Update on Resistant Hypertension

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DIAGNOSIS OF RESISTANT HYPERTENSION

Roland E. Schmieder, MD, University Hospital of the Friedrich Alexander University, Erlangen/Nürnberg, Germany, discussed the diagnosis of treatment-resistant hypertension. While the terminology may differ, a common definition is the failure of treatment that includes antihypertensive drugs and lifestyle modification to lower blood pressure (BP) to appropriate levels [Calhoun DA et al. *Circulation.* 2008; Mancia G et al. *Eur Heart J.* 2007].

A working definition of resistant hypertension is an office systolic/diastolic BP ≥ 140/90 mm Hg despite adequate medical therapy (defined as adequate doses of at least 3 classes of drugs, 1 of which is a diuretic). True treatment-resistant hypertension becomes evident when BP measurements are done at different times of the day, usually involving self-measurements at home or 24-hour ambulatory BP monitoring. In the United States, data from the National Health and Nutrition Examination Survey indicated a rate of resistant hypertension of 8.9% among all hypertensive adults and 12.8% among drug-treated hypertensive adults [Persell SD. *Hypertension.* 2011]. Clinical determinants of resistant hypertension included albuminuria; reduced renal function; and self-reported chronic kidney disease, chronic heart failure, stroke, and diabetes mellitus.

The estimated rate of apparent resistant hypertension has increased over the past 20 years in the United States [Egan BM et al. *Circulation.* 2011]. It is clear that treatment-resistant hypertension is associated with a worse long-term cardiovascular prognosis [Kumbhani DJ et al. *Eur Heart J.* 2013].

Resistant hypertension is treated by identifying and reducing the influence of contributing lifestyle factors, minimizing or discontinuing compounds that exacerbate the hypertension, and screening for secondary causes.

SECONDARY CAUSES OF RESISTANT HYPERTENSION

Xavier Jeunemaitre, MD, PhD, European Hospital Georges Pompidou, Paris, France, discussed secondary causes of resistant hypertension, which reflect the complexity of BP regulation, with inputs from the structure and function of blood vessels, heart, and kidney and with neuroendocrine influences. The workup of secondary causes of resistant hypertension includes ruling out pseudo treatment-resistant hypertension and nonadherence to prescribed treatments. Evaluation should focus on drug-related causes, lifestyle factors, and volume overload. Other modifiable causes of treatment-resistant hypertension include obstructive sleep apnea, primary aldosteronism, renal artery stenosis, renal parenchymal disease, drug or alcohol abuse, and thyroid disorders (Table 1) [Vongpatanasin W. *JAMA.* 2014].

Predictors of sleep apnea include age > 50 years, neck circumference (≥ 41 cm for women, ≥ 43 cm for men), and snoring [Pedrosa RP et al. *Hypertension.* 2011]. Continuous positive airway pressure, which provides small but significant reductions in BP in patients with obstructive sleep apnea, should be considered for appropriate patients [Schein AS et al. *J Hypertens.* 2014].

Primary aldosteronism, which is the most frequent cause of secondary hypertension, is caused by excess secretion of aldosterone [Fernandes-Rosa FL et al. *Hypertension.* 2014; Choi M et al. *Science.* 2011]. Primary aldosteronism has been associated with increasing age, duration of hypertension, systolic and diastolic BP, potassium concentration, plasma aldosterone concentration, and adenoma size [Fernandes-Rosa FL. *Hypertension.* 2014].

In summary, secondary forms of hypertension—most frequently, primary aldosteronism—are common in resistant hypertension. Screening for these secondary forms can aid in medication choice and is useful in assessing the feasibility of renal denervation.

Table 1. Secondary Causes of Resistant Hypertension

Conditions	Prevalence in Resistant Hypertension, %	Diagnostic Tests
Obstructive sleep apnea	60–70	Polysomnography
Primary aldosteronism	7–20	Serum aldosterone, plasma renin activity
Renal artery stenosis	2–24	Duplex Doppler ultrasonography, computed tomographic angiography, or magnetic resonance angiography
Renal parenchymal disease	1–2	Serum creatinine
Drug-induced or heavy alcohol use	2–4	History taking
Thyroid disorders	< 1	Thyrotropin, free thyroxine

Adapted from Vongpatanasin W. *JAMA.* 2014.

PHARMACOLOGIC TREATMENT

Pharmacologic treatment of resistant hypertension was discussed by Bryan Williams, MD, University College London, London, United Kingdom. At least one-quarter of patients are noncompliant with BP-lowering medications. Noncompliance has been associated with the number of drugs prescribed [Tomaszewski M et al. *Heart.* 2014; Strauch B et al. *J Hypertens.* 2013]. While some of these patients will respond to therapy, others (< 10%) are truly resistant. One potentially efficient way to identify those who have treatment-resistant hypertension may be to screen for renin, given that about two-thirds of patients with proven resistant hypertension have low plasma renin (< 0.5 nmol/L/h) despite diuretic therapy [Eide IK et al. *J Hypertens.* 2004].

Of the various drug options, the effect of low-dose spironolactone (25 or 50 mg, twice daily) has been shown in multiple studies [Chapman NC et al. *Hypertension.* 2007; Sharabi Y et al. *Am J Hypertens.* 2006]. Current European Society of Cardiology–European Society of Hypertension guidelines (2013) for the management of arterial hypertension support the use of spironolactone, eplerenone, or the alpha-1 blocker doxazosin [Mancia G et al. *Eur Heart J.* 2013] in patients with resistant hypertension. Amiloride can also be used but is not recommended in patients with markedly reduced estimated glomerular filtration rate (eGFR).

Whether the effect of spironolactone on resistant hypertension reflects specific blockade of the aldosterone receptor or augmentation of ongoing diuretic therapy is unclear. If spironolactone is not effective, options include boosting the dose of thiazide-like diuretic, use of amiloride, use of frusemide in patients with low eGFR, use of eplerenone despite its comparatively lower efficacy [Parthasarathy HK. *J Hypertens.* 2011], or combinations of these agents. Optimal pharmacologic treatment may involve treatment stratification, with spironolactone used in cases of low plasma renin, alpha-blockade medications used for intermediate-level renin, and beta-blockade drugs used in cases of high plasma renin. More evidence is needed to inform this strategy.

In summary, the pharmacologic treatment of resistant hypertension needs more study, but poor compliance to therapy and undetected secondary causes are both important and underappreciated. Low plasma renin is likely important, and it is possible that sodium overload may contribute to resistant hypertension. Careful screening for secondary causes is essential, especially for adrenal adenoma in those with low plasma renin activity. Spironolactone is the first-choice therapy, with other diuretic therapy as warranted.

RENAL DENERVATION 4 YEARS ON: FOCUS ON LONG-TERM RESULTS

Murray Esler, PhD, Baker IDI Heart and Diabetes Institute, Melbourne, Australia, provided an overview of renal denervation, a 7-year-old technique in which a catheter is used to deliver radiofrequency ablation to renal arteries. Neurogenic hypertension is claimed to be the basis of half the cases of high BP [Easler M. *J Appl Physiol.* 2010]. Some studies suggest that renal denervation can lower BP and reduce renal sympathetic afferent and efferent activity.

Registry data from a number of globally conducted trials of renal denervation have revealed the 1- and 6-month safety of the approach. Yet, the SYMPLICITY HTN-3 study—which was the first placebo-controlled cardiovascular outcomes trial of renal denervation—indicated no reduction in BP with renal denervation [Bhatt DL et al. *N Engl J Med.* 2014]. The trial included 535 patients allocated 2:1 in a blinded fashion to active and sham treatment. The trial's primary end point was the mean change in office systolic BP at 6 months, and treatment with renal denervation had no effect on this end point. At 6 months, the change in 24-hour ambulatory systolic BP was not significantly different between the groups.

Prof Esler noted that SYMPLICITY HTN-3 exemplifies the weak spot in renal denervation research. Animal studies have provided evidence of the effectiveness of the approach, but similar outcomes have not been shown in clinical trials performed in well-treated humans. The catheter-based process is not easy and is usually incomplete, and success relies on the experience and talent of the operator. In the trial, the interventionalists performing the procedure had little experience in renal denervation, and there was no way to determine if renal denervation actually occurred. Thus, the trial may have failed because of the execution of the procedure, not necessarily because renal denervation does not work for resistant hypertension [Henegar JR et al. *Am J Hypertens.* 2014].

The development of a more reliable molecular test of renal denervation is needed. One target being explored is fragments of tyrosine hydroxylase excreted in urine.