Advances in resistant hypertension

David A. Calhoun

Vascular Biology and Hypertension Program, University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence to: David A. Calhoun, MD. 430 BMR 2, 1530 3rd Avenue South, Birmingham, AL35242-2180, USA. Email: dcalhoun@uab.edu.

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Resistant hypertension (RHTN) has historically been defined as high blood pressure (BP) that remains uncontrolled despite use of 3 or more antihypertensive agents from different classes, including ideally, a diuretic. In 2008, the first American Heart Association Scientific Statement on RHTN included a new category of "controlled RHTN" as high BP controlled on 4 or more antihypertensive agents (1). Defining RHTN separate from hypertension in general is done so to identify patients with difficult-to-treat hypertension that may benefit from special diagnostic and/or therapeutic considerations. Toward that end, the definition has served well in that RHTN is characterized by a high prevalence of secondary causes of hypertension, including hyperaldosteronism, renal vascular disease, and obstructive sleep apnea, such that more extended diagnostic evaluation is more often indicated than in patients with more easily controlled hypertension (2). The definition has also served well in standardizing enrollment criteria for research studies of RHTN, including recent clinical trials assessing a variety of device-based treatment strategies.

In the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of Hypertension in Adults, the definition of RHTN remains largely unchanged being diagnosed "*…when a patient takes 3 antihypertensive medications with complementary mechanisms of action (a diuretic should be 1 component) but does not achieve control or when BP control is achieved but requires ≥4 medications*" (3). As stated above, this definition has worked well as an effective starting point in terms of identifying high-risk patients who warrant special clinical consideration. However, recent studies indicate, beyond the current definition based solely on the number of prescribed medications, it is important for clinicians treating such patients to confirm true RHTN before initiating potentially expensive diagnostic evaluations and/or intensifying pharmacologic treatment. In that regard, it is now recognized that most uncontrolled hypertension is not truly resistant to treatment, but instead simply appears resistant (i.e., "apparent" RHTN) based on the number of prescribed medications. Accordingly, the initial step in evaluating a patient diagnosed with apparent RHTN is distinguishing true from pseudoresistant hypertension. Recent study findings demonstrate that pseudoresistance antihypertensive treatment is common and often attributable to falsely elevated BP levels because of poor BP technique, clinical inertial resulting in persistent undertreatment, and poor medication adherence. Each of factors needs to excluded in order to confirm true RHTN.

BP is often measured inaccurately in routine clinical settings. As some of the most common mistakes (i.e., using too-small of BP cuff, not letting the patient sit quietly for several minutes before measurement, taking a single BP reading, putting the BP cuff over clothing) results in falsely high readings, uncontrolled HTN is often misdiagnosed. Such an effect was demonstrated recently to be especially true of patients referred to a hypertension specialty clinic for uncontrolled RHTN (4). In this study, 130 consecutive patients with suspected RHTN had their BP measured firstly in a routine triage setting and then by trained clinicians using a standardized regimen consistent with current guidelines, including serial readings with use of an automated device. Triage readings were consistently higher than the readings by trained clinicians, such that 33% of the patients would have been misdiagnosed has

having uncontrolled RHTN. The difference in systolic and diastolic BP between the two assessments was as high as –33/–21 mmHg, respectively, with a median difference of 23/13 mmHg (4).

Studies also indicate that undertreatment is a common cause of pseudoresistant HTN. In a cross-sectional analysis that included >450,000 hypertensive patients being treating in primary care clinics in the southeastern United States, Egan *et al.* found that 32% were uncontrolled, and of those, 30% were prescribed ≥3 antihypertensive agents, meaning consistent with uncontrolled RHTN (5). But only 15% of those patients were receiving what was considered an optimal treatment regimen, defined as a 3 or more drug regimen that included a diuretic and with all agents being prescribed at least 50% of the recommended maximum dose for treatment of hypertension. Among patients receiving an effective regimen, including a diuretic, the mean number of prescribed medications was 4.2 for the uncontrolled group versus 4.9 for the controlled group, indicating that lack of BP control is often attributable to lack of treatment intensification, i.e., clinical inertia, resulting in persistent undertreatment.

Another common cause of pseudoresistance is poor medication adherence. Systematic detection of medications in blood or urine samples of patients participating in studies of renal denervation for treatment of RHTN indicate that at study start only about 30% of patients are fully adherent with prescribed antihypertensive agents, 50% are partially compliant, and about 20% are taking none of their prescribed medications (6). While there may be a selection bias in patients interested in participating in a device-based antihypertensive trial, i.e., they may be especially interested in not having to take medications, the overall poor adherence documented in such studies emphasizes that many patients with suspected RHTN are in reality taking only some, if any, of their prescribed antihypertensive agents. Determining adherence in routine clinical settings is difficult as clinician impression is often wrong and self-reported adherence is often overstated. Broadening use of electronic medical records may allow better monitoring of prescription refill rates, but having a medication refilled, especially if done automatically through a mail order service, does not ensure use of the pill as prescribed. Commercial laboratories are increasingly offering standardized testing of blood and/or urine for the presence of prescribed medications, but issues of patient consent and lack of insurance coverage for the testing need to be resolved to allow for routine clinical use.

Beyond the importance of accurately diagnosing RHTN, the other major advance in the clinical management of RHTN is the recent confirmation that RHTN is broadly attributably to excess sodium and fluid retention induced by relative degrees of aldosterone excess, and relatedly, the definitive demonstration of the superiority of mineralocorticoid receptor antagonists (MRAs), specifically spironolactone, for treating RHTN. These observations were both critical findings of the landmark PATHWAY-2 study (7,8). In this study, patients with confirmed RHTN who were uncontrolled on a standardized triple regimen of an angiotensin converting enzyme inhibitor or a angiotensin receptor blocker, a calcium channel blocker, and a diuretic were randomized to a double-blinded, four-way cross-over comparison of 3 months each of placebo, spironolactone 25–50 mg, bisoprolol 5–10 mg, or doxazosin 5–10 mg daily. Spironolactone was clearly superior to the other 2 classes of agents and placebo. Importantly, PATHWAY-2 also demonstrated that the full antihypertensive benefit of spironolactone was equally divided between the 25 and 50 mg dose, indicating that titration up to 50 mg, as tolerated, is clinically appropriate for patients who remain uncontrolled with the lower dose.

PATHWAY-2 included several substudies designed to explore underlying causes of RHTN, specifically, the role of aldosterone and excess fluid retention as important mediator of treatment resistance (7). The investigators found that a high aldosterone-renin ratio (ARR) was a very strong predictor of the antihypertensive response of spironolactone in this group of patients, with the highest ratios being associated with a >20 mmHg decrease in systolic blood pressure (SBP). This observation is extraordinary in the degree of BP reduction that occurred in the patients with highest ARR values and that it was predicted by a simple biochemical assessment. In a separate substudy, the PATHWAY-2 investigators further related the benefit of spironolactone to reductions in intravascular volume as indexed by thoracic impedance. Combined, the PATHWAY-2 findings clearly implicate aldosterone excess as an important mediator of RHTN that is best overcome by use of an MRA.

Lastly, the 2017 Hypertension Guideline included for the first-time definition of refractory hypertension (RfHTN) as a novel phenotype of antihypertensive treatment failure. It refers to patients who are failing maximal or near maximal antihypertensive treatment defined as BP that is uncontrolled with use of ≥5 antihypertensive agents of different classes, including a long-acting thiazide

diuretic such as chlorthalidone and an MRA, such as spironolactone (3). Recent studies suggest that RfHTN is rare, present in <5% of patients referred to a hypertension specialty clinic for uncontrolled RHTN (9). Assessment of these patients has indicated that they tend to be more often African American and tend be younger and more often female than patients with controlled RHTN. Not surprising, given their history of poorly controlled, often severe HTN, patients with RfHTN have a high prevalence of cardiovascular disease, especially left ventricular hypertrophy and congestive heart failure with preserved ejection fraction.

Studies suggest that RfHTN may be mechanistically distinct from RHTN in general, in that, there is an absence of evidence of persistent fluid retention as the underlying cause of their treatment failure is (9,10). These patients do manifest evidence of heightened sympathetic tone compared to patients with controlled RHTN as indicated indirectly by persistently higher daytime and nighttime heart rates and greater levels of 24-hour urinary norepinephrine excretion (9,10). If RfHTN is attributable to heightened sympathetic tone, it would have important clinical implications in suggesting that continued intensification of diuretic therapy would not provide any additional BP benefit, but instead, patients might better respond to effective sympatholytic therapies, whether pharmacologic or device-based.

RHTN remains a common clinical problem characterized by high cardiovascular risk. Recent studies demonstrate the importance of distinguishing pseudo-treatment resistance secondary to inaccurate BP measurement, clinical inertia, and/or poor medication adherence. The PATWAY-2 findings clearly advance our understanding of RHTN in implicating sodium and fluid retention secondary to aldosterone excess as a broad underlying cause of antihypertensive treatment resistance. In addition, PATHWAY-2 firmly establishes spironolactone as the most appropriate fourth-line agent for treating RHTN. Lastly, RfHTN, an emerging phenotype of antihypertensive treatment failure has recently been defined. Studies suggest that it may be distinct from RHTN in general in that antihypertensive treatment failure is more likely neurogenic in etiology as opposed to being volume dependent.

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Footnote

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