally suggested that treatment-resistant hypertension is associated with several patient characteristics that predispose to difficulty in achieving goal BP. As summarized in the Table, these features include obesity, diabetes, chronic kidney disease, black race, female sex, and the presence of left ventricular hypertrophy. Overweight patients (defined as patients with a body mass index >27.8 kg/m^2 in men and >27.3 kg/m^2 in women) do not respond as well as leaner patients to antihypertensive medication. In both cross-sectional studies and treatment trials, obesity is associated with the use of an increased number of antihypertensive medications and a decreased likelihood of achieving goal BP control.[1,8] Clinical trials indicate that persons with diabetes are more resistant to antihypertensive treatment than nondiabetics, requiring more medications to achieve the same level of BP reduction.[9–11] In general, as renal function declines, more antihypertensive medications are required and achievement of goal BP becomes progressively more difficult.[1,12] The presence of left ventricular hypertrophy predicts difficulty in achieving BP control,[13] but it has not been established whether left ventricular hypertrophy is merely a result of more severe hypertension or has an independent effect on treatment resistance. While it is reasonable to suggest that these associated conditions will complicate attempts to control BP, it should be noted that we still lack a rigorous database to ascertain the frequency of such complications in well studied cohorts of patients with resistant hypertension.

Obstructive Sleep Apnea

There is a high degree of correlation between obstructive sleep apnea (OSA) and hypertension, particularly among patients with resistant hypertension. Epidemiologic studies[14–16] demonstrate that BP and the number of patients with hypertension increase with sleep apnea severity, as indicated by the respiratory disturbance index. In a study of patients with resistant hypertension, Logan and colleagues[15] diagnosed previously unsuspected OSA in 34 of 41 evaluated subjects (83%). In subjects with OSA, resistance to antihypertensive therapy is associated with a higher respiratory disturbance index compared with patients whose hypertension is more easily controlled.[14]

In spite of the strong correlation between OSA and hypertension, the mechanism by which OSA contributes to the development of resistant hypertension remains poorly elucidated. Calhoun et al[17] have demonstrated increased aldosterone excretion in subjects with resistant hypertension and symptoms of sleep apnea. Animal studies[18] suggest that acute hypercapnia or hypoxia separately increases plasma aldosterone concentration independent of increases in plasma renin activity, while the combination of hypercapnia and hypoxia is a potent stimulus of both plasma renin activity and plasma aldosterone concentration.

An alternative explanation for the high degree of association between OSA and hyperaldosteronism is that obesity and not OSA is the determinant of the greater aldosterone excretion. Several investigators[19,20] have reported higher aldosterone levels in obese individuals than in lean control subjects. Goodfriend and colleagues[21] reported that the higher aldosterone levels previously reported in obese hypertensive subjects may be attributable to an adipocyte-derived aldosterone secretagogue independent of renin activity. They described an adipocyte-derived factor, likely a free fatty acid derivative, which enhances the release of a hepatic stimulator of aldosterone synthesis.[22] While the precise mechanism(s) mediating the increased aldosterone levels remain to be established, it is reasonable to postulate that sleep apnea may contribute to the development of resistant hypertension in OSA patients by stimulating aldosterone excretion. We await future studies to further define this relationship and the efficacy of treatment with aldosterone blockers.

ALDOSTERONE IN THE PATHOGENESIS OF RESISTANT HYPERTENSION

One of the major advances in our understanding of the pathogenesis and management of resistant hypertension is the recent recognition of the importance of aldosterone. Several investigators have postulated a direct role of aldosterone excess or autonomy as an important mechanism for drug resistance in hypertension. Eide and colleagues[23] found a low-renin state in two thirds of patients with resistant hypertension. Several other reports also have found

that the prevalence of hyperaldosteronism is high in cases of resistant hypertension.[24–26] The high prevalence of hyperaldosteronism in these patients has led some clinicians to suggest treatment with add-on aldosterone blockade, even in the absence of hyperaldosteronism. Indeed, several recent studies have demonstrated the efficacy of add-on aldosterone blockers in patients with resistant hypertension. In one such study, Nishizaka and colleagues[27] prospectively assessed the BP response of spironolactone 12.5–50 mg daily added to existing antihypertensive regimens in patients whose BP remained elevated on 3 or more agents. After 6 months' follow-up, spironolactone (mean dose, 30 mg/d) reduced systolic BP by 25±20 mm Hg and diastolic BP by 12±12 mm Hg. Of interest, the BP response was not different in subjects with primary aldosteronism compared with those without primary aldosteronism. Furthermore, the reduction in BP did not correlate with the underlying aldosterone excretory rate.[27] The major reported adverse event attributed to spironolactone was breast tenderness, which occurred in about 10% of the men. Elsewhere in this supplement, Dr Calhoun reviews additional studies in support of the efficacy of add-on aldosterone blockade in the treatment of resistant hypertension.

The mechanisms whereby aldosterone blockade lowers BP merit consideration. Most physicians believe that aldosterone produces hypertension primarily by promoting sodium retention, with consequent hypervolemia. Recent studies of the nongenomic effects of aldosterone on vascular smooth muscle, however, have delineated several mechanisms whereby aldosterone produces hypertension primarily by its direct vasoconstrictor effects and by altering vascular compliance. Aldosterone increases arterial stiffness in salt-fed rats associated with fibronectin accumulation, an effect that is prevented by the selective aldosterone blocker eplerenone.[28] In that study, aldosterone administration produced a significant increase in pulse pressure, carotid artery stiffness, and fibronectin (which plays an important role in cell–matrix interactions) in the arterial wall of experimental rats. These effects were prevented in a dose-dependent manner by eplerenone.[28]

Primary aldosteronism is also associated with impaired baroreflex function, in part related to reduced arterial compliance.[29] Spironolactone, but not bendroflumetazide, has recently been demonstrated to reduce arterial stiffness; the reduction is partly independent of BP reduction, providing further evidence of a direct role for aldosterone in mediating hypertension.[30]

An intriguing mechanism that has recently been elucidated to explain the benefit of aldosterone blockade focuses on aldosterone's ability to impair endothelium-dependent vascular function through suppression of nitric oxide formation. Nishizaka et al[31] have recently demonstrated a strong association between aldosterone excess and impaired endothelial function in a large cohort of patients with resistant hypertension, as indicated by flow-mediated arterial vasodilation. These results suggest that chronic aldosteronism may have a BP-independent effect on cardiovascular disease progression in subjects with resistant hypertension. Consequently, aldosterone blockade may act in part by reversing or attenuating aldosterone-mediated endothelial dysfunction.

An additional subject of current investigative focus is research to attenuate target organ injury. As detailed in a recent review,[32] extensive preclinical and clinical evidence supports the efficacy of aldosterone blockade in attenuating proteinuria. Consequently, add-on aldosterone blockade may constitute a rational therapy for attenuating renal injury.

FUTURE PERSPECTIVES

Although the prevalence of resistant hypertension is unknown, data from recent hypertension outcome trials indicate that it is greater than previously thought.[33] Several recent studies have demonstrated a high prevalence of aldosterone excess in patients with resistant hypertension. The mechanisms mediating aldosterone excess have not been established and should therefore constitute a focus of future studies. Future studies should also investigate the mechanisms mediating the increased aldosterone excretion among patients with concomitant resistant hypertension and symptoms of OSA. An important priority should be given to conducting clinical trials delineating the efficacy of aldosterone blockade in achieving goal BP in patients with resistant hypertension. These studies should encompass intervention with either spironolactone or the selective aldosterone blocker eplerenone. Mechanistic studies should also be conducted to assess the effects of potassium repletion, to define the possible role of this therapeutic intervention in mediating the beneficial effects of aldosterone blockade. Because of the dire cardiovascular outcomes of uncontrolled resistant hypertension, the proposed increased investigative and clinical efforts outlined in this supplement should constitute a priority in the medical community.

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