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Emerging concepts for patients with treatment-resistant hypertension

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Abstract

Treatment resistant hypertension (TRH) is defined as elevated blood pressure despite treatment with three properly dosed antihypertensive drugs, and is associated with adverse cardiovascular and renal outcomes and increased mortality. Treatment of patients with TRH focuses on maximizing the doses of antihypertensive drugs and adding drugs with complementary mechanisms of action, including a combination of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, calcium channel blockers, and thiazide-like diuretics. Randomized clinical trials have demonstrated the efficacy of the mineralocorticoid receptor antagonist spironolactone as a fourth-line therapy for patients with TRH. Other pharmacologic considerations include adding α -blockers, combined α - β -blockers, centrally acting α -agonists, or direct vasodilators. However, a small, but important subset of patients remain hypertensive despite combination regimens with multiple antihypertensive drugs, underscoring the need for novel blood pressure-lowering therapies. Over recent years, alternative approaches for treating TRH have emerged, including agonists of natriuretic peptides, endothelin receptor antagonists, and additional vasoactive drugs. Lastly, device-based interventions, such as renal denervation or carotid baroreflex activation, may supplement drug therapy for these patients. This review summarizes current knowledge on the management of TRH, with focus on novel therapeutic strategies designed to achieve optimal blood pressure control.

Keywords

Resistant hypertension; uncontrolled hypertension; renal denervation

Introduction

Hypertension affects approximately 75 million adults in the United States and more than one billion people worldwide, and is responsible for as many as 9 million deaths each year [1].

Although multiple clinical studies have demonstrated the efficacy of antihypertensive drugs

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to both decrease blood pressure (BP) and reduce mortality rates, many hypertensive subjects fail to achieve goal BP and become a major challenge for physicians involved in their care [2].

According to the European society of hypertension/cardiology guidelines, treatment-resistant hypertension (TRH) is defined as BP>140/90mmHg despite adequate lifestyles and treatment with full doses of >3 antihypertensive drugs (including a diuretic) [3]. The American Heart Association extends the definition to include “controlled” resistant hypertension, thereby considering those requiring four or more antihypertensive drugs as being “treatment resistant” [4]. The reported prevalence of TRH ranges from 9–27%, and increased over the last decades [2]. Importantly, its presence is associated with a substantially increased risk of adverse renal and cardiovascular outcomes. A large randomized trial showed that TRH is associated with an increased risk for congestive heart failure, stroke, cardiovascular disease, end-stage renal disease, and all-cause mortality [5], consistent with additional data from a recent retrospective, longitudinal cohort study of 470,386 Kaiser Permanente members [6].

This review summarizes current approaches for treating patients with TRH, and the emergence of novel pharmacologic and device-based therapeutic strategies designed to more effectively achieve goal BP in this group.

Fluid expansion, salt sensitivity, and sympathetic activation

The precise mechanisms responsible for TRH remain uncertain and are likely multifactorial. Risk factors for TRH include obesity, male gender, older age, African American origin, insulin resistance, increased dietary sodium intake, and renal dysfunction, conditions all associated with excess fluid retention. Indeed, prospective studies suggest that inadequate diuretic administration is a common feature in TRH. Serial hemodynamic and impedance measurements in patients with TRH revealed its association with increased thoracic fluid content, supporting occult volume expansion as a mediator of antihypertensive drug resistance [7]. Addition of mineralocorticoid receptor blockade in patients with TRH regularly reduces BP and volume overload, supporting the contention that fluid retention is a major contributor to TRH.

Excessive dietary sodium ingestion also contributes to resistance to antihypertensive treatment. In subjects with TRH, a low-salt diet decreases BP, increases plasma renin activity, and decreases creatinine clearance and body weight, consistent with a reduction in intravascular volume [8]. Additionally, renin-angiotensin system blockade may partially contribute to increase “salt-sensitivity”, the tendency for BP to decrease during salt reduction and rise during salt repletion. Multiple genetic and environmental factors including age, body mass index, and ethnicity modulate the effects of dietary sodium on BP. Furthermore, potassium modulates the BP-elevating effects of sodium, as its dietary supplementation can abolish sodium sensitivity in both normotensive and hypertensive subjects [9].

Increased sympathetic activation may also contribute to some forms of TRH. Patients with hypertension associated with renal dysfunction, left ventricular hypertrophy, impaired left ventricular diastolic function, or systolic heart failure have greater sympathetic activation compared to those with uncomplicated hypertension. Furthermore, sympathetic activation is higher in patients with TRH than in individuals with elevated BP who respond to antihypertensive drug administration. In a recent study, Dudenbostel and colleagues found increased 24-hour urinary normetanephrine levels in patients with uncontrolled TRH, suggesting that heightened sympathetic tone might be partly responsible for antihypertensive treatment failure [10]. Importantly, these findings support expanded efforts to design denervation device-based interventions to treat TRH.

Current approaches for management of TRH

As with all forms of complex hypertension, initial steps in the management patients with TRH should confirm the diagnosis and identify secondary contributing factors (Figure 1). A detailed assessment of the medical history should address the time of the first diagnosis, duration, severity, and progression of arterial hypertension, predisposing factors (life style, cardiovascular risk factors, family history, etc.), current and past BP measurements, treatment adherence, response to prior medications, adverse reaction to antihypertensive therapies, history or current symptoms of target organ damage, and symptoms of possible secondary causes of hypertension.

A large fraction of failure to achieve goal BP is attributable to poor adherence, inadequate antihypertensive dosing, and “pseudoresistance”, which results from discrepancies between BP measurements using different methods. Poor medication adherence is an important cause of “pseudoresistance” among patients with TRH, and might be falsely interpreted as treatment resistance. In a recent study, either incomplete adherence or complete non-adherence were detected in as many as 53% of patients with apparent uncontrolled hypertension [11]. Likewise, evaluation of antihypertensive drug concentrations using toxicological serum analysis identified 23% partially and 24% totally non-adherent TRH patients [12]. “White-coat hypertension” and “masked hypertension”, for example, represent inaccurate labeling obtained by office readings. Levels recorded using 24h ambulatory BP measurements (ABPM) provide more accurate prediction of cardiovascular risk compared to office measurements, and allow identification of “non-dipper” patterns during nocturnal periods, which are associated with higher risk and secondary hypertension [13].

Secondary factors associated with TRH including obstructive sleep apnea, renal artery stenosis, primary hyperaldosteronism, renal parenchymal disease, drug-induced or heavy alcohol use, and thyroid disorders should be evaluated and treated. Imaging studies of the renal vasculature (renal angiography, duplex ultrasound, computed tomography, magnetic resonance imaging), routine metabolic profile, urinalysis (24h urinary cortisol and catecholamine levels), plasma aldosterone levels, and plasma renin activity (aldosterone-renin ratio) might help identifying secondary causes. These conditions often benefit from targeted therapies, such as treatment with continuous positive airway pressure (for obstructive sleep apnea), or withdrawal of drugs that may contribute to TRH, such as sympathomimetics and non-steroidal anti-inflammatory drugs.

Intensified therapy to address TRH

Lifestyle changes, such as weight loss, regular exercise, a high-fiber low-fat low-salt diet, smoking cessation, and decrease alcohol intake, should be included in the therapeutic approach to TRH (Figure), but most often do not achieve BP control alone, requiring additional pharmacologic intervention.

Antihypertensive drug therapy in TRH should be targeted to optimize the dosage and/or combinations of drugs that regulate different pathways involved in the pathogenesis of hypertension. International guidelines suggest combination triple antihypertensive therapy, also known as A+C+D, where “A” is an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker (ARB), “C” is a calcium channel blocker, and “D” a thiazide-like diuretic [14]. If patients remain hypertensive, addition of a fourth-line antihypertensive drug should be considered.

Several lines of evidence recommend the thiazide-like diuretic chlorthalidone as the first choice diuretic for treating TRH. Randomized clinical trials have shown that treatment with chlorthalidone was equally or more effective than other antihypertensive agents in cardiovascular risk reduction, and retrospective trials suggested greater reduction in cardiovascular morbidity compared to hydrochlorothiazide [15]. Importantly, potential adverse effects on the lipid profile, serum uric acid, and serum potassium levels are comparable.

Whether to use thiazides, loop diuretics, or their combination in patients with chronic renal failure and hypertension is a matter of debate. Although thiazides have longer antihypertensive effects than loop diuretics, the latter should be considered for patients with severe-to-moderate renal dysfunction, where fluid retention plays an important role in the development of hypertension. Surprisingly, hydrochlorothiazide increased the fractional excretion of sodium and chloride more than furosemide in a double-blind-randomized crossover trial in seven patients with severe renal failure and hypertension, possibly due to increased sodium delivery in the distal tubule (magnification phenomenon) [16]. Mean BP was similarly decreased by the two diuretics, failing to demonstrate greater efficacy of a combined regimen.

The PATHWAY-2 trial published in 2015 tested the hypothesis that TRH is primarily caused by excessive sodium retention by assessing whether addition of a mineralocorticoid receptor antagonist (MRA) as a fourth-line antihypertensive led to greater BP reduction than intensifying antihypertensive therapy with other BP-lowering regimens [17]. In this double-blind, placebo-controlled, crossover trial, patients confirmed as adherent, but resistant, to treatment with A+C+D rotated, through 12 weeks of once-daily treatment with MRA, β -blockers, α -blockers, or placebo, in addition to their baseline BP drugs (A+C+D). The study reported that MRA were by far the most effective BP-lowering treatment for patients with TRH, reducing BP in 60% of patients. Furthermore, BP reduction by spironolactone inversely correlated with baseline plasma renin levels, suggesting that the predominant underlying pathophysiological cause of TRH was sodium retention [17]. A meta-analysis of 12 studies confirmed a role for MRA in lowering BP [18], supporting its use as fourth-line drug for treatment of TRH. Selective aldosterone synthase inhibitors, such as LCI699, also

demonstrate tolerability and antihypertensive efficacy in patients with primary hypertension [19]. Moreover, LCI699 was effective in decreasing BP and reducing systemic aldosterone levels in patients with TRH, positioning aldosterone synthesis inhibition as an attractive therapy for these patients [20] (Figure). Further research is needed to confirm its clinical benefits and limitations in TRH.

In cases of persistent sympathetic over-activity, α -blockers (doxazosin), β -blockers (nebivolol), or combined α - β -blockers (carvedilol) could be considered as fourth- and fifth-line drugs to achieve BP control. Likewise, centrally acting α -agonists (clonidine) and direct vasodilators (hydralazine, minoxidil) may assist in reducing BP in patients with TRH, yet are currently reserved mainly as fourth-line (or beyond) therapy due to side effects.

Potential new directions for therapy of TRH

Accumulating evidence indicates that despite intensive antihypertensive treatment, a subset of patients with TRH do not achieve BP control. In a retrospective analysis of 304 patients with TRH, Acelayado et al. identified that 29 (9.5%) remained refractory to treatment, despite maximal antihypertensive therapy [21]. Likewise, a prospective analysis of 559 patients with TRH revealed that 15 (2.6%) of patients sustained uncontrolled BP, in spite of treatment with more than 5 classes of antihypertensive agents [10].

In an attempt to identify the mechanism responsible for large fractions of patients in the trials remaining uncontrolled for their high BP, Kjeldsen and colleagues used previously unpublished information from monitoring of clinical trials for TRH [22]. They found that “therapeutic inertia” (the failure to initiate, intensify, or change therapy in hypertensive patients) was a major cause of not reaching BP targets in the trials. Likewise, diagnostic inertia (failure to investigate the underlying cause of resistant hypertension) might be responsible for poorer BP control, as treatment of TRH is more effective if the right treatment is prescribed [23]. Nevertheless, the fact that a significant fraction of patients fail to achieve goal BP with established antihypertensive drugs and efforts to improve lifestyle supports a potential role for novel therapies (Figure 1).

Pharmacologic strategies

Agonist of natriuretic peptides—The natriuretic peptide system, which consists of neuro-hormones synthesized by the heart, brain and other organs, plays an important role in BP regulation and fluid-electrolyte balance. Human recombinant atrial and brain natriuretic peptides (ANP and BNP, respectively) have been approved in several countries for the treatment of heart failure based on their beneficial hemodynamic effects, including arterial and venous dilatation, enhanced sodium excretion, and suppression of the renin-angiotensin-aldosterone and sympathetic nervous systems. Importantly, the fact that these peptides regulate BP and fluid electrolyte balance, suggests that they may have a role as therapeutic alternatives in patients with TRH. Indeed, ANP and BNP administration has been shown to lower BP in hypertensive patients [24]. Furthermore, sacubitril/valsartan (LCZ696), recently approved in the US to treat patients with heart failure, combines inhibition of neprilysin (the enzyme responsible for degradation of the natriuretic peptides) and ARB functionality, leading to lower BP compared to ARB therapy alone [25]. Taken together, these

observations position natriuretic peptides agonists as a promising pharmacologic therapy for patients suffering from TRH.

Endothelin-receptor antagonists—Endothelin (ET)-1 is a potent vasoconstrictor peptide originally isolated from endothelial cells and implicated in development of vascular dysfunction and cardiovascular disease. Circulating levels of ET-1 are elevated in patients with hypertension, associated with increased risk of major cardiovascular and cerebrovascular events [26]. Indeed, a phase-2, randomized, double-blind, placebo-controlled forced dose-titration study showed that darusentan, an ET type-A selective-receptor antagonist, decreased systolic and diastolic BP compared with placebo in a dose-dependent manner in patients with TRH [27]. However, 30% of patients developed intolerable adverse events, including refractory edema, emphasizing the need for strict monitoring strategy and effective diuretic therapy. Similar adverse events were observed in a trial that tested the efficacy of ET-receptor antagonists to reduce proteinuria in patients with diabetes. Therefore, other antihypertensive strategies are preferred before considering the use of ET-receptor antagonists for TRH.

Additional vasoactive drugs—Vasoactive intestinal peptide (VIP) is a neuroendocrine mediator and potent systemic vasodilator, decreasing BP and increasing cardiac output in patients with pulmonary hypertension. Although single ascending doses of the VIP receptor-2 agonist vasomera are safe and well-tolerated in patients with essential hypertension, its potential for decreasing BP in patients with TRH remains unexplored. Similarly, dopamine β -hydroxylase (D β H) inhibitors, such as etamicastat, are currently under clinical development for treatment of hypertension and heart failure. These compounds produce reversible inhibition of D β H, acting mainly peripherally by decreasing noradrenaline levels in sympathetically innervated tissues. Although etamicastat is well-tolerated and reduces BP levels in patients with mild to moderate hypertension [28], further studies are needed to prove its efficacy in TRH.

Device-based therapies—In recent years, there has been a growing appetite for interventional management of TRH, based on the perception that current antihypertensive strategies do not suffice to achieve BP control. Several device-based interventions have been proposed for reduction in BP, primarily targeting reduction in sympathetic nerve activity. Unlike complex, multi-drug therapeutic regimens prone to non-adherence and adverse side effects, these procedures do not require active daily participation from the patient. They may also be less prone to problematic side effects of drug therapy. Initial studies have targeted patients with THR who remain hypertensive despite treatment with a combination triple therapy

Carotid baroreflex activation therapy—Carotid sinus baroreceptors normally detect a rise in BP and send afferent nerve impulses to the central nervous system, which increases parasympathetic tone and decreases sympathetic outflow to the heart, blood vessels, and kidney, ultimately decreasing BP. Over 50 years ago, Carlsen et al. demonstrated that electrical stimulation of the carotid sinus nerve decreases BP in men undergoing surgical resection of neck tumors [29]. Subsequent studies confirm the efficacy of device-based

carotid baroreflex activation in patients with TRH. However, technical and surgical difficulties, including adverse effects related to nerve injury, limited its clinical use.

In 2001, a surgically implantable bilateral carotid baroreceptor stimulator (Rheos®) system emerged as a novel approach to treat hypertensive patients. Early-phase clinical trials demonstrated a decrease in BP in severely TRH patients through sympathovagal modulation [30]. However, the Rheos Pivotal Trial, a double-blind, randomized, prospective, multicenter, placebo-controlled Phase III trial in 265 patients with TRH did not meet the endpoints for systolic BP response at 6 months or procedural safety, as 9% of patients developed facial nerve injury [31], precluding its approval by the FDA for treatment of TRH. Development of a second-generation unilateral carotid stimulator (Barostim-neo™) offers several advantages compared to the Rheos® system, including smaller surgical incisions, shorter recovery time, and longer battery life, with comparable antihypertensive efficacy [32]. An open-label phase-I and IIa trial in 30 patients with TRH showed no major adverse events 6 months after implantation, but additional studies are needed to test the efficacy and safety of Barostim-neo™ in patients with TRH.

Transcatheter renal denervation—Over the last decade, catheter-based renal denervation gained initial support for treatment of TRH. This invasive procedure, which consists of 4–6 ablations in the proximal or middle section of both renal arteries using single electrode catheters (Symplicity™) under fluoroscopic guidance, was first performed in humans in 2007 as part of the SYMPPLICITY HTN-1 trial [33]. This open-label uncontrolled study and the subsequent SYMPPLICITY HTN-2 trial demonstrated the safety and efficacy of this intervention in patients with TRH [34]. However, the SYMPPLICITY HTN-3 study, that used ABPM, failed to confirm significant reductions in BP, limiting the enthusiasm for this procedure [35].

More recently, several additional randomized-controlled trials failed to show significant reductions in BP in TRH patients treated with renal denervation compared to sham procedures [36]. Similarly, the Prague-15 study argues that renal denervation effect is comparable to that induced by intensified pharmacotherapy including spironolactone [37]. Interestingly, radiofrequency denervation of the distal aspect and segmental branches of the renal artery might be more effective than standard denervation, which may explain its failure in the SYMPPLICITY HTN-3 trial [38]. The French DENERHTN trial suggests slightly better BP control when adding renal denervation to standardized antihypertensive treatment [39]. Lastly, a recent study that assessed the safety and effectiveness of renal denervation using the Symplicity system in “real-world” patients with uncontrolled hypertension reported significant reductions in office and 24-hour BP at 6 months with a favorable safety profile [40]. Nevertheless, further well-designed proof-of-concept studies are needed to elucidate the ultimate role of renal denervation in patients with TRH.

Other interventional treatments—Percutaneous creation of an iliofemoral arteriovenous shunt using the Rox Anastomotic Coupler device (Anastomotic Coupler II; Rox Medical) can cause a sustained drop in systemic BP in hypertensive patients with chronic obstructive pulmonary disease. The mechanisms responsible for BP reduction may include a decrease in total systemic vascular resistance and afterload, or an increase in

cardiac volumes, resulting in an overall reduction in cardiac work despite increased cardiac output [41]. A European multicentric randomized study revealed that implantation of an arteriovenous coupler device plus current pharmaceutical therapy is associated with reduced BP and hypertensive complications 6 months after the procedure compared to medical therapy alone, suggesting that the mechanical characteristics of the arterial system could be important therapeutic targets for successful hypertension control [13].

Surgical removal of the carotid body performed in patients with respiratory conditions, such as bronchial asthma and chronic obstructive pulmonary disease, was found to trigger substantial reductions in BP. Interestingly, a recent study demonstrated that hypoglycemia was associated with decreased systolic and mean BP in patients with bilateral carotid body resection, supporting carotid body ablation as a potential therapeutic strategy to maintain optimal BP levels [42]. The efficacy of this intervention to decrease BP in patients with TRH has not yet been examined.

Conclusions and Perspectives

Recognition that an important proportion of hypertensive individuals are treatment resistant is becoming a major issue. Medication non-adherence, failure of recognition and “physician inertia” remain major causes for not reaching BP targets in clinical trials for patients with TRH. It is also important to appreciate the need for more individualized BP monitoring and management, as comorbidities like stroke or transient ischemic attacks may interfere with the treatment of TRH patients.

An initial work-up including ABPM is critical to confirm the diagnosis of TRH, and identification and treatment of secondary causes are important. Pharmacological therapy should focus on optimizing the doses of antihypertensive drugs and adding drugs with complementary mechanisms of actions. Strong evidence supports MRA as fourth-line antihypertensive agents. If BP remains elevated, α -blockers, combined α - β -blockers, centrally acting α -agonists, or direct vasodilators may serve as adjuvant therapies. Novel pharmacologic interventions, including agonists of natriuretic peptides and ET-receptor antagonists, hold promising potential for treating TRH, but further investigation is warranted. Moreover, creative well-tailored strategies to ensure adherence with multi-drug therapy need to be devised.

Although device-based interventions seem to be effective in reducing BP in hypertensive patients, their invasiveness and cost should be considered against the efficacy, adherence issues, and cost of lifetime drug therapy. Moreover, co-existing conditions that might interfere with interventional success, like hyperaldosteronism, need to be evaluated. Therefore, additional preclinical studies are needed to help in selecting patients likely to be benefitted from device-based methods, and large randomized prospective clinical trials to confirm their efficacy and safety in patients with TRH.

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Management of TRH

*Initial work-up to confirm the diagnosis
and rule-out secondary causes of TRH*

Standard treatment for TRH

Lifestyle changes:
*(Weight loss, regular exercise, a high-fiber
low-fat low-salt diet, smoking cessation,
and decrease alcohol intake)*

Treatment of secondary causes:
*(Continuous positive airway pressure, withdrawal
of drugs that may contribute to TRH)*

Pharmacological therapy:
*(A=angiotensin-converting enzyme inhibitor or
an angiotensin-receptor blocker + C= calcium
channel blocker + D=thiazide-like diuretic)*

Further antihypertensive therapy:
*Mineralocorticoid receptor antagonist, α -blockers, β -blocker,
combined α - β -blocker, centrally acting α -agonist, direct vasodilators)*

New directions for therapy of TRH

Pharmacologic strategies:

- Agonist of natriuretic peptides
- Endothelin-receptor antagonists
- Additional vasoactive drugs
- (Vasoactive intestinal peptide, dopamine β -hydroxylase inhibitors, selective aldosterone synthase inhibitors)

Device-based therapies:

- Carotid baroreflex activation therapy
- Transcatheter renal denervation
- Other interventional treatments

Figure 1.

Current approaches and new directions for treatment resistant hypertension (TRH).