Epidemiology of Resistant Hypertension

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Resistant hypertension is an entity that has gained a lot of attention in recent years. The prevalence and prognosis of resistant hypertension have not yet been examined by proper population studies, but data from several sources suggest that this entity is not uncommon and is associated with an elevated risk of hypertensive complications. Moreover, several factors and conditions that can interfere with blood pressure control such as excess sodium intake, obesity, diabetes, older age, kidney disease, and certain identifiable causes of hypertension were shown to be common among patients with resistance to antihypertensive treatment. Importantly, the prevalence of several of these conditions has been increasing continuously during the past years, suggesting a future increase in the frequency of resistant hypertension. This article will discuss current knowledge and associated future implications relevant to the epidemiology of resistant hypertension. *J Clin Hypertens (Greenwich).* 2011;13:523–528. ©2011 Wiley Periodicals, Inc.

Hypertension represents the most common chronic disease in the Western world, with an estimated prevalence in the adult population of more than 25%,[1] and a major risk factor for cardiovascular disease (CVD), including coronary artery disease, heart failure and stroke, chronic kidney disease (CKD), and death.[2–4] Thus, suboptimal blood pressure (BP) was previously characterized as the primary attributable risk for death worldwide, accounting for 62% of cerebrovascular disease, 49% of ischemic heart disease, and more than 7 million deaths per year.[5]

Essential hypertension is a disease with complex and incompletely understood etiology. The relative contribution of the numerous factors that have been implicated in the pathogenesis of hypertension can vary substantially among hypertensive individuals and, thus, efficacy of treatment regimens also varies among subgroups of patients.[2] Most importantly, activation of an increased number of etiologic mechanisms in one individual can result in great difficulties in controlling BP even with multiple drugs, ie, in hypertension that is resistant to treatment.

This article will discuss the epidemiology of resistant hypertension, including the prevalence and prognostic implications of the disease, as well as conditions associated with pseudoresistance and truly resistant hypertension.

DEFINITION OF RESISTANT HYPERTENSION

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines included a formal definition of resistant hypertension, which helped towards the formation of a stable reference context for both research activities and clinical discussions in the field in recent years. Resistant hypertension was described as failure to achieve goal BP (<140/90 mm Hg in the general hypertensive population and <130/80 mm Hg in patients with diabetes or CKD) when patients adhere to full doses of an appropriate regimen of 3 antihypertensive drugs, including a diuretic.[2] According to a relevant position statement,[6] although this definition may be arbitrary regarding the number of medications required, it has a clear scope from a clinical standpoint, ie, to identify patients who are at high risk of having reversible causes of hypertension and/or patients who, because of persistently high BP levels, may benefit from special diagnostic and therapeutic considerations.

Importantly, the above definition does not apply to patients who have recently been given a diagnosis of hypertension and/or have not yet received appropriate treatment regardless of their BP level.[7] In addition, "resistant hypertension" is not synonymous with "uncontrolled hypertension," which includes all hypertensive patients without BP control under treatment, ie, those receiving an inadequate treatment regimen, those with poor adherence, those with undetected secondary hypertension, and those with true treatment resistance. Further, a small portion of patients can have at the same time resistant and controlled hypertension, ie, patients whose BP is controlled with full doses of ≥4 medications.[6,8]

PREVALENCE OF RESISTANT HYPERTENSION

Despite the growing number of clinical studies on resistant hypertension in the past decade, the prevalence of this entity has not yet been properly examined. An accurate determination of it would require a prospective cohort study in a large hypertensive population performing estimations after forced titration to full doses of at least 3 antihypertensive medications,

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including a diuretic, as well as exclusion of causes of pseudoresistance. A less informative alternative would be a cross-sectional study that included an adequate sample of the overall population of unselected hypertensive patients. As of this writing, however, there is a characteristic paucity of studies like the above, and the relevant information is derived from 3 types of studies: (1) retrospective cohort studies, (2) data on the control of hypertension from population studies, and (3) data from the selected populations of major outcome trials.

Several retrospective studies have examined the prevalence of resistant hypertension in various settings. Overall, smaller studies suggest a prevalence ranging from around 5% in general practice, with little selection of patients, to 50% or higher in nephrology clinics, including patients with CKD.[9] Among studies in larger cohorts that examine the epidemiologic characteristics of resistant hypertension, two included patients visiting a tertiary hypertension facility for the first time and showed the prevalence to be 11%[10] and 21%,[11] respectively. Perhaps the situation in the general hypertensive population is best reflected in a recent retrospective study that examined records of an electronic medical database including data from about 100 practice sites and 9700 clinicians (mostly primary care specialists). In this study, among 29,474 adult patients with a diagnosis of hypertension who completed a yearly follow-up within the system, a diagnosis of resistant hypertension based on the formal definition could be made in about 9%. Interestingly, another 6% of the population could not achieve adequate control despite taking 3, 4, or more drugs in the absence of a thiazide diuretic.[12] Overall, studies of this type provide important information, but suffer from several limitations, including the retrospective type of the analysis and the fact that relevant data were based on simple clinical readings and, therefore, no distinction can be made between pseudoresistance and true resistance, as described below.

Data from major population studies on prevalence, awareness, treatment, and control of hypertension can also be used to approximate the prevalence of resistant hypertension. In the United States, the series of the National Health and Nutrition Examination Surveys (NHANES) suggest that the net and age-adjusted prevalence of hypertension has been constantly increasing through the past decades, but the proportions of adults with hypertension who are aware of their disease, receive antihypertensive treatment, and keep their BP under control have also considerably improved from 1976 to 2000.[13,14] Recent data suggest that about 37% of the total hypertensive population and 58% of patients taking antihypertensive medication achieve BP levels <140/90 mm Hg.[14] However, control rates among high-risk individuals, ie, patients with diabetes and CKD, are much lower, especially with application of the more strict BP goal of 130/80 mm Hg for these groups.[14–17] Of note, either in the general hypertensive population or in patients with diabetes or CKD, inadequate control of systolic BP (SBP) is the main culprit responsible for poor control rates.[14,17,18] Similar data from Europe suggest a much worse situation, with control rates among treated hypertensives ranging between 19% and 40% in 5 countries examined in large surveys.[19] These low rates of control suggest that resistant hypertension is not uncommon, but accurate estimations cannot be made from such studies since they do not provide information on the number, type, and dosage of antihypertensive agents used.

Another indirect source of data regarding the burden of resistant hypertension is the control rates of major outcome trials in hypertension, especially of those with large and diverse cohorts.[6,7,20] In such studies, medications are provided at no charge, adherence is closely monitored, and titration is dictated by the protocol. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) enrolled more than 33,000 patients older than 55 years with hypertension and at least one additional cardiovascular risk factor. After 5 years, about 49% of participants were controlled on 1 or 2 drugs, and, at study completion, 27.3% of patients were taking ≥3 drugs. However, only 68% of patients taking chlorthalidone, 66.3% taking amlodipine, and 61.2% taking lisinopril achieved goal BP.[21] In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, which included patients with hypertension and left ventricular hypertrophy (LVH), only 48% of patients taking losartan and 45% taking atenolol achieved BP <140/90 mm Hg after a mean follow-up of 4.8 years.[22] In the International Verapamil-Trandolapril Study (INVEST), enrolling more than 22,000 patients with hypertension and CVD, 65% of participants in the calcium antagonist arm and 64% in the non–calcium antagonist arm achieved the goal for SBP at 24 months of follow-up. These control levels were achieved with the use of an average of 3.2 drugs.[23] Recent data from the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension trial, including hypertensive patients with 1 or 2 additional risk factors, suggest that better BP control (around 80% of participants) can be achieved with a strategy of starting with fixed-dose combination therapy. However, for these control rates to be possible, about 60% of participants had to receive maximal doses of combination therapy at 6 months, and 32% of them to be taking ≥3 drugs after 1 year of follow-up.[24] All these studies also suggest that resistant hypertension is not uncommon. However, such data provide at best only rough approximations of the actual burden of resistant hypertension, because, in most cases, a combination of 3 drugs of the classes most commonly prescribed in the clinical setting was not feasible due to the actual comparisons of each protocol, the populations studied were relatively older and had additional risk factors,

and in some cases patients with difficult to treat hypertension were excluded.[6]

PROGNOSIS OF RESISTANT HYPERTENSION

Similar to the actual prevalence of resistant hypertension, the long-term prognosis of individuals with resistant hypertension compared with hypertensive patients without this syndrome, ie, with hypertension controlled with an appropriate regimen of $\leq$3 antihypertensive drugs, has not been accurately determined. However, relevant lines of evidence again suggest that prognosis in treatment-resistant patients who typically present with a longstanding history of poorly controlled hypertension is likely to be unfavorable. Previous case control studies show that patients with resistant hypertension carry a higher burden of target organ damage, such as LVH, carotid intima-media thickening, retinal lesions, and microalbuminuria than those with satisfactory BP control.[25] Most importantly, major population studies on hypertension prognosis indicate that the relative risks of myocardial infarction, stroke, heart failure, renal failure, and other morbidities are directly related to the degree of BP elevation.[3,4] Further, patients with resistant hypertension usually present with a combination of other cardiovascular risk factors, such as obesity, diabetes, and CKD, that further elevate the risks of morbidity and mortality.[26]

Of note, recent studies suggest that ambulatory BP monitoring (ABPM) may have a special role in assessing cardiovascular risk in resistant hypertension. A prospective cohort study including 556 resistant hypertensive patients showed that elevations in ambulatory SBP and diastolic BP were associated with cardiovascular morbidity and mortality after adjustment for age, sex, body mass index, diabetes, smoking, physical inactivity, dyslipidemia, previous cardiovascular diseases, serum creatinine, number of antihypertensive drugs used, and office BP, whereas office BP did not have independent prognostic value.[27] Subsequent analyses of the same authors showed that other parameters derived from ABPM recordings, such as non-dipping nighttime BP pattern and ambulatory arterial stiffness index, were also independently associated with cardiovascular morbidity and mortality.[28,29] These data suggest that ABPM may be useful in resistant hypertension not only for diagnostic (ie, recognizing patients with white coat effect and pseudoresistance) but also for prognostic purposes.

To what extent the risks of morbidity and mortality related to resistant hypertension are reduced with adequate therapy has not been evaluated.[26] However, the benefits of successful treatment in these individuals are likely to be substantial, as evidenced by major outcome studies in the field, where the greater the baseline BP levels and/or the larger the decrease in BP, the greater the reductions in hypertension-associated target organ damage.[30,31]

PATIENT CHARACTERISTICS AND ASSOCIATED CONDITIONS

Factors Related to ''Pseudoresistance''

Pseudoresistance describes the appearance of lack of BP control under appropriate treatment in a patient who does not actually have resistant hypertension. Several factors may contribute to elevated BP readings and produce the perception of resistant hypertension (Table I).[6,7,9,20] Previous studies have shown that such interfering factors are particularly common in patients referred to hypertension clinics with the diagnosis of resistant hypertension.[10,11] Thus, treating physicians should carefully evaluate the patient to exclude such factors before labeling someone as resistant hypertensive and perform further diagnostic testing and overtreatment.

Improper office BP measurement technique is a frequent cause of pseudoresistance. Several common mistakes (not leaving the patient to sit quietly for adequate time, single instead of triple readings, use of small cuffs, recent smoking) often result in falsely high BP readings.[6,7,20] The white coat effect (elevation of BP during a clinical visit resulting in higher BP readings in the office than those in the home or with the use of ABPM) is also common, since about 25% of patients with perceived resistant hypertension turn out to have controlled BP when ABPM is used.[32] Further, the presence of heavily calcified or arteriosclerotic arteries that cannot be fully compressed (usually in elderly individuals) can also result in overestimation of intra-arterial BP.[20]

Another frequent finding in patients who appear to have resistant hypertension is a suboptimal antihypertensive regimen (eg, inappropriate choices of drugs and combinations for the given patient characteristics, inadequate doses, inappropriate use of diuretics, no intensification of therapy).[10,11] Absence of proper changes in antihypertensive medication when the

TABLE I. Factors Related to ''Pseudoresistance''

Improper blood pressure measurement
White coat effect
Heavily calcified or arteriosclerotic arteries that are difficult to compress (in elderly individuals)
Related to antihypertensive medication
Inadequate doses
Inappropriate combinations
Physician inertia (failure to change or increase dose regimens when not at goal)
Poor patient adherence
Side effects of medication
Complicated dosing schedules
Memory or psychiatric problems
Poor relations between doctor and patient
Inadequate patient education
Costs of medication

patient is not at goal reflects the phenomenon of clinical inertia, which is defined as the conscious decision of clinicians to not adequately treat a condition despite knowing that it is present in the patient. Relevant studies suggest that this phenomenon is common among American physicians who treat patients with hypertension.[33] Poor adherence of the patient to an adequate antihypertensive regimen is another important cause of pseudoresistance.[26] Previous studies report that up to 40% of newly diagnosed hypertensives will discontinue their medications during the first year and <40% will continue taking their drugs during 10 years of follow-up.[34,35] Potential causes of limited adherence include side effects of drugs, complicated dosing schedules, presence of memory deficits or psychiatric disorders, poor patient-doctor relationships, failing to educate the patient on the importance of achieving BP goals, and high cost of medication, which can be very important in countries without public health systems.

Factors Contributing to Truly Resistant Hypertension

Apart from the aforementioned parameters, a number of lifestyle or biological factors and associated conditions can contribute to failure of achieving BP goals despite effective treatment, ie, to true resistance (Table II).

Excess dietary salt leading to volume overload in susceptible patients is a factor involved in many cases of resistant hypertension. About 90% of patients with resistant hypertension were shown to have expanded plasma volume.[36] Excessive sodium intake is frequent in Western societies and processed foods represent its most common source.[6,20] Most hypertensive patients have inordinately high salt intake, but in patients with resistant hypertension, this may be even higher, exceeding 10 g/d.[37] This can contribute to resistant hypertension both by increasing BP and by blunting the BP-lowering effect of several classes of antihypertensive agents, effects that are more pronounced in salt-sensitive patients, ie, African American, elderly, obese, and those with CKD. Modest consumption of alcohol is not generally associated with BP increases, but large amounts (>3–4 drinks daily) are related to increases in BP and the risk of hypertension, while reduction of alcohol ingestion was associated with reductions in BP levels.[2,38] Earlier data have shown that heavy drinkers were much less likely to achieve control of BP compared with hypertensive patients who did not consume large alcohol quantities.[39] It has therefore been suggested that heavy alcohol intake may contribute to resistant hypertension.[6,7]

Increased body weight is also associated with more severe hypertension, need for an increased number of antihypertensive medications, and a decreased likelihood of achieving BP control.[40] Obesity contributes to BP elevation through various mechanisms, such as insulin resistance/hyperinsulinemia, impaired sodium excretion, increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone system, presence of obstructive sleep apnea, and relative reductions in active drug levels.[6,20] Importantly, the prevalence of obesity is constantly increasing in developed societies and is the main factor driving the upward trends in the incidence of relevant disorders (diabetes, hypertension, and high cholesterol) within the context of the metabolic syndrome.[41] Given the associations between obesity and treatment resistance, these trends may result in increasing prevalence of resistant hypertension. The presence of diabetes also makes hypertension control difficult, as evident from several population studies, where control rates of hypertension in diabetic patients were low, especially with the threshold of 130/80 mm Hg, despite the efforts to increase physicians' awareness on the importance of control.[14,42] The increased prevalence of obesity and CKD among individuals with diabetes are among the major causes of treatment resistance. The continuous rise in the prevalence of diabetes[41] can also further deteriorate the problem of resistant hypertension.

In addition, older age has been associated with poor hypertension control.[20] Arterial stiffening with increasing age is the cause of a continuous increase in SBP

TABLE II. Factors Contributing to Resistant Hypertension

Volume overload
Excess sodium intake
Inadequate diuretic therapy
Volume retention from kidney disease
Excess alcohol intake
Obesity
Diabetes
Older age
Drug-induced
Nonsteroidal anti-inflammatory drugs (including cyclooxygenase-2 inhibitors)
Sympathomimetics (decongestants, anorectics)
Cocaine, amphetamines, other illicit drugs
Oral contraceptive hormones
Adrenal steroid hormones
Erythropoietin
Cyclosporine and tacrolimus
Licorice (included in some chewing tobacco)
Over-the-counter dietary and herbal supplements (eg, ginseng, ma huang)
Identifiable causes of hypertension
Renal parenchymal disease
Renovascular disease
Primary aldosteronism
Obstructive sleep apnea
Pheochromocytoma
Cushing's syndrome
Thyroid diseases
Aortic coarctation

after the age of 55 to 60 years, which together with stability or small decreases in diastolic BP produces the phenomenon of isolated systolic hypertension.[2,20] The fact that high SBP levels is the main culprit responsible for poor control rates both in the general population of hypertensives and patients with diabetes or CKD,[14,17,18] also supports the association between increasing age and resistant hypertension. Obviously, the aging of the Western populations[43] will be a major factor driving the future rise in the prevalence of hypertension (including resistant hypertension), particularly since the frequency of all related conditions (eg, obesity, diabetes, CKD) also increases with advancing age.[13,41,44]

Another common cause of treatment resistance is intake of pharmacologic agents that increase BP.[6,20] The effect of such agents are individualized. Most people manifest little effect, but some may experience severe BP elevation. Nonsteroidal anti-inflammatory drugs are the most commonly used drugs of this category. They increase mean BP by about 5.0 mm Hg and interfere with the BP-lowering effect of several antihypertensive drug classes through inhibition of renal prostaglandin production with subsequent sodium and fluid retention, effects that may be worse in individuals with reduced renal reserve. Use of selective cyclooxygenase-2 inhibitors has similar effects.[6,26] Sympathomimetic agents (nasal decongestants, anorectic pills, cocaine), oral contraceptives, glucocorticoids, anabolic steroids, erythropoietin, cyclosporine, and licorice (included in oral tobacco and herbal supplements) are also commonly used agents that may raise BP.[6,26]

The presence of CKD is perhaps the most frequent unappreciated medical cause of resistant hypertension.[26] Kidney disease can be both a cause and a consequence of hypertension. Identification of renal parenchymal disease as a cause of hypertension usually occurs only in severe cases of patients with recently diagnosed hypertension. In most cases, essential hypertension, which is practically the most important contributor to CKD,[31] will lead to progressive renal damage. The impaired ability to excrete sodium loads with kidney function deterioration will interfere with BP control, establishing a vicious circle between hypertension and CKD. This difficulty in achieving hypertension control is exemplified by the high number of antihypertensive compounds (average, 3 or 4) needed to achieve conventional BP goals in major clinical trials on CKD.[20] Reliance on serum creatinine measurements, which can be normal or near normal in many patients with mild renal dysfunction,[31] will hide this contribution of CKD in patients with resistant hypertension. This can lead to use of inappropriate antihypertensive medication (especially regarding type and dosing of diuretics) and treatment resistance.[26]

Apart from renal parenchymal disease, other causes of secondary hypertension can also be present in patients with resistant hypertension. Although the exact prevalence is largely unknown, about 5% to 10% of patients with resistant hypertension may have an undiagnosed identifiable cause.[10,11] Previous studies suggested that primary aldosteronism and obstructive sleep apnea are particularly common in patients with resistant hypertension,[6,45,46] and research interest has turned towards the efficacy of aldosterone blockade in such individuals. A recent population study including more than 1600 individuals presenting in a tertiary clinic with resistant hypertension showed that a definite diagnosis of primary aldosteronism after extensive work-up could be made in about 11% of patients.[47] Although this percentage is lower than reported in smaller studies, it clearly suggests that aldosterone excess is an important cause of treatment resistance. Thus, in patients with resistant hypertension, the presence of the above causes of secondary hypertension should always be examined and a concerted search for other identifiable causes, such as renovascular disease, pheochromocytoma, Cushing's syndrome, hyperparathyroidism and hypoparathyroidism, and others (Table II) may be needed according to clinical and laboratory findings.

CONCLUSIONS

The epidemiology of resistant hypertension is an important but still relatively understudied field. Although the prevalence of resistant hypertension has not been properly examined, indirect evidence from both population studies and clinical trials suggest that it is a common clinical problem. Similarly, previous data directly connecting the risk of hypertensive complications with the level of BP and showing resistant hypertension to carry a higher burden of target organ damage suggest that this entity has an unfavorable prognosis. Factors that produce a false impression of resistance are common in patients referred with ''resistant hypertension'' and should be carefully excluded. However, the most important notion from an epidemiologic standpoint is that factors and conditions that cause true elevations of BP (eg, excess sodium or alcohol intake, use of exogenous substances, obesity, diabetes, older age, CKD, and certain identifiable causes of hypertension) are not only common but in many countries are also continuously increasing in prevalence. These observations suggest that resistant hypertension will be a major clinical problem in the future and call for additional research activities and clinical focus on this particular field.

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