Treatment of Resistant Hypertension in 2013: Do we have a magic bullet?

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May 31, 2013

This is to acknowledge that Wanpen Vongpatanasin, MD has received funding for research and/or consulting work with commercial concerns related to this program. Dr. Vongpatanasin will also be discussing off-label uses in her presentation.

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- Purpose & Overview – To determine prevalence, etiology, and management of resistant hypertension
- Objectives –
  1. To determine prevalence of resistant hypertension in the U.S.
  2. To determine etiology of resistant hypertension
  3. To determine pharmacologic and nonpharmacologic treatment of resistant hypertension

Definition and Prevalence of Resistant Hypertension

Resistant hypertension is defined as inability to achieve BP goal, despite maximal or near maximal doses of three or more antihypertensive medications, including a diuretic by the JNC 7 [1]. The AHA positional statement in 2008 has similar definition but also expanded resistant hypertension to include ability to achieve BP < 140/90 mmHg but requiring at least 4 antihypertensive drugs [2]. Although the overall prevalence of hypertension in the US remains unchanged in the past decade, the prevalence of uncontrolled hypertension among treated hypertensive patients requiring 3 or more drugs, has almost doubled in recent years from 16 to 28% [3]. It is estimated that 8.9% of all hypertensive patients [4] and 12.9 % of treated hypertensive patients have resistant form of hypertension [5]. Presence of resistant hypertension, particularly despite ≥ 5 drugs is independently associated with poor cardiovascular prognosis [6]. Therefore, complete understanding of pathogenesis and treatment of resistant hypertension is essential in preventing these unfavorable outcomes. Generally, systolic BP is more difficult to control than diastolic BP and most clinical trials of hypertension demonstrate that only 60% of patients achieve systolic BP below 140 mmHg whereas 90% of patients reach diastolic BP goal below 90 mmHg despite frequent follow-up and careful titration of medications [7]. Patients with truly resistant hypertension, both at home and in the office, have higher prevalence of target organ damage such as left ventricular hypertrophy, retinopathy, and albuminuria [8] and experienced worse cardiovascular events than patients who have BP elevation only in the clinic and patients with well-controlled hypertension both in and out of office [9, 10].

White coat effect

The first step in the evaluation of patients with resistant hypertension is to exclude presence of pseudo-resistance from white coat effect or nonadherence to medications. Systolic BP may drop significantly between 10-20 mmHg after period of rest for 3-30 minutes in the office [11]. Thus, clinic BP should be obtained at least twice after resting for at least 5 minutes. Even with appropriate measurement technique, white-coat effect (WCE) is known to be larger when BP is obtained by physicians than by the nurses or automatic BP monitors without any healthcare providers present in the room [12]. Isolated elevation of BP in the office in the presence of normal home BP or ambulatory BP, is common during treatment with antihypertensive medications and may lead clinicians to label patients with resistant hypertension. Prevalence of isolated office BP elevation or false resistant hypertension in treated hypertensive is reported to be between 15-30% in recent studies. [9, 13]

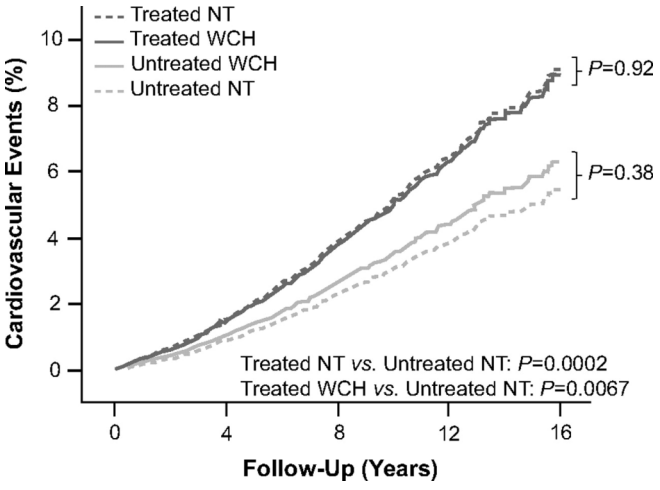


Fig 1. Meta-analysis of International Database on Ambulatory Blood Pressure Monitoring from 11 countries showing similar cardiovascular events in hypertensive patients with normal BP both at home and in the clinic (Treated NT) vs treated patients with high BP only in the office with normal ambulatory BP (Treated WCH).

Patients with BP elevation only in the office have lower cardiovascular mortality than those with BP elevation both in and out-of-office [14], but is similar those with normal BP both in and out-of-office according to the recent meta-analysis of International Database on Ambulatory Blood Pressure Monitoring from 11 countries (fig 1) [10]. Therefore, regular home BP monitoring and/or ambulatory BP monitoring should be an essential part of evaluation in patients with apparently resistant hypertension in the office.

Nonadherence to medications

Nonadherence to pharmacological treatment is another cause of apparently resistant hypertension. Data from studies using electronic pillboxes indicated that only 50-60% of hypertensive patients enrolled in hypertension research studies adhered to single drug prescription after 1 year [15]. In older studies, prevalence of medication nonadherence among patients with resistant hypertension (RH) referred to hypertension centers was found to be only between 10-16% [16, 17]. Reliance on patient self-report of adherence or physician judgment alone however, may underestimate the true prevalence in previous studies since they are notoriously far from accurate [18, 19].

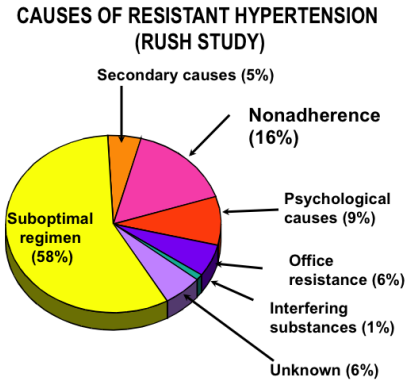


Fig 2. Prevalence of nonadherence to antihypertensive medications and etiology of resistant hypertension in patients referred to a tertiary care clinic.

In contrast, one recent study from a hypertension referral center in Germany using therapeutic drug monitoring (TDM) showed an extremely high prevalence of nonadherence of 53% as evidenced by undetected levels of at least 1 antihypertensive drug prescribed in the urine samples (fig 3) [20].

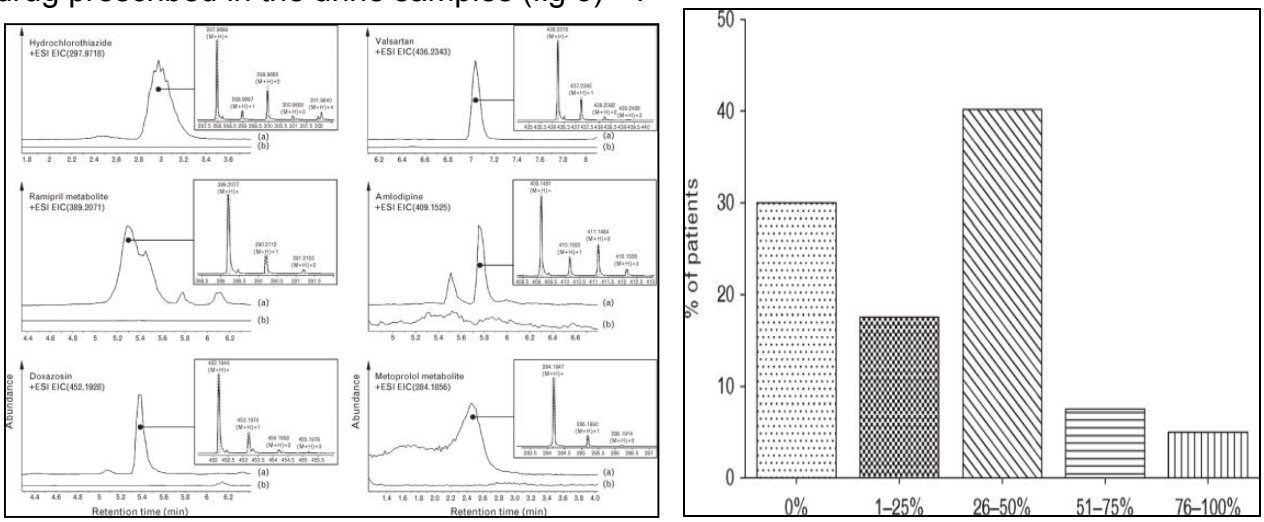


Fig 3. (left) Analytical data of six antihypertensive drugs in urine samples of compliant patients (a) and of patients without the respective medication (b, blank urine). (right) Percentage of prescribed drugs taken by nonadherent patients.

In addition to TDM, adherence to medications can be assessed by variety of techniques including electronic pillboxes, pill count, or prescription fill rate. Electronic monitoring with pillboxes which record the date and time of bottle cap openings is still strictly limited to research, due to high cost of the pill boxes, requirement for specialized computer software, and the fact that it is not reimbursable by any insurance carrier in the U.S. [21]. Pill count is accurate in determining adherence only in 50-70% of patients when compared to electronic pillboxes [22, 23] and 68% when compared to therapeutic drug monitoring [24]. Prescription fill rate is time consuming to track and information may not be accurate if the patients are not in the integrated health care system or do not take the dispensed medication. Since assay for many antihypertensive drug levels are now commercially available, screening for nonadherence with TDM represents a promising modality in clinical practice given the ease of use. However, its widespread application in the primary care setting requires further evaluation.

Dietary Sodium

After excluding pseudo-resistance, efforts should be made to identify potential lifestyle factors contributing to uncontrolled hypertension, such as high sodium intake, obesity, and excessive alcohol use. Among these factors, sodium intake is a major factor contributing resistant hypertension. Salt consumption in the United States has increased by 50% in the past 2 decades due to increased availability of processed food and fast food vendors [25]. Meta-analysis of clinical trials of sodium restriction indicates that reduction in sodium intake to approximately 75 mmol/day, which is half of average sodium intake in adults, reduces BP by 5/3 mmHg in hypertensive patients [26]. Low sodium diet when combined with diet rich in fruit, vegetables, and low fat diary product or the "DASH" diet, effects on BP is even more dramatic up to 12/6 mmHg [27]. Although this magnitude of reduction appears to be modest, effects are even more pronounced in patients with resistant hypertension as a recent study showed additional reduction in 24-hour ambulatory BP by 23/9 mmHg when sodium intake was decreased from 250 mmol/day to 50 mmol/day ($p < 0.01$) [28].

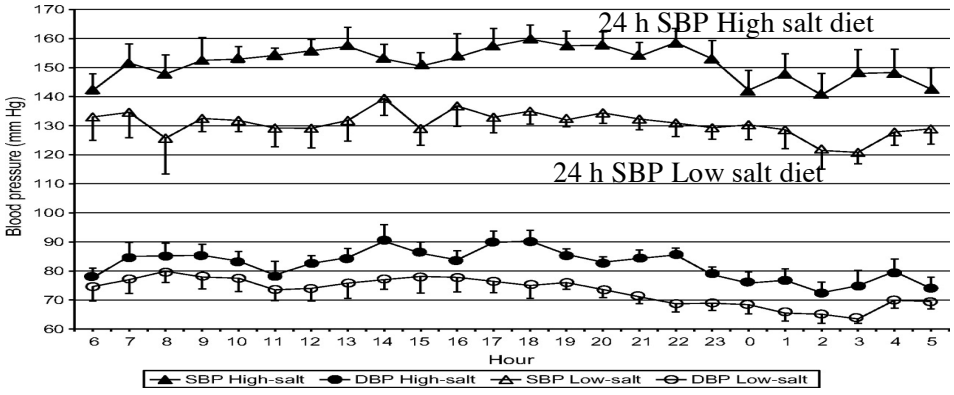


Fig 4. Changes in 24 hr ambulatory BP with when dietary sodium was decreased from 250 mmol/ to 50 mmol/day in patients with resistant hypertension despite 3 medications, including a diuretic.

According to the Dietary Guidelines for Americans, 2010, all U.S. residents aged ≥2 years should limit daily sodium intake to <2,300 mg. Population subgroups that would benefit from further reducing sodium intake to 1,500 mg (or 65 mmol) daily include 1) persons aged ≥51 years, 2) blacks, and 3) persons with hypertension, diabetes, or chronic kidney disease. Unfortunately, the average sodium consumption in the U.S. is far above recommended range of 3,400 mg /day (8.5 grams of salt) and 98.6% of Americans with a 1,500 mg daily recommendation, consumed >1,500 mg sodium on a

usual daily basis, while 88.2% of persons with a sodium recommendation of <2,300 mg daily, consumed ≥ 2,300 mg on a usual daily basis [29]. Approximately 75% of sodium consumed in the U.S. is added to processed foods or to restaurant foods during preparation and only about 25% of sodium is added at the table [30]. Thus, avoiding table salt alone will not be adequate and advising patients to read nutritional label carefully will be an essential part in limiting sodium intake and getting BP under control as much as possible.

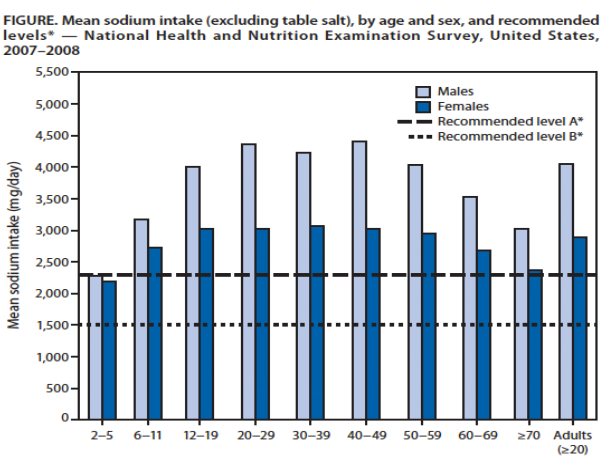


Fig 5. Mean sodium intake, NHANES 2007-2008 data. Average daily sodium consumption is above 2300 mg/day (100 mmol/d, level A) for healthy people and almost all of the U.S. population consumes > 1,500 mg/day, which is the level recommended for hypertensive patients (65 mmol/d, level B).

Obesity

Obesity is a well known risk factor for hypertension and even modest amount of weight gain of 1 kilogram of per year is associated with increased risk of hypertension by 20-40% in prospective studies [31]. Prevalence of obesity in resistant hypertension confirmed by 24-hour ambulatory BP monitoring was reported to be between 40-50% [8]. Treatment of obesity with life-style modification or pharmacologic therapy can reduce systolic BP by 4-6 mmHg per each 10-kilogram reduction in body weight [32]. Bariatric surgery causes a more dramatic reduction in body weight. However, BP lowering effects of bariatric surgery during long-term follow-up appears to be more modest despite sustained reduction in body weight [32, 33].

Drug-induced hypertension

Concomitant administration of prescription and nonprescription drugs can raise BP or interfere with efficacy of antihypertensive medications. It was estimated that 25% of patients in primary care clinic settings use at least one nonprescription drug on a regular basis. Substances that may raise BP, contribute to resistant hypertension is shown in table 1. Exogenous glucocorticoids and mineralocorticoids are the main component in many over the counter supplements known as “stress tablets” and can promote unexplained hypertension and hypokalemia. Administration of many stimulants and sympathomimetics for weight loss such as ephedra or amphetamine or treatment of attention-deficit/hyperactivity disorder with methylphenidate or amphetamine derivatives can cause sustained BP elevations. Nasal decongestants such as pseudoephedrine and phenylpropanolamine can raise BP by alpha-adrenergic mediated vasoconstriction [34]. Oral contraceptives use in premenopausal women and oral estrogen administration for postmenopausal women can cause a small but significant increase in BP, even with lower estrogenic content in modern preparation. [35] Nonsteroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitor can interfere with BP lowering effects of many classes of drugs, particularly angiotensin-converting enzyme inhibitor (ACEI),

angiotensin receptor blocker (ARB), and diuretics. Another relatively common ingredient in many over the counter supplements includes licorice, which induces hypertension by inhibiting 11-β hydroxysteroid dehydrogenase 2 causing syndrome of apparent mineralocorticoid excess. Thus, detailed history of over the counter supplements should be obtained in all patients.

Secondary Hypertension

Secondary hypertension contributes to 10-20% of all resistant hypertensive cases. Common secondary causes of resistant hypertension are obstructive sleep apnea, primary aldosteronism, renal parenchymal diseases, and renal artery stenosis. Pheochromocytoma, and other endocrine hypertension are much less common causes of resistant hypertension. Screening for secondary causes in patients with truly resistant hypertension should be conducted according to clinical presentation since work up is often costly.

Primary aldosteronism

Aldosterone excess, either from idiopathic bilateral adrenal hyperplasia or aldosterone producing adenoma, is another common cause of resistant hypertension. Although aldosterone is known to increase blood pressure (BP) by promoting renal sodium retention, an increasing body of evidence indicates that aldosterone also acts centrally to stimulate the sympathetic nervous system, which may further contribute to resistance to pharmacologic treatment of hypertension alone [36-38]. A recent study showed presence of sympathetic overactivity in patients with PA which is normalized in a subset of subjects after removal of aldosterone-producing adenoma [39]. Previous studies have indicated that 10-20% of patients referred to hypertension clinic at a tertiary care center have primary aldosteronism (PA) confirmed by salt loading test. [40-42] Patients with PA experienced higher cardiovascular event rates than those with essential hypertension [43, 44], which is reduced after surgery or spironolactone treatment. Patients with primary aldosteronism frequently have concomitant obstructive sleep apnea by a mechanism that is still not fully elucidated. [45] Therefore, history of insomnia and sleep apnea should carefully be obtained in patients with hyperaldosteronism. Patients with bilateral disease should be treated with either spironolactone or eplerenone.

Variables	Preop	Postop
BP (mmHg)	**157/96**	**127/79**
Normotensive off BP meds	**0**	**4 (16%)**
Number of BP meds	**3**	**1.8**
Serum K (mmol/L)	**3.5**	**4.3**
Potassium supplements (mmol/d)	**25**	**0**

Table 1: Clinical outcomes in patients with aldosterone producing adenoma after surgical resection of tumor (UTSW experience) [46].

However, higher doses of mineralocorticoid receptor antagonists, particularly eplerenone, are often required to control BP [47]. Patients with unilateral tumor should undergo surgical removal of adenoma as it was shown to cure hypertension in between 16-86% [46, 48]. Furthermore, quality of life was shown to be impaired before surgery but was improved after surgery to similar level found in normal population [48].

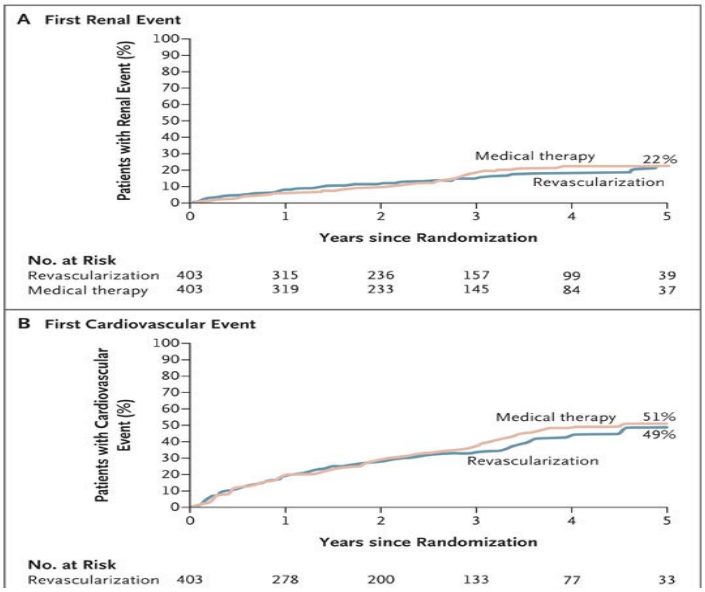
Renal parenchymal disease

Renal parenchymal disease could be a cause or a consequence of hypertension. Recent epidemiological study indicates that 11% of adult population in the U.S. have chronic kidney disease (CKD). [49] Hypertension is very common in CKD but is much more difficult to control. Despite requirement for larger numbers of antihypertensive medications, hypertension control rate in the U.S. in CKD patients is less than 30% compared with 50% in non CKD patients. [50] Diabetes mellitus and hypertension are two major causes of ESRD in the adults, whereas glomerulonephritis and cystic disease of the kidney are less frequent. Hypertension related to renal parenchymal disease has traditionally been viewed as being largely volume dependent, due to the failing kidney's inability to excrete salt and water. However, in the overwhelming majority of patients, the main hemodynamic fault is the increased systemic vascular resistance from activation of renin-angiotensin-aldosterone system or sympathetic nervous system.

Renovascular hypertension

Renovascular hypertension is another relatively common cause of secondary hypertension, accounting for 5-7% of hypertension in patients over the age of 60 [51]. The minimal degree of stenosis that reduces renal perfusion in humans is not known but, in dogs, diameter stenosis of > 70% is needed to decrease renal blood flow and increase the systemic arterial pressure [52]. Diameter stenosis between 50-70% is also considered to be significant stenosis by some investigators, if the systolic pressure gradient across the lesion is more than 20 mmHg based on canine studies [53]. Atherosclerosis is the major form of renal artery pathology in the elderly, as fibromuscular dysplasia is seen predominantly in young adults. Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory vascular disease that may involve not only the renal arteries, but also many other vascular beds such as extracranial carotid and vertebral arteries. The largest series of FMD, the United States registry for Fibromuscular Dysplasia including 447 FMD patients showed that aneurysm and dissection of any vascular bed occurred in 17-20% of patients [54]. Hypertension, headache, and pulsatile tinnitus were the most common presenting symptoms of the disease. Assessing severity of FMD by angiography alone is difficult given multiple beaded and aneurysmal appearance of the lesion and measurement of pressure gradient across the stenosis is often needed. Angioplasty is the most common mode of revascularization and stenting is rarely needed unless in the usual circumstance. In a recent meta-analysis, revascularization of FMD resulted in hypertension cure rate of approximately 25% [55].

In contrast to FMD, stent implantation is usually required for atherosclerotic renal artery stenosis (RAS). Furthermore, the outcomes are less impressive for revascularization of atherosclerotic diseases. The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial randomized 806 patients with atherosclerotic renal artery stenosis to revascularization plus medical therapy vs medical therapy alone and showed no difference in BP or renal function between the 2 groups during the average follow up of 34 months [56]. The study was criticized for its study design as randomization included only patients whom benefits of revascularization was uncertain as per their physician judgment. Thus, many high-risk patients were excluded from the study. However, another smaller trial, the **ST**ent placement and blood pressure and lipid-lowering for the



prevention of progressive renal dysfunction caused by **A**therosclerotic ostial stenosis of the **R**enal artery (STAR) trial, also showed no benefit of revascularization in a smaller number of patients with atherosclerotic renal artery stenosis [57]. Meta-analysis of percutaneous renal intervention (PTRI) trials to date showed only modest effect of PTRI on BP control of 3 mmHg with no significant effect on serum creatinine of –7.26 mmol/L or 0.08 mg/dL (p = 0.07) [58].

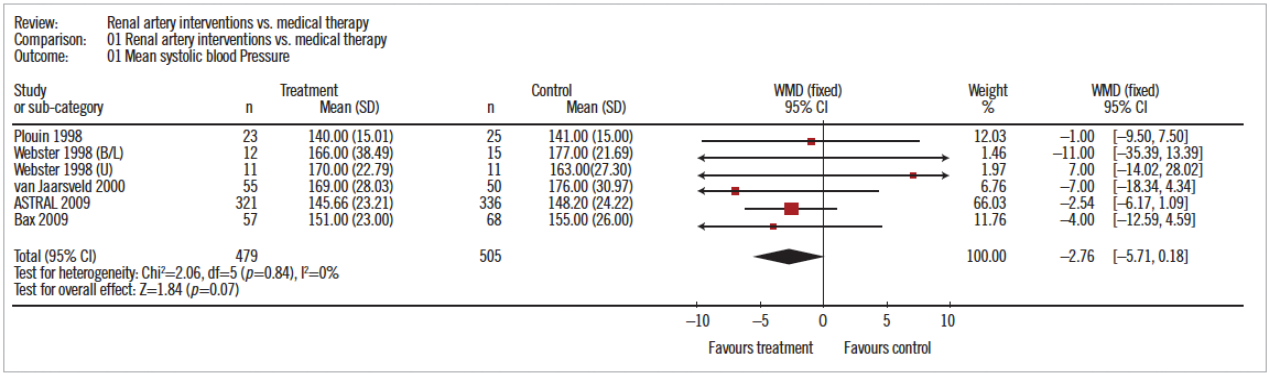


Fig 7. Meta-analysis of clinical trials comparing changes in systolic BP in response to PRI vs medical therapy.

Mechanisms underlying lack of benefit of revascularization on BP control or renal function are unknown but could be related to distal embolization causing platelet activation and occlusion of microcirculation during percutaneous intervention. However, a small randomized study showed no benefit of either embolic protection device Angioguard alone or monoclonal antibody against platelet glycoprotein (GP) IIb/IIIa receptor Abciximab alone in improving renal function or BP after percutaneous revascularization [59].

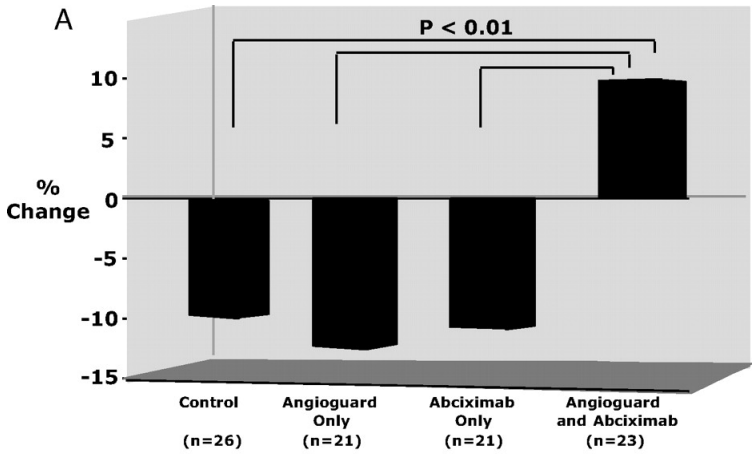


Fig 8. Changes in eGFR in response to renal stenting alone (control), stentingplus embolic protection device alone (Angioguard only), stenting plus IIb/IIIa inhibitor (Abciximab only), or stenting plus Angioguard and Abciximab in the RESIST study [59].

Only the group of patients who received both embolic protection device and abciximab showed improvement of renal function after stent implantation. The finding remains to be further confirmed in larger clinical trials [59]. Another explanation underlying modest effect of revascularization on BP to date is inclusion of patients with relative mild stenosis. In the ASTRAL trial, approximately 40% of patients had angiographic stenosis < 70% while 30% of patients in the STAR trial had angiographic stenosis between 50-70%. The challenge in the renal revascularization arena is the lack of gold standard in establishing functional severity of renal artery stenosis. Although resting pressure gradient across the lesion of at least 20 mmHg may suggest presence of hemodynamically significant lesion, it is well known that pressure gradient across any given vascular bed is flow-dependent.

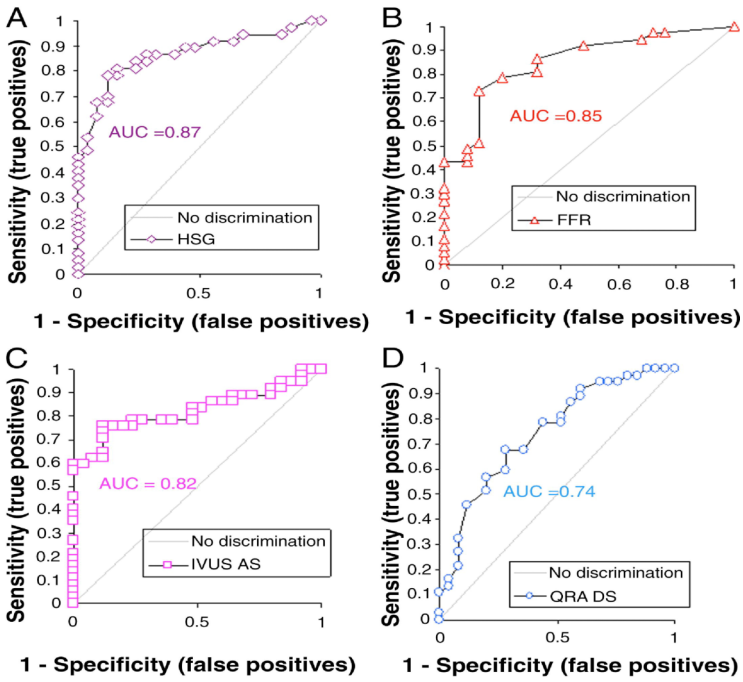


Fig 9. ROC analyses showing higher AUC of hyperemic systolic pressure gradient (HSG) and fractional flow reserve (FFR) in predicting BP response to PRI compared with angiographic diameter stenosis (QRA DS)

Thus, pressure gradient during maximal flow may be more indicative of severity of stenosis. Indeed, a recent large observation study suggested hyperemic systolic pressure gradient during papaverine infusion to be a better predictor of BP improvement after renal revascularization than resting pressure gradient or angiographic stenosis [60].

The NIH-sponsored **C**ardiovascular **O**utcomes in **R**enal **A**therosclerotic **L**esions (CORAL) trial addressed some of the limitations in previous trials by randomizing patients with atherosclerotic renal artery stenosis of at least 60% to stenting plus embolic protection device on top of optimal medical therapy. Only patients with pressure gradient across the lesion of at least 20 mmHg are eligible for the study. Results of the CORAL trial will be announced in November this year. Until the results of CORAL trial is available, revascularization of renal artery stenosis should be limited to patients with resistant hypertension and significant (≥ 70%) RAS in the presence of: a) unilateral small kidney (but avoiding atrophic kidney with size < 7 cm), b) progressive renal dysfunction despite medical therapy, c) bilateral RAS or RAS to a solitary functioning kidney, and d) unexplained CHF or sudden pulmonary edema. It is important to emphasize that ACEIs and ARBs are not contraindicated in patients with unilateral RAS since they are included part of medical therapy in most randomized trials such as ASTRAL and STAR. Treatment with statin drugs with or without ezetimibe should also be part of medical therapy in these patients since they have been shown to reduce cardiovascular events in patients with advanced chronic kidney diseases in the SHARP

clinical trial [61] and attenuate the decline in renal function in patients with atherosclerotic RAS in an observation study [62].

Obstructive Sleep Apnea (OSA)

OSA is a well-established independent risk factor for development of hypertension. As majority of the population in the U.S. are overweight or obese, OSA is now a common condition, affecting that 9-24% of population in the United States [63, 64]. Prevalence of OSA in patients with heart failure and chronic kidney disease is reported to be higher between 60-70 % while prevalence of OSA in patients with resistant hypertension is as high as 70-83% [65, 66]. Treatment with continuous positive airway pressure (CPAP) was shown to have modest effect on BP (reduction of only 2-3 mmHg) in hypertensive patients with OSA. [67, 68] This is mainly due to poor long-term compliance as less than 50% of patients still continue to use CPAP after 6 months [69]. Therefore, target BP is rarely achieved with addition of CPAP alone without further adjustment of antihypertensive medications. Interestingly, rostral fluid redistribution at bedtime from the lower extremities was recently shown to be associated with narrowing of airway in the supine position and worsening of OSA, which may contribute to uncontrolled hypertension [70, 71]. Gaddam et al. [72] tested the potential effects of spironolactone in a small number of patients with resistant hypertension and found that spironolactone significantly reduced weight, ambulatory BP, and OSA severity. However, the number of subjects participated in the study is small and the role of diuretics in reducing sleep apnea needs to be further investigated.

Clinical approach to resistant hypertension

Presence of pseudo-resistance should be excluded in patients with treatment resistant hypertension. If white coat effect is suspected, home BP and/or 24-hour ambulatory BP monitoring should be obtained, particularly in patients with minimal or no evidence of target organ damage. Next, nonadherence to pharmacologic and nonpharmacologic should be assessed. Detailed history taking is helpful in assessing levels of salt intake. However, 24-hour urine sodium is more accurate and may needed in some patients whom reliable history of salt intake cannot be obtained.

Examining remaining pills in the bottles and frequency of medication refill from the pharmacy is helpful in assessing adherence to BP medications. Presence of persistently elevated heart rate despite high doses of beta blockers, diltiazem, or verapamil or absence of side effects to specific BP medications such as lack of drug mouth or drowsiness despite high dose of clonidine or lack of hypertrichosis or edema despite high dose of minoxidil should prompt clinicians to suspect nonadherence to medications. Serum or urinary levels of many older antihypertensive agents such as beta-blockers, clonidine, spironolactone, amlodipine, diltiazem and verapamil are commercially available and may be helpful in some patients who are highly suspected to be nonadherent to medical regimen. Detailed history of prescription and nonprescription drugs and herbal supplement use should also be obtained. Urinary toxicological screening may be needed in some patients whom substance abuses are suspected.

Work up for secondary hypertension should be considered in patients with suspected features. Hypokalemia should prompt screening test for aldosteronism and cortisol excess. Plasma renin and serum aldosterone levels can be obtained while patients are taking most antihypertensive drugs except for mineralocorticoid receptor antagonists or direct renin inhibitors. However, confirmation test with salt loading test should be done after discontinuation of thiazide diuretics, angiotensin converting enzyme inhibitor, and angiotensin receptor blocker for 2-3 weeks and discontinuation of aldosterone antagonists for at least 6 weeks. During the period of workup, patients need to be on other antihypertensive agents such as calcium channel blockers, beta blockers, alpha blockers, or central sympatholytic drug. Patients who are found to have suppressed renin levels or activity in the presence of elevated serum aldosterone levels of 15 ng/dl or greater should undergo salt loading test or be referred to hypertension specialists. Patients who have insuppressible aldosterone levels after salt loading should undergo adrenal vein sampling as imaging of adrenal glands is not reliable in separating patients with idiopathic hyperplasia from those with aldosterone-producing adenoma [46]. Patients with history of loud snoring, insomnia, and/or daytime fatigue should under polysomnography. Imaging of renal arteries with CT angiography or MR angiography should also be obtained in patients with resistant hypertension to exclude renal artery stenosis. Hormonal testing to exclude other less common endocrine hypertension such as pheochromocytoma, Cushing syndrome, thyrotoxicosis, should be performed in selected patients based on clinical presentation.

Screening for renovascular hypertension should be considered in patients with a) onset of hypertension at <30 years of age or severe hypertension at >55 years of age, b) accelerated or malignant hypertension, c) unexplained atrophic kidney or size discrepancy >1.5 cm between kidneys, d) sudden, unexplained pulmonary edema, e) unexplained renal dysfunction, including individuals starting renal replacement therapy, and f) development of new azotemia or worsening renal function after administration of an ACE inhibitor or ARB agent. [73]

Management

The first simple step in managing resistant hypertension, after excluding white-coat effect, medical nonadherence, and secondary hypertension, is to determine if patients are on appropriate class of diuretics based on renal function. While patients with eGFR less than 30 ml/min/ 1.73 m^2 should be treated with loop diuretics, those with eGFR of at least 30 ml/min/ 1.73 m^2 should be thiazide-type diuretics, given longer half-life and efficacy in lowering BP. On a milligram to milligram basis, chlorthalidone was shown to be at least twice as potent

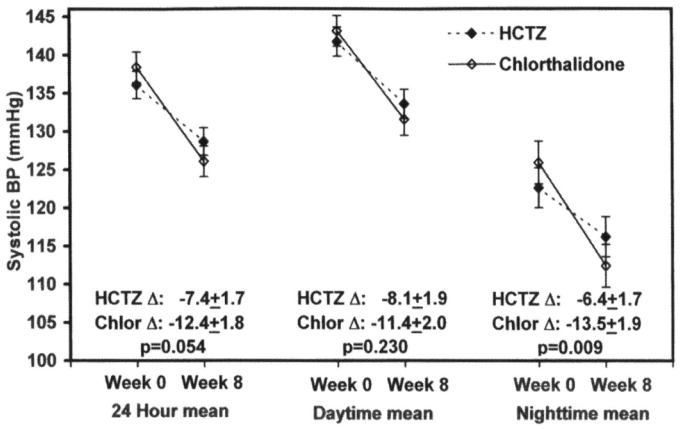


Fig 9. Changes in ambulatory BP in response to HCTZ 25 mg vs chlorthalidone 12.5 mg daily.

as hydrochlorothiazide (HCTZ) in lowering BP. Even with twice higher dose, HCTZ is not as effective as chlorthalidone in lowering 24 hr ambulatory BP, particularly nighttime BP (fig 9) [74]. However, the dose of chlorthalidone should be limited to 25 mg/day or less since higher doses are associated with increased metabolic side effects, particularly type 2 diabetes mellitus. A recent study has demonstrated that the diabetogenic side effects of chlorthalidone can be reversed by co-administration of spironolactone, which was independent of serum potassium or BP, suggesting mineralocorticoid receptor mediated process [75].

Assessment of hemodynamic variables is also helpful in deciding appropriate drug combination. Addition of beta-adrenergic receptor (AR) blockers and central sympatholytic drug should be avoided in patients with very slow heart rate, as it may exacerbate bradyarrhythmia or heart block. These patients should be treated with vasodilators such as dihydropyridine calcium channel blockers (CCB), ACEI, ARB, hydralazine, etc. Patients with elevated resting heart rate is more likely to derive large BP reduction with beta blockers, diltiazem, or verapamil as elevated heart rate is usually a good indicator for hyperkinetic circulation in hypertensive patients.

Addition of spironolactone should also be considered in the patients with resistant hypertension despite adjustment of medications as mentioned above. There is increasing evidence that low-dose spironolactone between 12.5-25 mg/day, which is not likely to produce a major diuretic effect, causes a dramatic fall in BP on average of 25/12 mmHg, when used as add-on therapy in patients with uncontrolled hypertension in numerous observation studies [76, 77]. In a recent randomized placebo controlled trial ASPIRANT, spironolactone was found to reduce 24-hour ambulatory BP by 10 mmHg when compared to placebo in patients with resistant hypertension [78]. Antihypertensive effect of spironolactone is observed even in patients with essential hypertension without elevated aldosterone-to-renin ratio [79]. Combination of dihydropyridine and nondihydropyridine appears to have additive effects on peripheral vasodilation and BP, possibly due to binding to different sites of the receptors [80, 81] and should also be considered in these patients if BP fails to reduce with either subclass alone. In contrast, addition of ARB to ACEI has modest effects on BP on average of only 5/4 mmHg [82]. Addition of long-acting nitrates should also be considered in patients with isolated systolic hypertension who are refractory to treatment as it has been shown to beneficial in one small study [83].

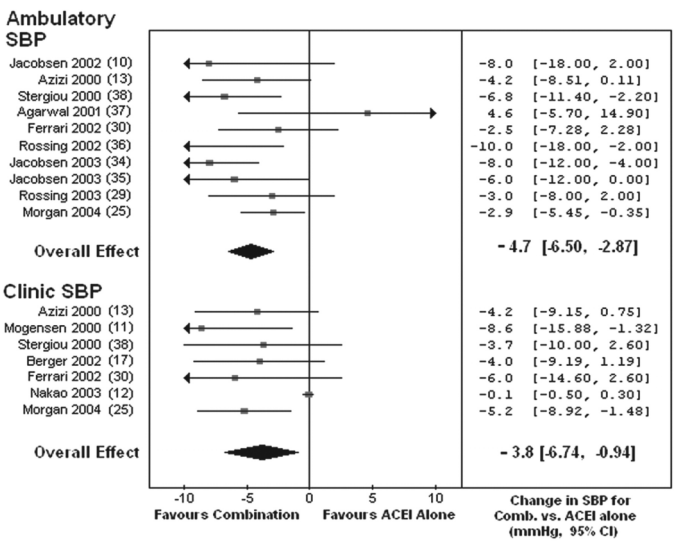
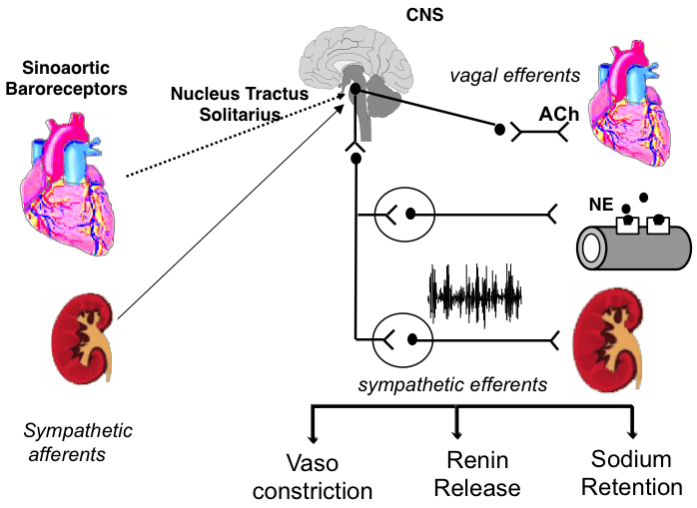


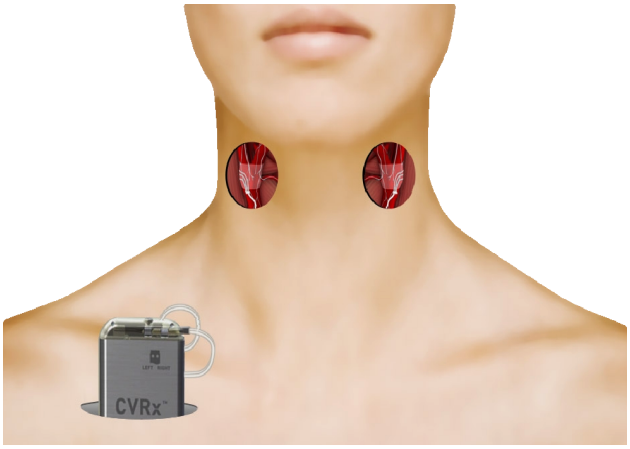
Fig 10. Meta-analysis of clinic trials showing modest BP responses to combination of ACEIs with angiotensin receptor blockers

Role of device therapy



In the past decade, an increasing number of devices have been developed as an adjunctive treatment for resistant hypertension. These devices mainly target sympathetic nervous system, which is known to play a crucial role in the pathogenesis of hypertension. Activation of sympathetic nerve efferent fibers, which are projected from the brainstem centers triggers norepinephrine release, which induces increase in heart rate and cardiac output causing increased BP. Sympathetic efferent innervation in the vascular smooth muscle of the skeletal muscle and viscera also promotes peripheral vasoconstriction via alpha adrenergic receptor mediated vasoconstriction. Activation of efferent sympathetic nerve activity in the kidney also cause BP elevation by causing vasoconstriction in the afferent arterioles, increase renin release from the juxtaglomerular cells, and sodium absorption in the renal proximal tubules and thick ascending limb. The increase in BP causes stretching of the carotid sinus and aortic arch ("high pressure") baroreceptors, which project centrally via the glossopharyngeal or vagus nerve to the nucleus tractus solitarius into the brainstem. The reflex response is to decrease sympathetic efferent discharge to the blood vessels to increase vascular resistance and to the sinus node to decrease heart rate and cardiac output. Activation of cardiac vagal activity causes further reduction in the heart rate, which further buffers the rise in BP from stress and various stimuli in daily activity. In contrast, activation of afferent nerve fiber in the kidneys from various chemical stimuli can further stimulate central sympathetic discharge and BP.

<u>Baroreflex Activation Therapy</u>



Because of inhibitory influence of baroreflex on sympathetic nerve activity (SNA) and BP, devices have been developed to stimulate carotid baroreceptor in humans. Initial studies have demonstrated acute reduction in muscle sympathetic nerve activity and BP in hypertensive patients when the devices were turned on to stimulate carotid sinus nerves [84]. The baroreflex activation device, the Rheos system,

consists of electrodes connected to a pulse generator. Efficacy and safety of the devices in patients with resistant hypertension was tested in the Rheos Pivotal Trial. Although there was a large reduction in BP when the group whom devices were on when compared to baseline, the control group also showed a large reduction in BP when the devices were turned off causing no net effects of the Rheos system on BP [85]. The underlying explanation for improvement in BP in the control group is unknown but may be related to improved compliance to medications when patients are enrolled in the clinical trial, i.e. "Hawthorne effect" or additional titration of antihypertensive drugs during the study. Surgical implantation of the first generation electrodes around the carotid arteries bilaterally is limited by the relatively large size of electrodes, which may explains high incidence of transient or permanent nerve injury of 4.4% [85]. Future clinical trials are required to test efficacy and safety of the newer generation electrodes, which are much smaller than the first generation.

Renal sympathetic denervation (RDN)

Surgical denervation has been used in the early part of 1940's to treat hypertension. The surgical procedures pioneered by Dr. Smithwick and others mainly consisted of resection of sympathetic nerves and ganglia in the lower thoracic vertebra [86] with or without resection of the splanchnic nerves [87], celiac ganglion [88], or first to second lumbar sympathetic ganglion [86]. Surgery was reported to reduce BP in 51-60% of patients with surgical mortality between 5-15%. Only 12-19 % of patients experienced reduction in BP to normal range and most patients continued to have hypertension after surgery [89]. It is poorly tolerated by most patients given its associated bowel, bladder, or erectile dysfunction, in addition to loss of sweating and profound orthostatic hypotension. Sympathectomy required a prolonged hospital stay (2–4 weeks) and a long recovery period (1-2 months). Thus, it was abandoned after development of many effective classes of antihypertensive drugs.

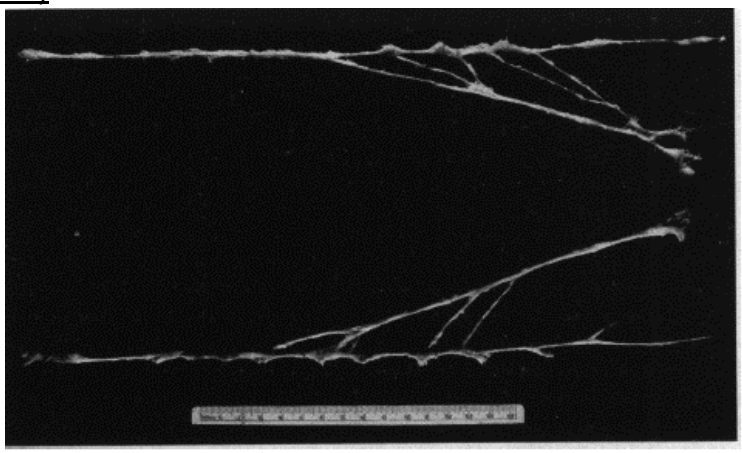


FIG. 7.—A photograph of the operative specimens removed from Case 10 during the bilateral thoracic operations. The stellate ganglia; splanchnic nerves; celiac ganglia; and, on one side, the first lumbar ganglion are shown.

TABLE IV

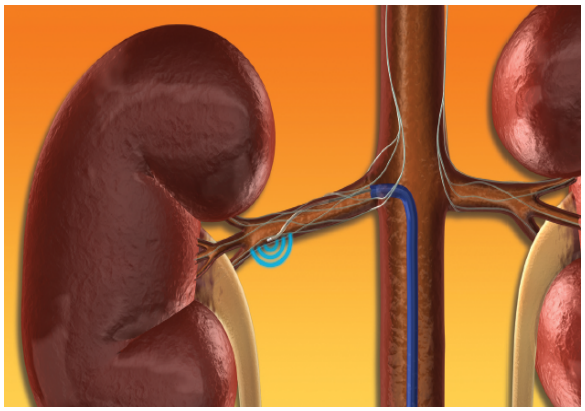
SURGICAL TREATMENT OF HYPERTENSION

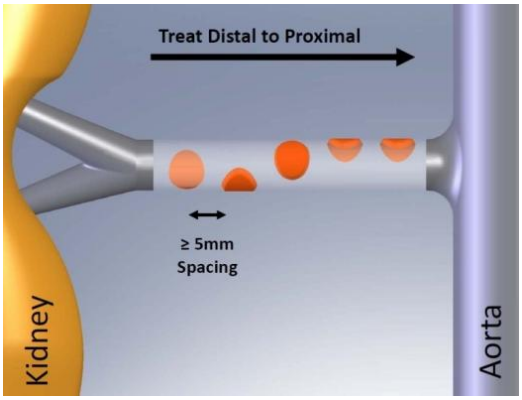
Early Results of Sympathectomy and Splanchnicectomy by Various Technics in Patients Followed from Months to Five Years or More

Author	No. Cases	Subjective and Objective Improvement	Subjective Improvement, No change, or Worse	Deaths
		(per cent)	(per cent)	(per cent)
Allen and Adson[5] (1940)	224	31.0	53.8	15.2
Peet, Woods, Braden[6] (1940)	350	42.6	26.8	30.6
Hammarström[7] (1947)	82	54.9	18.2	26.9
Smithwick[3] (1947)	439	61.7	23.7	14.6
Poppen and Lemmon[8] (1947)	100	71.0	22.0	7.0
Grimson[9] (1946)	41	76.0	6.3	17.7

In the recent years, catheter-based sympathetic denervation has been developed as adjunctive treatment in patients with resistant hypertension despite medical therapy.

The technique employs radiofrequency energy to ablate renal nerves which run along side of the renal arteries in the adventitial layers [90]. SIMPLICITY-1 was a proof-of-concept, first-in-man, pilot studies that tested efficacy of RDN that was initiated in Australia with Dr. Henry Krum's group. The study demonstrated feasibility in patients whose BP was uncontrolled on 3 drugs or more, in terms of BP reduction and safety in about 50 patients with no control arm [91].





SIMPLICITY-2 is a randomized clinical trial in approximately 100 patients with 50% to a medication arm and 50% to the device intervention arm in open-label fashion [92]. The study showed that in the RDN group there was 33/11 mmHg of additional systolic blood pressure reduction without adding another drug. However, ambulatory BP monitoring which was conducted in about 50% of patients show reduction in 24-hr ambulatory of only 11/7 mmHg [92]. There was no serious adverse event related to procedure reported. Renal imaging at 6 months showed no vascular abnormalities at any treatment sites [92].

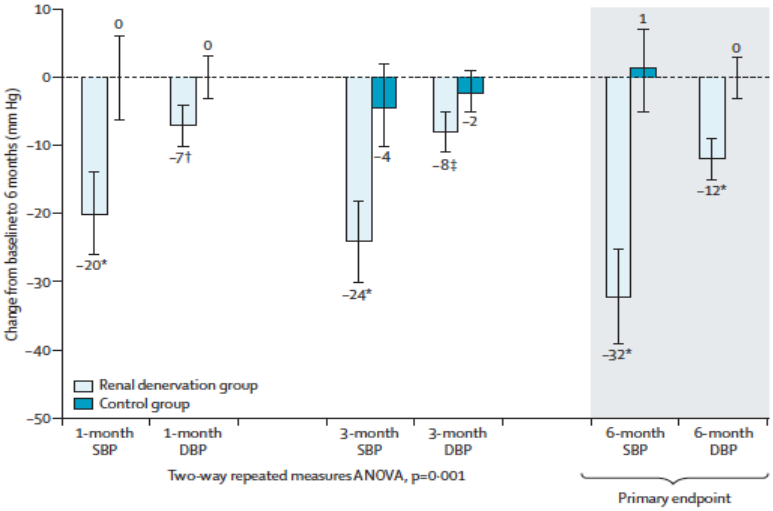


Fig 15. Changes in office BP in the SIMPLICITY-2 trial.

However, a recent study showed presence of vascular wall edema and thrombus formation at the ablation sites up to 89% of patients as evidenced by optical coherence tomography which was not otherwise detected by conventional angiography [93]. Significance of these findings remained to be further determined with long-term followup.

SIMPLICITY-3 is a multi-center, prospective, single-blinded, randomized, sham-controlled study (N=530 randomized patients) in 60 US centers including approximately 500 patients with severe resistant hypertension (systolic BP ≥ 160 mmHg despite treatment ≥ 3 drugs). Patients were randomized in 2:1 ratio to RDN vs. sham procedure. The primary endpoint is the difference in clinic systolic BP between groups at 6 months

with change in ambulatory BP at six month as one the pre-specified endpoints. The enrollment is recently completed and follow-up is planned for 3 years.

The advantage of catheter-based procedure is relatively free of side effects with ability to eliminate both renal efferent and afferent fibers, which may provide signal to stimulate central sympathetic outflow to other organs or vascular bed involved in BP regulation such as splanchnic beds and skeletal muscle. The potential limitation of RDN is the completeness of denervation since sympathetic nerve activity (SNA) is not monitored during the procedure and SNA may remain elevated after the procedure [94]. Furthermore, a population of renal afferent fibers which inhibit central sympathetic activity have recently been identified and loss of inhibitory influence of these fibers may counteract effects of ablation of excitatory fibers [95]. Potential reinnervation over time may also limit efficacy of the approach. Thus, long term efficacy of RDN in reducing BP remains to be determined.

Conclusion

Management of resistant hypertension continued to be a challenge in clinical practice. Even under hypertension specialist care, hypertension control rate to goal of < 140/90 mmHg in patients is resistant to 3 or more drugs is still only about 50% [16]. However, substantial reduction in BP can be achieved in most patients if detailed clinical assessment, individualized laboratory evaluation, and optimization of antihypertensive medications, particularly related to choice of diuretic, is implemented. Because hypertension is mostly asymptomatic disease until target organ damage develops, involvement of patients in the treatment plan and patient education regarding the need to take life-long therapy for asymptomatic disease is important for long-term adherence to medications and clinical outcomes, even if target BP goal cannot be reached. Future studies are needed to determine if emerging therapy in hypertension such as carotid sinus baroreflex activating system or renal sympathetic denervation will have improve hypertension control rate in these patients.

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