What is new in the management of resistant hypertension?

Resistant hypertension, generally defined as blood pressure that remains above goal in spite of the use of three antihypertensive medications prescribed at optimal dose amounts, is an increasingly common medical problem, and patients with this condition are at high risk of cardiovascular events. Recent studies have shown that new technologies, such as carotid stimulation and renal denervation, and more established approaches, such as low dietary salt and mineralocorticoid receptor blockers, effectively reduce blood pressure in patients with resistant hypertension. In this article, we discuss the background, safety and effectiveness of these and other treatment approaches.

KEYWORDS: hypertension ■ resistant hypertension ■ uncontrolled blood pressure

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Resistant hypertension is generally defined as blood pressure (BP) that remains above goal, in spite of the use of three antihypertensive medications prescribed at optimal dose amounts. According to the scientific statement for diagnosis and treatment of resistant hypertension published by the American Heart Association in 2009, one of the three agents should, ideally, be a diuretic [1]. Subjects with hypertension whose BP is controlled, but require four or more medications, are also considered to be resistant to treatment. In addition, patients who have uncontrolled BP on regimens of three drugs from other classes and who are intolerant of diuretics are considered to have resistant hypertension.

Clinical trials suggest that 20–30% of hypertensive subjects may be resistant to antihypertensive treatment [2,3]. For example, in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), 34% of participants remained with uncontrolled BP, despite an average of two antihypertensive medications, after approximately 5 years of follow-up [2]. At the end of the ALLHAT, 27% of participants were controlled on three or more medications and, overall, 49% of participants were controlled on one or two medications, meaning that approximately 50% of participants needed three or more BP medications. However, ALLHAT may underestimate the prevalence of treatment-resistant hypertension as patients with a history of difficult-to-treat hypertension (defined as two or more medications to achieve a BP of <160/100 mmHg) were precluded from enrolling in the study. The current trend towards decreasing physical activity and increasing life expectancy and obesity rates has almost certainly contributed to an increasing prevalence of resistant hypertension.

The prevalence of secondary causes of hypertension and, in particular, primary aldosteronism (PA), obstructive sleep apnea, chronic kidney disease and renal artery stenosis, is increased in patients with resistant hypertension [1,4–6]. Therefore, all patients confirmed to have resistant hypertension should be considered for screening for these secondary causes with referral to an appropriate specialist as needed [1]. Most important of these are the specifically treatable and potentially curable endocrine forms, and especially PA, as specific medical or surgical management can result in a marked improvement or even cure of hypertension, associated with improved quality of life and reduced risk of morbidity in patients with otherwise resistant hypertension and a poor prognosis [7,8].

The impact of the treatment of resistant hypertension on cardiovascular morbidity and mortality has not been specifically addressed. Also, there are surprisingly few high-quality data comparing cardiovascular risk in patients with resistant hypertension with those with more easily controlled hypertension. However, taking into consideration that cardiovascular risk increases linearly and progressively with BP levels, and that lowering of BP reduces cardiovascular and renal morbidity and mortality [9], it is reasonable to assume that patients with resistant hypertension are likely to have higher risk of cardiovascular events and benefit from antihypertensive treatment. For example, in the Veterans Administration Cooperative Study,

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patients with severe hypertension (diastolic BP: 115–129 mmHg), who were treated with a triple antihypertensive regimen, had a 96% reduction in cardiovascular events compared with those treated with placebo [10].

Pseudoresistance, defined as factitious lack of BP control caused by inaccurate measurement of BP, inappropriate drug choices/doses, nonadherence to prescribed therapy, or the white-coat effect, should be ruled out in patients with uncontrolled BP. Identification of pseudoresistance avoids overtreatment and excessive and expensive evaluation [5]. Poor adherence to prescribed medications is a common problem in patients with hypertension and a common cause of uncontrolled hypertension.

Patient characteristics that predispose to the development of resistant hypertension include obesity, decreased physical activity and older age. The more aggressive BP goals recommended by guidelines also contribute to the high prevalence of resistance to antihypertensive treatment [5]. However, BP goals now tend to be less aggressive following recent trial results, but the inclusion of new levels into BP guidelines are still pending.

In this article, we discuss new pharmacological and nonpharmacological approaches, specifically tested in patients with confirmed resistant hypertension. We have also discussed the background for each intervention. We searched the words 'treatment', 'resistant hypertension' and 'refractory hypertension' in the PubMed database, and selected articles published from January 2000 to December 2010.

Pharmacological treatment

Aldosterone receptor blockers

Backgound

In animal studies, aldosterone excess, in combination with high dietary salt intake, has been shown to promote target-organ deterioration independent of increases in BP [11,12]. Target-organ deterioration induced by aldosterone is characterized by perivascular inflammation and necrosis, progressing to diffuse fibrosis. These proinflammatory and profibrotic effects of aldosterone, observed experimentally, are consistent with observational studies of patients with PA, indicating an increased likelihood of left ventricular hypertrophy [13,14], chronic kidney disease [15,16] and endothelial dysfunction [17], each of which independently predicts increased cardiovascular risk.

The prevalence of PA is greater than previously thought. In the early 1990s the Greenslopes Hospital Hypertension Unit in Brisbane, Australia, reported a surprisingly high prevalence of PA at approximately 12% among 52 hypertensive subjects who responded to a newspaper advertisement for participation in an antihypertensive drug trial [18]. A follow-up study of 199 subjects referred to our hypertension clinic, confirmed the high occurrence of PA, with an estimated prevalence of at least 9.5%, and perhaps as high as 13% [19].

Since these reports, multiple studies have confirmed that PA is much more common than had been demonstrated historically and that the prevalence is positively correlated with the severity of BP. Mosso *et al*. screened over 600 patients with hypertension for PA [20]. The severity of the untreated hypertension based on Joint National Committee (JNC) VI stages (stage 1: 140–159/90–99 mmHg; stage 2: 160–179/100–109 mmHg and stage 3: ≥180/110 mmHg) was known for each subject. The overall prevalence of PA was 6.1%. However, the prevalence increased progressively with increasing severity of hypertension. In subjects with stage 1 hypertension, the PA prevalence was only 2%, which was not different from normotensive controls; in subjects with stage 2 hypertension, the PA prevalence was 8%, and in subjects with stage 3 hypertension, the prevalence was 13%. The results are clinically relevant in demonstrating that the likelihood of PA increases with increasing severity of hypertension such that patients with mild hypertension are at lower risk, while patients with severe hypertension are at a high risk of having PA.

Primary aldosteronism is particularly common in patients with resistant hypertension with a prevalence of approximately 20%. In an evaluation of 88 patients with resistant hypertension referred to the University of Alabama, AL, USA, 18 (20%) were diagnosed with PA based on a suppressed plasma renin activity (<1.0 ng/ml/h), and a high 24-h urinary aldosterone excretion (>12 µg/24-h) during high dietary sodium intake (>200 mEq/24-h) [6]. The prevalence of PA was similar in African–American and Caucasian patients. Different studies worldwide have been consistent in demonstrating similar prevalence. In a study conducted in Seattle (WA, USA), PA was diagnosed in 17% of patients with difficult-to-control hypertension [21]. Investigators in Oslo, Norway, have also confirmed PA in 23% of patients with resistant hypertension [22], and investigators in Prague, Czech Republic, have reported a prevalence of PA of 19% in patients referred to a university hypertension clinic for moderate-to-severe hypertension [23].

Patients with resistant hypertension are characterized by higher aldosterone levels. In a cross-sectional analysis, 279 consecutive patients with resistant hypertension were compared with 53 control subjects (with normotension or hypertension controlled on no more than two antihypertensive medications). Plasma aldosterone, aldosterone:renin ratio and 24-h urinary aldosterone were significantly higher in patients with resistant hypertension than in control subjects. Furthermore, lower levels of plasma renin activity and higher levels of brain and atrial natriuretic peptides among patients with resistant hypertension compared with control subjects provided evidence that intravascular fluid retention plays an important role in hypertension resistant to treatment. It is of note that 85% of patients with resistant hypertension were on recommended doses of thiazide diuretics.

Clinical evidence

Recent studies have reported that mineralocorticoid receptor blockers in low doses promote significant additional BP reduction in patients with resistant hypertension [24–30]. In one study, patients with resistant hypertension on an average of four medications, including an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a diuretic, received low doses of spironolactone (12.5–25 mg/day) in addition to their current treatment [26]. After 6 months of follow-up, systolic and diastolic BP reduced by 25 and 12 mmHg, respectively. There was a similar BP reduction in patients with PA compared with those without PA. BP reduction was not predicted by baseline plasma aldosterone or renin levels or by 24-h urinary aldosterone. Furthermore, there was no difference in BP reduction between African–American and Caucasian subjects. Overall, these studies support the recommendation to maximize diuretic therapy, including the possible addition of a mineralocorticoid receptor antagonist, to effectively manage resistant hypertension [1].

In a different study, Lane *et al*. reported the effect of spironolactone (25–50 mg) in 133 patients with resistant hypertension [24]. The addition of spironolactone (median dose: 25 mg) to previous treatment, including an angiotensin-blocking drug, was associated with a reduction in systolic and diastolic BP of 21.7 and 8.5 mmHg, respectively. In the Anglo–Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT), 1411 participants with uncontrolled BP on three antihypertensive agents received spironolactone as a fourth drug [27]. The median duration of treatment with spironolactone was 1.3 years and the mean dose was 25 mg, both at the start and end of the observation period. Systolic and diastolic BP were reduced by 21.9 and 9.5 mmHg, respectively, independently of age, sex, smoking and diabetes status.

Dual or triple blockade of the renin–angiotensin–aldosterone system (RAAS) has been used in an attempt to control BP. However, the dual blockade of the RAAS with spironolactone, in combination with an ACE inhibitor or ARB, is more effective than dual blockade with an ACE inhibitor and an ARB. In a prospective, open-label and crossover study, 42 patients with true resistant hypertension (determined by ambulatory BP monitoring) received, in addition to their treatment, an ACE inhibitor for 12 weeks if they were already being treated with an ARB, or an ARB if they were being treated with an ACE inhibitor [31]. After 4 weeks of wash-out without the added RAAS blocker, spironolactone 25 mg was administered for 4 weeks and increased to 50 mg if necessary, in addition to the 12-week current treatment. The combination of an ACE inhibitor with an ARB reduced office BP by 12.9/2.2 mmHg and 24-h BP by 7.1/3.4 mmHg. By contrast, the addition of spironolactone reduced office BP by 32.2/10.9 mmHg and 24-h BP by 20.8/8.8 mmHg. The study not only showed the small BP effect of combining an ACE inhibitor and an ARB, but also confirmed that spironolactone should be considered for all patients with uncontrolled hypertension on three or more antihypertensive agents [32].

Eplerenone, a more selective mineralocorticoid receptor blocker, also effectively reduces BP in patients with uncontrolled hypertension, despite treatment with multiple agents. In an open-label nonplacebo-controlled study, 52 patients with resistant hypertension (baseline BP: 150.5/84.1 mmHg with an average of 3.7 antihypertensive medications) received 50–100 mg of eplerenone daily for 12 weeks [33]. Eplerenone reduced clinic BP by 17.6/7.9 mmHg and 24-h BP by 12.2/6.0 mmHg. Reductions in clinic and ambulatory BP were weakly related to baseline serum aldosterone and unrelated to plasma renin activity, age, gender or race. This study demonstrated that similar to spironolactone, the more selective mineralocorticoid receptor blocker, eplerenone, is effective in reducing BP in patients with resistant hypertension.

Spironolactone is usually well tolerated, even in combination with ACE inhibitors or ARBs. In the ASCOT study, spironolactone had to be discontinued in 6% of patients [27]. Spironolactone-associated hyperkalemia is uncommon in patients with normal renal function, but it can occur, necessitating close monitoring. Risk of hyperkalemia is increased in older patients, in patients with chronic kidney disease or diabetes, and in patients receiving ACE inhibitors or ARBs and/or nonsteroidal anti-inflammatory drugs. In these higher risk patients, spironolactone can be started at 12.5 mg daily (requires splitting of a 25-mg tablet). Serum potassium and creatinine levels should be monitored in patients treated with mineralocorticoid receptor antagonists. Potassium supplementation or salt substitutes that contain potassium should be discontinued or reduced in patients who are started on these agents.

Breast tenderness occurs in less than 10% of men taking a spironolactone dose of 25 mg daily [26,27]. Occurrence of breast tenderness with or without gynecomastia increases sharply with higher doses. The more selective mineralocorticoid receptor antagonist eplerenone, with a lower affinity for progesterone and androgen receptors, is better tolerated than spironolactone with a low incidence of breast tenderness, gynecomastia, sexual dysfunction and menstrual irregularities [34].

Amiloride, a potassium-sparing diuretic that blocks the epithelial sodium channel and, thereby, antagonizes aldosterone action, has been documented to be effective in treating aldosterone-related hypertension, but there is less experience using it to specifically treat resistant hypertension [22,35]. It is well tolerated, lacking sex hormone-related adverse effects, and can serve as a useful alternative or can even be used in combination with small doses of spironolactone when such side effects occur with higher doses. As with direct mineralocorticoid receptor antagonists, there is a risk of hyperkalemia.

While not the focus of this article, it should be pointed out that, for those subjects confirmed as having PA and showing lateralization of aldosterone overproduction to one adrenal on adrenal venous sampling, unilateral adrenalectomy usually has a major beneficial effect not only on hypertension control, but also on quality of life and reduction in risk of cardiovascular and renal target-organ damage and risk of events [7,8]. Hence, wherever possible, efforts should be made to detect patients with PA, and to undertake in those individuals further testing to distinguish unilateral (surgically correctable) from bilateral (usually medically treated) forms. It is of note that, owing to the poor specificity of image tests to identify an aldosterone-producing adenoma, the decision as to whether to proceed to adrenalectomy should be based primarily on whether autonomous adrenal aldosterone production is unilateral or bilateral, as determined by the results of adrenal venous sampling [36,37]. However, not infrequently among patients with resistant hypertension is it not feasible to withdraw all medications that interfere with diagnostic testing (e.g., diuretics, ACE inhibitors and ARBs, which can mask the diagnosis of PA by causing false-negative aldosterone:renin ratios) without risking unacceptable loss of hypertension control. In those circumstances, it would seem reasonable to attempt an empiric trial of an aldosterone antagonist in the first instance, given the existing data supporting an important role for aldosterone and volume expansion as a contributor to hypertension resistance in this population.

Endothelin receptor blockers

Backgound

Endothelin (ET) has been recognized as a potent vasoconstrictor factor that modulates cardiovascular function. ET plays an important role in the vascular system and is secreted by the endothelium in response to intra-arterial pressure, low shear stress, angiotensin II, vasopressin, catecholamines and TGF-β [38]. Stimulation of ET receptors in the vascular system produces marked sustained hypertension [39]. In the kidneys, ET administration results in renal vasoconstriction associated with a decrease in sodium excretion [40]. The ET type A receptor is the main receptor of the ET system in the vascular smooth muscle, and is widely expressed [38]. Infusion of ET into the hand veins of patients with hypertension significantly enhances vasoconstrictor responses [41].

Elevated circulating levels of ET have been described in patients with hypertension and diabetes [42,43]. ET-1, which mostly acts in the cardiovascular system, was measured in 20 patients with essential hypertension and 12 age-matched control subjects [42]. Levels of plasma ET-1 were significantly higher among hypertensive patients as compared with control subjects. Furthermore, plasma ET-1 was higher among patients with stage 2 or 3 as compared with stage 1 hypertension. These findings have led researchers to target ET receptors as a mechanism to reduce BP in addition to other antihypertensive agents.

Clinical evidence

Since plasma ET levels have been related to severity of hypertension, ET antagonists have been tested in patients with resistant hypertension. Darusentan, a selective ET type A receptor antagonist (ERA), has been tested in patients with resistant hypertension. A randomized, double-blind, placebo-controlled trial tested darusentan in 379 patients with resistant hypertension [44]. Participants received placebo or darusentan 50, 100 or 300 mg for 14 weeks. All patients were receiving at least three antihypertensive medications, including a diuretic. Clinic systolic and diastolic BP were reduced by 9 ± 14/5 ± 8, 17 ± 15/10 ± 9, 18 ± 16/10 ± 9 and 18 ± 18/11 ± 10 mmHg with placebo, darusentan 50, 100 and 300 mg, respectively ($p < 0.0001$ for all three darusentan doses compared with placebo). There were no significant differences between darusentan dose groups. Edema and fluid retention occurred in 27% of patients within the darusentan group and 14% among those who received placebo, despite all patients being treated with diuretics. Modest increases in serum creatinine and decreases in estimated glomerular filtration rate were noted with 100 and 300 mg of darusentan.

In a different study, patients with uncontrolled BP despite treatment with at least three antihypertensive agents, including a diuretic, were randomly assigned to receive the selective ERA darusentan, central α-2 agonist guanfacine or placebo for 14 weeks [45]. Reduction in office systolic BP achieved with darusentan (15 ± 14 mmHg) was significantly greater than for guanfacine (12 ± 13 mmHg), but not greater than placebo (14 ± 14 mmHg). However, 24-h systolic BP reduction with darusentan (9 ± 12 mmHg) was significantly higher than guanfacine (4 ± 12 mmHg) or placebo (2 ± 12 mmHg). Similar to the previous study, adverse effects related to fluid retention occurred in approximately 30% of patients treated with darusentan, despite use of diuretics. Changes in the kidney function were not reported.

The ERA darusentan seems to be effective in the treatment of resistant hypertension. However, volume retention and exacerbation of heart failure, in spite of diuretic use, occur in almost a third of patients. More data on BP, as well as hypertension-related target-organ damage and cardiovascular events, and more safety data, are needed before ERA can be employed in the routine treatment of patients with resistant hypertension.

Nonpharmacological treatment

Dietary intervention

Background

Sodium causes target-organ damage, not only through hemodynamic (i.e., BP), but also through nonhemodynamic mechanisms. Dietary salt intake induces a complex series of events in the endothelium that appear to be independent of BP and the RAAS and culminate in the intravascular production of TGF-β and nitric oxide [46]. Furthermore, interstitial sodium storage may also be related to hypertension. Machnik *et al.* have demonstrated that a high-salt diet in rats induces interstitial hypertonic sodium accumulation and VEGF-C secretion by macrophages [47]. VEGF-C secretion leads to subsequent increase in density and hyperplasia of the lymph capillary network. VEGF-C blockade or macrophage depletion increased interstitial hypertonic volume retention, reduced endothelial nitric oxide synthase expression and elevated BP in the rats. In the same study, patients with resistant hypertension presented with significantly higher levels of VEGF-C compared with normotensive patients [47]. These results suggest that sodium storage in the tissues may be related to hypertension in humans, and that a new salt equilibrium may take longer to be achieved than previously thought with changes in dietary salt.

A relationship between salt and health was first observed more than 100 years ago [48]. Since then, numerous observational studies and clinical trials performed in general populations indicate that a high dietary salt intake is associated with higher BP. For example, in the International Study of Sodium, Potassium, and Blood Pressure (INTERSALT) study, a multinational evaluation that included more than 10,000 normotensive and hypertensive subjects from 52 populations, differences in dietary sodium ingestion of 100 mmol/day were associated with differences in systolic BP of approximately 2.2 mmHg after adjustment for age, sex, potassium excretion, BMI and alcohol intake [49]. When limited to hypertensive subjects, the positive relationship between salt ingestion and high levels of BP appears to be stronger. Meta-analyses of low-salt intervention trials indicate decreases in systolic BP of 3.7–7.0 mmHg and diastolic BP of 0.9–2.5 mmHg in hypertensive patients [50–52]. Despite wide evidence supporting the introduction of dietary salt restriction in the general hypertensive population, there is little evidence that this manoeuvre is of benefit in reducing BP

or preventing adverse outcomes during hypertensive pregnancies, and the practice has largely fallen out of favor.

Although the effects of reducing dietary sodium intake on office BP levels have been evaluated in the general hypertensive population, few studies have examined the role of dietary salt in patients with resistant hypertension *per se*.

Clinical evidence

Gavras *et al*. studied 16 patients with 'refractory' hypertension, defined as uncontrolled BP on maximum doses of at least one diuretic and one sympatholytic agent. Those patients were admitted to hospital and underwent extreme dietary salt restriction (10 mmol of sodium/day) in combination with intense diuretic therapy (either hydrochlorothiazide 100 mg or furosemide 80–200 mg daily) after ceasing other antihypertensive therapies [53]. BP decreased on average by 21/7 mmHg. However, this study had limited practical implications to the current practice as:

- The definition of refractory hypertension differs from the current definition;
- Such extreme sodium restriction (<1.0 g of salt) would be almost impossible to accomplish and maintain by patients in an outpatient setting without home delivery of specially prepared meals;
- The study was not able to assess the effects of low-salt diet in combination with other antihypertensive therapies as patients had their medications withdrawn before the study.

More recently, we published the results of a 4-week, randomized, crossover evaluation of 12 patients with resistant hypertension [54]. Subjects were on an average of 3.4 ± 0.5 medications, which included a thiazide diuretic (hydrochlorothiazide 25 mg daily) and an ACE inhibitor or ARB in all subjects. All patients remained on antihypertensive treatment during the study. Participants were randomized to the low- or high-salt diet for 1 week, and crossed over to the opposite diet for 1 week after 2 weeks of washout. The low-salt meals were formulated to provide 50 mmol of sodium per day (2.8 g of salt). During the period of high dietary salt intake, NaCl tablets (6 g/day) were added to the subject's regular diet with the intention to increase dietary sodium intake to more than 250 mmol/day (14.3 g of salt). Adherence to diet was confirmed by measurement of 24-h urinary sodium excretion.

Mean office systolic and diastolic BP were reduced by 22.7/9.1 mmHg during low- compared with high-salt diets. Low-salt diet decreased office, daytime, night-time and 24-h systolic and diastolic BP, to a similar degree to office BP when compared with high-salt ingestion (Figure 1). The BP reduction achieved during low-salt ingestion was estimated as being equivalent to adding two antihypertensive medications [55]. Considering BP reductions that have been observed in our study compared with clinical trials with untreated hypertensive subjects who were otherwise unselected, our study suggested that patients with resistant hypertension are particularly salt sensitive [55]. The fact that patients born with reduced renal mass and low birthweight demonstrate salt sensitivity raises the possibility that they may be predisposed to resistant forms of hypertension.

Resistant hypertension seems to be caused, among other factors, by volume retention, arterial stiffness and endothelial dysfunction. In our study, plasma renin activity increased and brain natriuretic peptide, body weight and creatinine clearance decreased significantly with low- as compared with high-salt diet. These findings suggest that intravascular fluid retention occurs during consumption of a high-salt diet in spite of the use of a conventional diuretic therapy. Augmentation index and aortic pulse-wave velocity, which are markers of arterial stiffness, tended to decrease with low- compared with high-salt diet, suggesting improvement (reduction) in vascular stiffness [54]. Last, endothelial function evaluated by brachial artery flow-mediated vasodilatation was significantly higher during low- compared with high-salt diet suggesting that high-salt intake impairs endothelial function in patients with resistant hypertension [Pimenta E & Calhoun DA, Unpublished Data].

It is of note that intravascular fluid retention observed during consumption of the high-salt diet occurred in spite of use of conventional diuretic therapy (hydrochlorothiazide 25 mg daily). Previous studies have indicated that adequate diuretic therapy may overcome salt-induced fluid retention. In a retrospective study, 53% of patients with uncontrolled hypertension had their BP controlled with proper use of diuretics, including use of appropriate diuretic (frusemide) based on renal function, increased dose of diuretics or combination of loop diuretic and thiazide or potassium-sparing diuretic [56]. The large BP reduction achieved with mineralocorticoid receptor blockers is probably related at least in part to their diuretic effect [57].

Weaknesses of our study included evaluation of a relatively small number of subjects and the short duration of the dietary treatment periods. However, analysis of data from other trials of salt reduction suggests that an even greater BP reduction would be expected with a longer intervention period [52]. Careful analysis of our data indicated that the crossover design did provide sufficient power to assess changes in office BP.

Continuous positive airway pressure

Background

Obstructive sleep apnea (OSA), defined as collapse of the upper airway structures during sleep resulting in disruption of breathing, which occurs periodically throughout sleep, is a strong and independent risk factor for the presence and future development of hypertension and cardiovascular diseases [58–62]. Cross-sectional studies indicate that the severity of OSA is related to BP and that hypertension occurring in subjects with OSA is more likely to be severe and resistant to treatment [58,62,63]. In 42 subjects with resistant hypertension referred to a university center, Logan *et al.* found that 83% of subjects had unsuspected OSA (apnea hypopnea index [AHI] ≥ 10 events/h) [64].

Clinical evidence

The effect of continuous positive airway pressure (CPAP) use on BP in patients with OSA has been minimal in most published reports [65–67]. However, the subgroup of patients with more severe hypertension may achieve greater benefits with CPAP treatment. In a retrospective study, long-term effects of CPAP therapy were assessed in patients with OSA (AHI > 5 events/h) and hypertension. After 1 year of follow-up, treatment with CPAP significantly reduced mean arterial pressure in patients with resistant hypertension, but not in patients with controlled hypertension. In a multivariate regression analysis, baseline and diuretic therapy, but not severity of OSA, were independently associated with a decrease in mean arterial pressure [68]. In a different study, 64 patients with resistant hypertension (office BP >140/90 mmHg) and OSA (AHI >15 events/h) were randomized to treatment with CPAP added to conventional medical treatment or conventional treatment alone for 3 months. Patients with confirmed resistant hypertension (24-h BP >125/80 mmHg) treated with CPAP (n = 20) showed a greater decrease in 24-h diastolic BP compared with those treated with conventional treatment (n = 21; -4.9 ± 6.4 vs 0.1 ± 7.3 mmHg; p = 0.027). Reductions in daytime diastolic, 24-h diastolic and systolic BP were significantly greater among patients who used CPAP for longer than 5.8 h [69]. Taking these results into consideration, OSA should be investigated in patients with resistant hypertension, and CPAP therapy is recommended for those with OSA. However, more studies are necessary to confirm the CPAP effects on BP reduction.

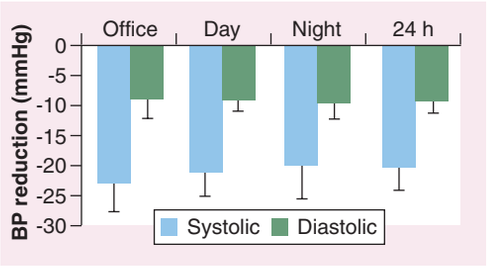

Figure 1. Blood pressure reduction achieved in office, daytime and night-time, and 24-h blood pressure with a low-salt compared with a high-salt diet.
BP: Blood pressure.

Baroreflex activation

Background

The carotid sinus is an important modulator of autonomic tone and regulates BP. The brain receives signals from the baroreceptors through afferent nerves, which subsequently reduces sympathetic outflow and BP. However, it is not clear whether baroreceptors play a major role in the short- or long-term BP regulation. Studies in the 1950s suggested not only that the carotid sinus could be involved in long-term BP regulation, but also that carotid stimulation acutely reduced BP. McCubbin *et al.* demonstrated reduced sinus nerve activity in renin-induced chronic hypertensive dogs and proposed that the carotid sinus functioned to maintain rather than lower BP [70]. Warner showed that electrical stimulation of the carotid artery in anesthetized dogs reduces BP and its antihypertensive effects were maintained after 90 min of discontinuing the stimulation [71]. In the same year, Carlsten *et al.* demonstrated a similar response in a normotensive man to that described in dogs [72].

Subsequent studies tested electrical carotid sinus nerve stimulation for treatment of human hypertension [73–75]. For example, 11 patients with severely elevated BP, ranging 190–300/110–220 mmHg (mean: 240/190 mmHg), received a rechargeable radiofrequency-induced stimulator [73]. Follow-up

data for a period of 5 months to 2.5 years was available in eight patients. BP reduction ranging 30–100/24–80 mmHg (mean: 48/42 mmHg). However, electrical carotid sinus nerve stimulation did present some limitations. Technical problems, such as reduced long-term effect, amount of stimulation required, size of the device and orthostatic hypotension, and also the development of new and effective antihypertensive medications, prevented the development of new devices for some time.

Experimental studies performed by Guyton *et al*. demonstrated that the baroreflex is an important mechanism for short-term regulation of BP, but is less important than other mechanisms, such as the RAAS, for chronic control [76]. However, subsequent studies carried out by Lohmeier *et al*. showed that arterial baroreceptors are rapidly reset in response to chronic high BP [77]. Since then, it has been hypothesized that, in response to high BP, baroreceptor afferents initially respond with discharges, but this response is reduced in the presence of sustained elevated BP establishing a new threshold for activation [70,78,79]. This led researchers to revisit treatment approaches targeting sympathetic deactivation through carotid stimulation in patients with hypertension.

Clinical evidence

Carotid sinus stimulation for the treatment of hypertension has been brought back into the limelight with a new device. A nonrandomized prospective feasibility study assessed safety and efficacy of a new implantable pulse generator [80]. In total, 45 patients with resistant hypertension, defined as BP at least 160/90 mmHg despite the use of at least three antihypertensive agents, received the device. The generator is implanted in the chest, similarly to a pacemaker, with leads that tunnel subcutaneously and are bilaterally attached to the carotid sinuses. Baseline mean BP was 179/105 mmHg, with a median of five antihypertensive medications. Only 37, 26 and 17 patients completed 3-month, 1- and 2-year follow-up, respectively. For these time points, office BP was reduced by 21/12, 30/20 and 33/22 mmHg (Figure 2). Mean 24-h ambulatory BP was reduced by 6/4, 13/8 and 24/13 mmHg for the same periods. One patient died 6 days after operation owing to angioneurotic edema before device activation. Two participants had the generator and leads removed owing to infection. One patient had the generator removed and reimplanted after 12 months. Another patient needed a second operation for repositioning of the generator. Other serious adverse events included preoperative stroke, tongue paresis, probably owing to hypoglossal nerve injury, and moderate pulmonary edema.

Despite good results overall, BP responses to baroreflex activation are very variable, with some patients not demonstrating any BP reduction at all. Furthermore, the procedure is not a minor one and surgical complications, such as hemorrhage, infection and cranial nerve injury, limit its wide applicability.

Renal denervation

Background

The sympathetic nervous system is an important contributory mechanism in both acute and chronic BP pressure elevation. Interruption of sympathetic nervous activation for treatment of hypertension has been targeted by radical surgical procedures. Although thoracic, abdominal or pelvic sympathectomy effectively reduced BP in patients with malignant hypertension, these procedures were associated with high rates of short- and long-term complications [81–84]. Severe postural hypotension and erectile, bladder and bowel dysfunction were commonly encountered in patients who underwent the procedure.

Reduction in BP after surgical renal denervation, and the demonstration that the sympathetic outflow to the kidneys is commonly activated in patients with essential hypertension and other diseases that present with sympathetic system overactivity, such as congestive heart failure, has stimulated novel treatments [85,86].

Ablation of afferent and efferent renal nerves, which lie in the wall of the renal artery, using radiofrequency energy has been successfully achieved using a percutaneous catheter-based approach. Unpublished studies using juvenile swine have shown that this reduced noradrenaline content in the kidney by more than 85% [87].

Clinical evidence

In a safety and proof-of-principle study, 45 patients with resistant hypertension underwent renal sympathetic denervation through a percutaneous radiofrequency catheter-based approach. Office BP was reduced by 14/10, 21/10, 22/1, 24/11 and 27/17 mmHg after 1, 3, 6, 9 and 12 months of follow-up, respectively. Renal noradrenaline spillover was measured in ten patients, and demonstrated a mean 47% reduction. Two patients developed periprocedure complications. One patient had renal artery dissection related to the catheter placement before delivery of radiofrequency energy. Another

patient developed pseudoaneurism of the femoral artery, which is a complication common to any femoral percutaneous procedure. A total of 14 patients had renal angiography repeated 14–18 days after renal sympathetic ablation and showed no evidence of renal artery stenosis. MRI was performed after 6 months following ablation in 14 patients. A nonobstructive lesion in an untreated location was seen in one patient [87].

In the Simplicity HTN-2 Trial, 106 patients with resistant hypertension were randomly assigned to renal denervation or control groups [88]. Patients randomized to renal denervation had baseline BP of 178/97 mmHg on 5.2 antihypertensive medications. Baseline BP was 178/98 mmHg, in spite of the use of 5.3 antihypertensive agents in the control group. Change to baseline doses of antihypertensive medications were not allowed in either group, unless judged medically necessary due to signs and symptoms related to BP elevation. BP fell by 32/12 mmHg ($p < 0.0001$ both for systolic and diastolic) 6 months after renal denervation and by 1/0 mmHg in the control group (p = not significant) (Figure 3). Data from 24-h ambulatory BP monitoring available for 32 patients who underwent renal denervation showed a BP reduction of 11/7 mmHg.

Although the results of these studies are striking, some issues should be taken into consideration. Although several studies have consistently demonstrated the efficacy of mineralocorticoid receptor blockers in resistant hypertension, only 17% of patients in this study were taking aldosterone antagonists. Second, 24-h ambulatory BP results were inferior to the office BP results, and to those seen with other modalities of treatment, such as spironolactone and low dietary salt. Nevertheless, this procedure holds promise as a potentially major new addition to the range of treatment options that can be offered to patients with otherwise poorly controlled hypertension. Importantly, as well, it has provided interesting new information and opened up new avenues of exploration regarding the role of sympathetic activity in BP regulation and the development of essential hypertension. Future studies are needed to further address the long-term effects of renal denervation and its safety and effectiveness in other disease states, such as congestive heart failure.

Conclusion & future perspective

Resistant hypertension is an increasingly common medical problem, and patients with this condition are at high risk of cardiovascular events. Secondary hypertension may be the underlying cause of resistant hypertension and, because a specific, and sometimes definite, treatment is available, a thorough investigation is mandatory in patients with uncontrolled BP despite treatment with multiple antihypertensive medications. However, for the majority of these patients in whom an underlying cause cannot be found, strategies towards improved control, including the use of mineralocorticoid antagonists and low-sodium diet, and new technologies, such as renal sympathetic denervation, hold promise as new treatment approaches (Table 1). For now, until further data regarding long-term efficacy and safety of those procedures become available, it would seem prudent to recommend the less expensive and less invasive strategies as

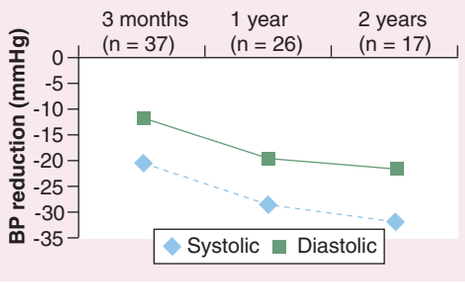

Figure 2. Mean change in office blood pressure with baroreflex activation therapy.
BP: Blood pressure.

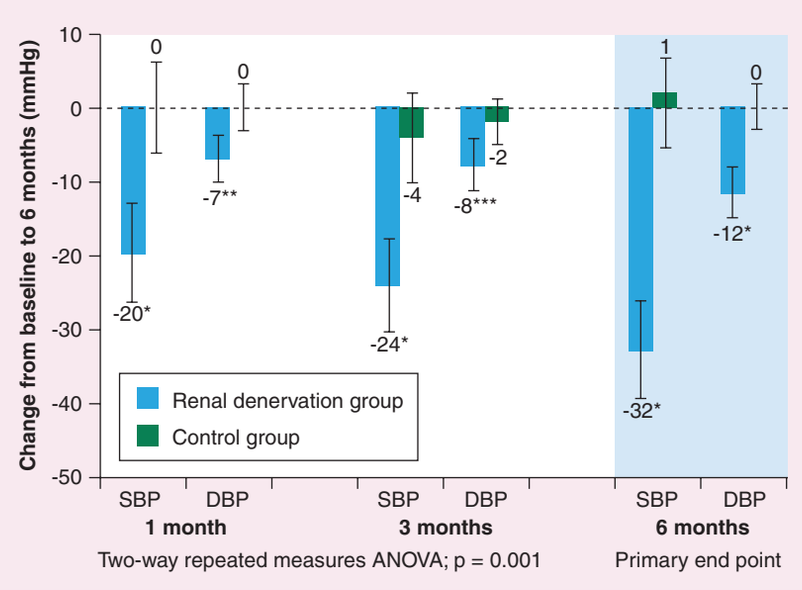

Figure 3. Paired changes in office systolic and diastolic blood pressures at 1, 3 and 6 months for renal denervation and control groups. Error bars are 95% CI.
*$p < 0.0001$; **p = 0.002; ***p = 0.005.
DBP: Diastolic blood pressure; SBP: Systolic blood pressure.

Table 1. Effectiveness data from some studies involving patients with resistant hypertension.

Intervention	Number of participants	Baseline office BP (mmHg)	Number of medications	Follow-up	Office BP reduction (mmHg)	24-h BP reduction (mmHg)	Ref.
Spironolactone							
Ouzan *et al.* (2002)	25	152/86[†]	≥2	1 month		24/10	[25]
Mahmud *et al.* (2005)	39	167/95	≥3	3.7 months	28/13		[29]
Nishizaka *et al.* (2003)	76	163/91	4.0	6 months	25/12		[26]
Chapman *et al.* (2007)	1411	157/85	2.9	1.3 years (mean)	22/10		[27]
Lane *et al.* (2007)	119	178/93	3.7	3 months	21.7/8.5		[24]
Alvarez-Alvarez *et al.* (2010)	42	158/80	4.1	12 weeks	32/21	21/9	[31]
Eplerenone							
Calhoun and White (2008)	52	151/84	3.6	12 weeks	18/10	12/6	[33]
Darusentan							
Weber *et al.* (2009)	85[‡]	151/86	≥3	14 weeks	18/11		[44]
Bakris *et al.* (2010)	364	151/88	≥3	14 weeks	15/10	9/–	[45]
Salt reduction							
Pimenta *et al.* (2009)	12	146/84	3.4	1 week	21/10	20/10	[54]
Baroreflex activation							
Scheffers *et al.* (2010)	45	179/105	5	2 years	33/22 (from 17 patients)	24/13 (from 17 patients)	[80]
Renal denervation							
Krum *et al.* (2009)	45	177/101	4.7	1 year	27/17 (from 9 patients)		[87]
Esler *et al.* (2010)	52	178/97	5.2	6 months	32/12	11/7 (from 20 patients)	[88]

[†]24-h ambulatory blood pressure.
[‡]Patients treated with 300 mg of darusentan.
BP: Blood pressure.

first line, reserving invasive procedures for those patients who remain poorly controlled and at high risk of cardiovascular events.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Resistant hypertension is a common medical problem, and patients with this condition are at high risk of cardiovascular events.
- Since the prevalence of secondary causes of hypertension is increased in patients with resistant hypertension, all patients should be investigated for secondary causes with referral to an appropriate specialist as needed.
- Spironolactone and a low-salt diet should be considered in all patients with resistant hypertension.
- New antihypertensive medications, such as selective endothelin type A receptor antagonists, and new technologies, such as carotid stimulation and renal denervation, hold promise as new treatment approaches.

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