Ambulatory Blood Pressure and Adherence Monitoring: Diagnosing Pseudoresistant Hypertension

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Summary: A small proportion of the treated hypertensive population consistently has a blood pressure greater than 140/90 mm Hg despite a triple therapy including a diuretic, a calcium channel blocker, and a blocker of the renin-angiotensin system. According to guidelines, these patients have so-called *resistant hypertension*. The prevalence of this clinical condition is higher in tertiary than primary care centers and often is associated with chronic kidney disease, diabetes, obesity, and sleep apnea syndrome. Exclusion of pseudoresistant hypertension using ambulatory or home blood pressure monitoring is a crucial step in the investigation of patients with resistant hypertension. Thus, among the multiple factors to consider when investigating patients with resistant hypertension, ambulatory blood pressure monitoring should be performed very early. Among other factors to consider, physicians should investigate patient adherence to therapy, assess the adequacy of treatment, exclude interfering factors, and, finally, look for secondary forms of hypertension. Poor adherence to therapy accounts for 30% to 50% of cases of resistance to therapy depending on the methodology used to diagnose adherence problems. This review discusses the clinical factors implicated in the pathogenesis of resistant hypertension with a particular emphasis on pseudoresistance, drug adherence, and the use of ambulatory blood pressure monitoring for the diagnosis and management of resistant hypertension.

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According to most recent European and American clinical hypertension guidelines, the main objective of the management of hypertensive patients is to lower blood pressure (BP) to less than 140 mm Hg systolic and 90 mmHg diastolic in all patients unless patients are older (<150/90 mm Hg if patients are >80 years according to European Society of Hypertension/European Society of Cardiology guidelines, >60 in US guidelines), or have a renal disease with high-grade proteinuria (<130/90 mm Hg according to European Society of Hypertension/European Society of Cardiology guidelines).[1,2] These BP targets have been set to reduce the high risk safely and effectively of cardiovascular and renal outcomes and the cardiovascular mortality that characterized hypertensive patients. Large clinical trials have shown that adequate blood pressure control can be achieved in approximately 80% of treated patients.[1] However, national surveys consistently have reported much lower rates of BP control in the general populations.[3]

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In some patients BP remains uncontrolled despite apparently adequate treatment. Thus, resistant hypertension has been defined as the persistence of BP of 140/90 mm Hg or higher when patients are receiving at least 3 drugs (including a diuretic) in adequate doses after exclusion of spurious hypertension.[1] In some analyses, resistant hypertension also is considered if patients have received 4 or more drugs but their blood pressure is on target. More recently, a new extreme phenotype of resistant hypertension has been proposed that has been referred to as *refractory hypertension*, and is defined as the failure to control systolic and diastolic BP to less than 140/90 mm Hg after a minimum of 6 months of treatment by a hypertension expert despite multiple therapies.[4]

According to the literature, the prevalence of resistant hypertension in the hypertensive population is rather variable.[5–9] Thus, depending on the criteria used to define resistant hypertension and the type of population studied, resistant hypertension is estimated to affect 10% to 30% of hypertensive patients. In the National Health and Nutrition Examination Survey conducted between 2003 and 2008, 8.9% of all US adults with hypertension and 12.8% of the treated hypertensive population met the criteria for resistant hypertension (Fig. 1).[7] A large Spanish survey recently examined the clinical characteristics of patients with resistant hypertension and found it to be present in 12% of the treated population, although approximately one third of these patients had white-coat hypertension during ambulatory blood pressure monitoring (ABPM).[9] Of note, these 2 studies included patients

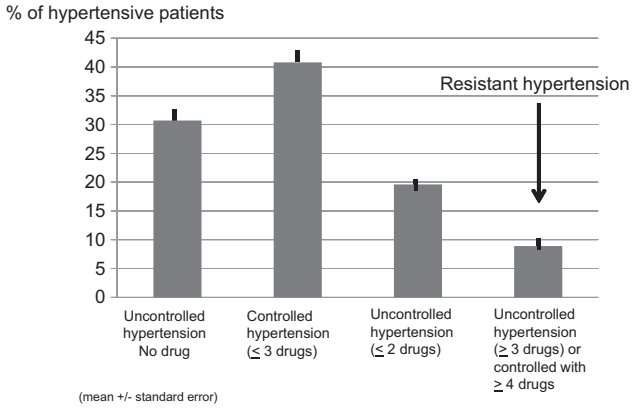

Figure 1. Prevalence of resistant hypertension in the US population. Uncontrolled hypertension means a blood pressure greater than 140/90 mm Hg. Data from Persell.[7]

with controlled resistant hypertension (ie, patients controlled with ≥4 medications) in their evaluation. In a very recent analysis, the prevalence of refractory hypertension was investigated in a large population cohort of more than 30,000 hypertensive patients in North America. The prevalence of refractory hypertension was found to be 0.5% in the general hypertensive population and 3.6% among patients with resistant hypertension.[10] In this analysis, the prevalence of refractory hypertension was higher among blacks, diabetic patients, and patients with albuminuria when compared with patients with resistant hypertension. In a retrospective study, 2% of patients with newly diagnosed hypertension developed resistant hypertension within 2 years.[11] These figures suggest that resistant hypertension is an important issue that largely has been disregarded until recently. The early identification of patients with resistant hypertension is nonetheless of upmost importance because these patients have a 50% increase in their relative risk of developing cardiovascular outcomes compared with the usual hypertensive population.[11] In this respect, clinical as well as observational studies have shown that resistant hypertension is associated strongly with the presence of obesity, type 2 diabetes, and chronic kidney disease.[7,9,12]

PSEUDORESISTANCE VERSUS TRUE RESISTANCE: THE ROLE OF AMBULATORY BLOOD PRESSURE

There are multiple reasons why a patient may be or become resistant to the prescribed antihypertensive therapy and hence does not reach their target BP values (Table 1). Before discussing in more detail the various mechanisms involved in resistance to therapy it is crucial to consider the distinction between *true resistance* and *pseudoresistance*, which essentially result from issues of blood pressure measurement and adherence to therapy. Indeed, the definition of resistant hypertension implies

Table 1. Multiple Causes of Resistant Hypertension

Diagnostic causes of resistance
Pseudoresistance caused by white-coat hypertension
Secondary forms of hypertension: primary hyperaldosteronism, renal artery stenosis, chronic kidney disease, sleep apnea syndrome, diabetes
Diet-related causes of resistance
Excessive salt intake
High alcohol consumption
Obesity
Metabolic syndrome
Medication-related causes of resistance
Inadequate dosages
Inappropriate drug combinations
Inappropriate diuretic therapy or dosage
Medication intolerance
Drug with vasopressive properties (eg, nonsteroidal anti-inflammatory drugs, sympathicomimetics, contraceptives, cyclosporines, corticosteroids)
Herbal medicines
Drug interactions: inhibitors of CYP17A1
Poor drug adherence (low persistence)

that spurious causes of resistant hypertension are excluded.[1] In most epidemiologic and observational studies published to date, the prevalence of resistant hypertension has been based mainly on office blood pressure measurements. Although office BP remains the reference for general practitioners, one has to re-emphasize some important limitations of this method of assessing BP, particularly when used for classifications. Indeed, office BP may be increased spuriously, leading to misdiagnosis of resistant hypertension.

AMBULATORY BP MONITORING FOR THE DIAGNOSIS OF RESISTANT HYPERTENSION

The limitations of office BP measurements to diagnose essential hypertension were recognized more than 30 years ago and it was at this time that ambulatory BP monitoring was developed to improve the recognition of hypertension. The multiple advantages of 24-hour ABPM have been reviewed recently and include the following: the absence of a white-coat effect as a result of the hospital environment, the absence of a placebo effect, a better assessment of BP at night, and indications of BP variability.[13] In addition, as shown by Waeber et al,[14] ABPM enables the identification of patients who legitimately need a therapeutic intervention for hypertension because they truly are hypertensive. ABPM is now promoted by the British Hypertension guidelines, which have recognized not only its usefulness for the management of hypertension, but also its cost effectiveness.[15] In more recent years, important information has been gathered with