Resistant Hypertension
An Update of Experimental and Clinical Findings

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An estimated 10% to 30% of hypertensive patients can be considered to be resistant to treatment defined as controlled or uncontrolled blood pressure (BP) with use of ≥4 medications, including a diuretic.[1–4] A large number of cross-sectional and longitudinal studies have demonstrated that patients with treatment-resistant hypertension compared with patients with more easily controlled hypertension have increased cardiovascular risk, including coronary artery disease, congestive heart failure, stroke, and chronic kidney disease (CKD).

Since publication of the first Scientific Statement on the Diagnosis, Evaluation, and Treatment of Resistant Hypertension by the American Heart Association in 2008, which coincided with development of device-based strategies for treating resistant hypertension, resistant hypertension has become a major focus of intensive experimental and clinical investigation.[1] In that context, this review highlights scientific advances specific for resistant hypertension that have occurred in the last 2 years, including important findings related to prognosis, medication adherence, clinical use of aldosterone antagonists, and application of device-based therapies.

Prognosis

Multiple cross-sectional studies have related resistant hypertension to prevalent cardiovascular and renal diseases.[2–8] Recent analyses have strengthened those associations with use of longitudinal or prospective assessments. From a secondary analysis of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) results, which included 1870 participants with resistant hypertension, Muntner et al[9] reported that compared with study participants without resistant hypertension, participants with resistant hypertension had a 44%, 57%, 23%, 88%, 95%, and 30% higher risk of incident coronary heart disease, stroke, peripheral artery disease, heart failure, end-stage renal disease, and all-cause mortality, respectively, during the almost 5-year duration of the study after adjustment for multiple traditional risk factors, such as age, smoking, diabetes mellitus, and low-density lipoprotein cholesterol. Because of the ALLHAT study design, diuretic use in this analysis was not required to define resistant hypertension; however, in the sensitivity analysis, which was restricted to subjects with diuretic treatment, resistant hypertension remained significantly associated with the specified clinical outcomes, except for stroke and all-cause mortality.

Diaz et al[10] evaluated the association of 6 different healthy lifestyle factors (normal waist circumference, physical activity ≥4 times/week, nonsmoking, moderate alcohol ingestion, high Dietary Approaches to Stop Hypertension diet score, low sodium-to-potassium ratio) and risk of cardiovascular complications and all-cause mortality among the 2043 participants with resistant hypertension in the REGARDS study (Reasons for Geographic and Racial Differences in Stroke). After a median follow-up of 4.5 years, compared with study participants with generally unhealthy lifestyles (ie, presence of ≤1 healthy lifestyle factor), those with healthy lifestyles (ie, presence of all 6 healthy lifestyle factors) had a substantially lower risk of cardiovascular events. Overall, a greater number of healthy lifestyle factors was associated with a lower risk of cardiovascular events, cardiovascular mortality, and all-cause mortality. Among the 6 healthy lifestyle factors, physical activity and nonsmoking were the most favorable in terms of prognosis.

Epidemiological studies have shown that CKD patients have a much higher prevalence of resistant hypertension than general hypertensive populations and that CKD patients with resistant hypertension have an increased prevalence of cardiovascular diseases compared with patients without resistant hypertension.[8,11]

Recently, 2 large multicenter, prospective studies further delineated the prognostic significance of resistant hypertension in CKD populations. de Beus et al[12] evaluated 788 CKD patients with a mean estimated glomerular filtration rate of 38±15 mL/min per 1.73 m^2. Around 34% of these patients met the diagnostic criteria for having resistant hypertension. After a median follow-up of 5.3 years, nearly 17% of the subjects with resistant hypertension had experienced a cardiovascular complication, including myocardial infarction, ischemic stroke, or death, and 27% had developed end-stage renal disease. Compared with subjects without resistant hypertension, those with resistant hypertension had a 1.5-fold and 2.3-fold higher risk of composite cardiovascular events and end-stage renal disease, respectively.

Analysis of data from the CRIC (Chronic Renal Insufficiency Cohort) Study indicated that among the 3367 CKD patients with an estimated glomerular filtration rate of 20 to 70 mL/min per 1.73 m^2, the prevalence of resistant hypertension was 40.4%.[13] Every 5 mL/min per 1.73 m^2 decrease in

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estimated glomerular filtration rate was associated with a 14% higher risk of having resistant hypertension. Compared with those without resistant hypertension, subjects with resistant hypertension had a poorer prognosis, with a 38%, 28%, 66%, and 24% higher risk of experiencing a cardiovascular complication, renal complication, incident heart failure, or death, respectively. Despite some differences in how resistant hypertension was defined between the above studies, these recent longitudinal analyses are important in consistently demonstrating that patients with resistant hypertension, especially those with concurrent CKD, have substantially impaired cardiovascular and renal prognosis compared with patients with more easily controlled hypertension.

While recent analyses clearly indicate that resistant hypertension is associated with a poorer prognosis than more easily controlled hypertension, data elucidating to what extent this increased risk can be reversed with treatment is still lacking. The SPRINT (Systolic Blood Pressure Intervention Trial) would have included a large proportion of subjects with resistant hypertension.[14] It will be of clinical interest to know if those subjects with resistant hypertension at baseline and randomized to intensive BP control (systolic BP <120 mm Hg) did better than those patients with resistant hypertension but randomized to routine BP control (systolic BP <140 mm Hg), consistent with the overall study findings. Such a subgroup analysis, however, has not yet been reported, but will no doubt be informative in terms of quantifying the benefit of intensive versus routine antihypertensive treatment.

Drug Adherence and Optimal Treatment

Prior studies have demonstrated that poor adherence is common in patients with presumed resistant hypertension. In that regard, the study by Jung et al,[15] which used liquid chromatography–mass spectrometry to assay the presence of prescribed antihypertensive medications or their corresponding metabolites in urine, was pivotal in finding that among 76 patients with presumed resistant hypertension, the majority (53%) were in fact nonadherent, including 30% of whom were taking none of the prescribed medications. Other studies have indicated that undertreatment is also common in patients with apparent resistant hypertension such that poor adherence and suboptimal therapy likely represent the 2 most important reasons for lack of BP control as opposed to true antihypertensive treatment resistance.[6]

Using population-based data of participants enrolled in a large, healthcare organization in Israel, Weitzman et al[16] reported that among the 172 432 hypertensive patients, the proportion of patients with uncontrolled hypertension was 35.9%. Of these, almost all were undertreated because of either receiving less than maximal dosages of prescribed medications (21%), not receiving a diuretic (9%), having been dispensed <3 agents (48%), or having been dispensed none of the prescribed agents (20%). Having excluded these patients, it was estimated that only ≈2.2% of the patients with uncontrolled hypertension met the strict criteria for resistant hypertension. These findings, combined with the demonstrations that poor adherence is common among patients with presumed resistant hypertension, suggest that lack of BP control in treated patients is much more likely attributable to the combination of undertreatment and poor adherence versus true treatment resistance.

Similar findings of undertreatment were documented by Hwang et al[17] who analyzed trends in antihypertensive medication use among US patients with resistant hypertension from 2008 to 2014. Using a large, national claims database, which contains medical and prescription claims data that is representative of patients covered by employer-based insurance programs, the authors found that among patients with resistant hypertension (ie, prescribed ≥4 antihypertensive agents), the use of chlorthalidone and spironolactone, the recommended diuretics for treatment of resistant hypertension, remains extremely low. In spite of recognized superiority over hydrochlorothiazide and recommendations to use it preferentially for treatment of resistant hypertension, chlorthalidone use had increased only by 2.6% between 2008 and 2014 in patients with resistant hypertension, such that, by the end of 2014, 92.9% of patients were still receiving hydrochlorothiazide versus the 6.4% receiving chlorthalidone. Likewise, in spite of a large body of literature clearly establishing the benefit of spironolactone for treatment of resistant hypertension, use of spironolactone remained low, being prescribed to only ≈10% of patients. Because it is well recognized that optimization of diuretic treatment is essential for the effective treatment of resistant hypertension, these findings highlight the need for better education of practitioners on how to optimize antihypertensive regimens, including specifically, use of chlorthalidone and spironolactone.

In a separate study, Fadl Elmula et al[18] further demonstrated the effectiveness of optimized pharmacological therapy for treatment of resistant hypertension. After excluding subjects who were likely nonadherent with prescribed medications, patients with resistant hypertension were randomized to renal nerve denervation (RND) or to adjustment of pharmacological therapy as guided by measurement of thoracic impedance. Although the number of study subjects was small (9 randomized to titration of drug therapy and 10 to RND), guided medication adjustment was superior to RND as indicated by reduction in office systolic and diastolic BP at 6-month follow-up. The change in office BP levels was likewise reflected by corresponding changes in ambulatory BP levels. These findings further support the contention that seemingly resistant hypertension is often attributable to poor medication adherence or undertreatment.

Renal Nerve Denervation

Substantial antihypertensive benefit of RND for treatment of resistant hypertension has been observed in randomized, but unblinded clinical trials.[19,20] In contrast, more rigorous blinded trials have not confirmed benefit of RND compared with sham procedure.[21] In the last 2 to 3 years, many experimental and clinical studies have been done exploring potentially mediating factors related to the BP or lack of BP response with RND. One important factor may be the presence of accessory renal arteries, which, because of small diameters, may have precluded effective denervation. Such an effect was supported by de Jong et al[22] who found that in patients treated with RND, increases in BP induced by renal nerve stimulation were substantially blunted after denervation of the main renal arteries.

In contrast, renal nerve stimulation–induced BP elevations remained intact if accessory renal arteries had not been denervated. These findings suggest that the presence of accessory renal arteries that cannot be denervated may serve as important residual sources of sympathetic output.

Another potential factor related to long-term antihypertensive effectiveness of RND may be the degree of reinnervation of renal nerves postprocedure. In that regard, Booth et al[23] used functional, anatomic, and biochemical assessments to investigate the degree of reinnervation of the kidneys in normotensive sheep after RND. Immediately after denervation, renal sympathetic nerve activity was absent, and responses to renal nerve stimulation were blunted. However, at 11-month postprocedure, renal sympathetic nerve activity and responses to electric stimulation had returned to normal. This functional recovery was corroborated by histological and biochemical findings consistent with regrowth of ablated nerves.

In spite of the above experimental findings indicating reinnervation of kidneys in <1 year after RND, recent studies seemingly confirm persistent sympatholytic effects of RND in humans for at least 1 year. For example, Ewen et al[24] found that the suppressive effects of RND on BP and heart rate at rest and during physical exertion and recovery were still present 12 months postprocedure. Likewise, in the EnligHTN I First-in-Human Study, Papademetriou et al[25] reported that RND-induced reductions in office and ambulatory BP levels in patients with resistant hypertension were sustained 1-year postintervention. The apparent functional reinnervation of kidneys post-RND in less than a year that is observed in animal studies versus the >1-year antihypertensive benefit of RND that is observed in humans suggests that the mechanisms of the presumed sympatholytic effects of RND likely cannot be attributed simply to long-term renal nerve ligation and that other, as of yet unexplained, effects must be occurring.

Patients with long-standing and often severe hypertension typical of resistant hypertension likely have some alteration in renal nerve or renal function that could mediate or even blunt the response to RND. If true, one might anticipate a more favorable response to RND in patients with less severe hypertension, that is, mild resistant hypertension. To test for such a difference, Desch et al[26] evaluated the benefit of RND in 71 patients with mild resistant hypertension defined as daytime systolic BP of 135 to 149 mm Hg or daytime diastolic BP of 90 to 94 mm Hg as measured by ambulatory BP monitoring. The study was done as a blinded, randomized comparison to sham procedure. Interestingly, there was no significant reduction in 24-hour systolic BP compared with sham RND at 6-month follow-up as analyzed per intention-to-treat, although there was a small, but significant difference in favor of RND when analyzed per protocol. These findings are informative in suggesting that the benefit of RND likely varies between patient subgroups, particularly in regards to duration or severity of the underlying hypertension.

Relatedly, evaluation of 731 patients with resistant hypertension referred to 11 different European hypertension specialty centers for consideration of RND for treatment of resistant hypertension found that only 40% of patients were eligible for RND.[27] The main reasons of being ineligible were normalization of BP after adjustment of the antihypertensive regimen, recognition of secondary hypertension, and unsuitable renal artery anatomy. These findings, combined with recent study findings discussed earlier, emphasize that even among patients with presumed true resistant hypertension, a large proportion will not benefit from RND from simply being ineligible, based on currently applied guidelines, or because of limited or no BP reduction. The findings, however, also highlight the need to better identify which patients are likely to benefit from the intervention; to what extent eligibility criteria can be modified to potentially broaden the clinical role of RND for treatment of resistant or even nonresistant hypertension; and to identify and overcome current technological limitations that may blunt the effectiveness of RND.

Baroreflex Activation Therapy

Two recent clinical studies provided important insight into the potential benefit of baroreflex activation therapy for treatment of resistant hypertension based on unilateral as opposed to bilateral carotid sinus stimulation. In the first study, Heusser et al[28] found that acute stimulation of the carotid sinus via a unilaterally implanted electrode acutely lowered both systolic and diastolic BP in 18 patients with uncontrolled resistant hypertension. There was not a significant change in muscle sympathetic nerve activity, but overall, reductions in diastolic BP did correlate with reductions in muscle sympathetic nerve activity. There was a wide range in the magnitude of BP and muscle sympathetic nerve activity reduction after acute carotid sinus stimulation, and about two thirds of the subjects experienced stimulation-related adverse effects, necessitating reduction in the stimulation intensity.

The acute findings described by Heusser et al[28] were extended by Wallbach et al[29] who reported, based on an unblinded, uncontrolled assessment, that unilateral carotid sinus stimulation significantly reduced 24-hour ambulatory systolic and diastolic BP in 65 patients with uncontrolled resistant hypertension 6 months after device implantation. The achieved reduction in BP allowed for a small decrease in the average number of prescribed antihypertensive medications (from 6.5 to 6.0). Combined, these 2 studies are important in demonstrating the efficacy of unilateral carotid sinus stimulation for treatment of resistant hypertension. Randomized controlled trials are now needed to confirm and quantify this benefit.

Use of Aldosterone Antagonists

A large number of studies have demonstrated the efficacy of spironolactone for treatment of resistant hypertension.[30–32] These studies, however, were often limited in being single center studies of small cohorts or having been done in an unblinded and uncontrolled fashion. These limitations were overcome with publication of the PATHWAY-2 results.[33] In a rigorous, blinded, placebo-controlled, crossover evaluation of a large cohort of patients with confirmed resistant hypertension, Williams et al[33] reported that spironolactone, as a fourth antihypertensive agent, was superior to doxazosin and bisoprolol based on reduction of home systolic BP. The PATHWAY-2 findings are clinically important in that they firmly establish spironolactone as the most appropriate fourth agent for treatment of resistant hypertension. The preferential benefit of aldosterone blockade for treatment of resistant hypertension is consistent with a large body of literature demonstrating that resistant hypertension is commonly characterized by varying degrees of hyperaldosteronism and accompanying intravascular fluid retention.

In a randomized, open-label, multicenter evaluation, intensification of pharmacological therapy, including use of spironolactone, was compared with RND for treatment of resistant hypertension in the PRAGUE-15 Study.[34] The cohort consisted of 106 patients with confirmed resistant hypertension based on documentation of medication adherence, exclusion of secondary causes of hypertension, and exclusion of white coat effects by 24-hour ambulatory BP monitoring. At 6- and 12-month follow-up, the 2 interventions had induced comparable reductions in 24-hour ambulatory systolic BP.[34] In the DENERHTN trial (Renal Denervation for Hypertension), intensification of pharmacological therapy, including the addition of spironolactone, was compared, in open-label fashion, with RND in combination with intensification of pharmacological therapy in patients with confirmed resistant hypertension.[35] After 6-month follow-up, both interventions had significantly reduced 24-hour systolic BP, but RND had provided an additional 5.9 mm Hg reduction compared with intensification of pharmacological therapy alone. The divergent results of the PRAGUE-15 Study and the DENERHTN trial need to be reconciled with further evaluations, but the findings of the 2 studies suggest that RND and intensified pharmacological treatment with use of spironolactone will be complimentary and that, on an individual patient basis, both will be important options for overcoming treatment resistance.

Refractory Hypertension

Historically, the terms resistant and refractory hypertension have been interchangeable to refer to patients with difficult-to-treat hypertension. Recently, refractory hypertension has been applied in reference to an extreme phenotype of antihypertensive failure.[36,37] While the definition of refractory hypertension has been broadly based on failure to control BP with use of ≥5 antihypertensive agents of different classes, the most stringent definition has specifically required use of ≥5 agents, including a long-acting thiazide or thiazide-like diuretic, such as chlorthalidone, and an aldosterone antagonist, such as spironolactone. Based on the latter definition, refractory hypertension is rare, affecting only 5% to 10% of patients referred to a hypertension specialty clinic for uncontrolled resistant hypertension.[36,37]

Early studies of the phenotype suggest that it is more common in Blacks, women, and in patients with CKD and diabetes mellitus.[37–39] Unlike resistant hypertension, in general, indices of intravascular fluid status do not suggest that refractory hypertension is characterized by persistent fluid retention. Instead, indirect assessments of sympathetic tone suggest that refractory hypertension may be more neurogenic in pathogenesis, that is, secondary to heightened sympathetic to output.[37] While undertreatment, a common cause of pseudoresistance, is excluded by the definition of refractory hypertension, unknown is to what extent other pseudo-causes of treatment failure, such as poor medication adherence and white coat effect, contribute to apparent treatment failure.

Summary

Resistant hypertension remains a strong focus of both experimental and clinical research. Recent studies indicate that patients with resistant hypertension, particularly in the setting of CKD, have a worse prognosis than patients with more easily controlled hypertension. Apparent versus true resistant hypertension is an important clinical distinction, with the former often being attributable to pseudocauses of treatment resistance. Important study results indicate that poor adherence and undertreatment likely represent the 2 most common causes of lack of BP control versus true treatment resistance. From a treatment perspective, rigorous clinical trials have firmly established spironolactone as the most appropriate fourth agent for treating resistant hypertension. In regards to device-based therapies, experimental and translational studies suggest that RND will not likely be a universal solution for resistant hypertension. Recent study findings indicate that the presence of accessory arteries that cannot be accessed by ablation catheters may preclude adequate RND, thereby, minimizing benefit, while reinnervation of kidneys may be an important mediator of duration of antihypertensive benefit. Finally, initial studies of refractory hypertension, an extreme phenotype of antihypertensive failure, suggest that it is rare, but may represent a unique phenotype distinct from resistant hypertension in general by having a neurogenic pathogenesis as opposed to being volume dependent.

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