VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2007, Vol. 14, No. 4, pp. 329–339

ISSN 1897–5593

Evaluation and treatment of resistant hypertension

James A. Sloand[1], Sangeetha L. Balakrishnan[2], Michael W. Fong[2] and John D. Bisognano[2]

[1]Division of Nephrology, Department of Internal Medicine, University of Rochester, New York, USA
[2]Division of Cardiology, Department of Internal Medicine, University of Rochester, New York, USA

Abstract

Hypertension is a major cause and contributor to stroke, heart and kidney disease. Despite the development of an arsenal of medication to treat hypertension over the past half-century, adequate treatment continues to be a major problem in the United States. The Third National Health and Nutrition Examination Survey (NHANES-III) shows that only 29% of hypertensive patients reach a blood pressure less than 140/90 mm Hg. Resistant hypertension is defined as a blood pressure greater than 140/90 mm Hg despite a rational *combination of three or more blood pressure medications including a diuretic. The prevalence of true resistant hypertension in hypertension clinics is only about 11–13%. Higher prevalence rates are evident in populations with evidence of end-organ disease such as cardiac or renal disease where lower blood pressure targets have now been established. Ascertaining the possible cause(s) for resistant hypertension is a challenge to all clinicians, but critical in eventual determination of a therapeutic solution. The following review will hopefully help guide clinicians in their discernment of causes and potential treatments for resistant hypertension. The diagnosis and treatment of the more common secondary causes will be described and treatment options for patients with resistant hypertension are discussed. Newer options, some still under clinical investigation, will be described and their future utility will be discussed.* (Cardiol J 2007; 14: 329–339)

Key words: resistant hypertension, etiology, treatment

Introduction

Hypertension is a major cause and contributor to stroke, heart and kidney disease. Despite the development of an arsenal of medication to treat hypertension over the past half-century, adequate treatment continues to be a major problem in the United States. The Third National Health and Nutrition Examination Survey (NHANES-III) shows that only 29% of hypertensives reach a blood pressure less than 140/90 mm Hg [1]. Despite major reductions in age-adjusted death rates from coronary heart disease and stroke, these continue to be the leading and third most common causes of death, respectively, in the United States [2]. In particular, for every 20 mm Hg increase in systolic blood pressure or 10 mm Hg in diastolic blood pressure, there is a doubling of stroke and coronary artery disease death rates [3]. Kidney Failure related to hypertension continues to grow, especially among the African-American population [4, 5]. The risk of both stroke and renal disease is higher in African-Americans compared to Caucasians. This may have more to do with the duration of hypertension than it does the severity of hypertension in this population given evidence that African-Americans tend to develop hypertension at a much earlier age [6–8],

Address for correspondence: John D. Bisognano, MD, PhD
Associate Professor of Medicine
Cardiology Division, Department of Internal Medicine
University of Rochester Medical Center
601 Elmwood Avenue, Box 679-7, Rochester, NY 14642, USA
Tel: 585 275 6168, fax: 585 276 0073
e-mail: John_Bisognano@urmc.rochester.edu
Received: 6.07.2007 Accepted: 6.07.2007

possibly related to lower birth weight [9]. Additionally, hypertension and its vascular effects may go undetected in this population given the non-dipping pattern that is more prevalent in these individuals [10, 11].

The increasing body of evidence demonstrating the critical role of hypertension in the development of end organ disease has lead to a significant lowering of recommended blood pressure targets by the American Heart Association, the American Diabetes Association and the National Kidney Foundation [12–14]. In spite of these lowered targets, clinical benefit can only be realized with successful blood pressure reduction.

Definition of resistant hypertension

Resistant hypertension is defined as a blood pressure greater than 140/90 mm Hg despite a *rational* combination of three or more blood pressure medications including a diuretic [15]. The prevalence of true resistant hypertension in hypertension clinics is only about 11–13% [16]. Higher prevalence rates are evident in populations with evidence of end-organ disease such as cardiac or renal disease where lower blood pressure targets have now been established. In a study by Muxfeldt et al, only 56% of individuals diagnosed with resistant hypertension in an office setting were demonstrated to be truly hypertensive [17]. The presence of left ventricular hypertrophy, chronic kidney disease, and other evidence of vascular disease increase the likelihood of true resistant hypertension. Attenuation of the normal 10–20% reduction in nocturnal blood pressure (i.e. a "non-dipping" pattern) observed by ambulatory blood pressure monitoring is also suggestive of true resistance.

Confirmation of resistance depends upon exclusions of both pseudo-hypertension and labile or "white coat" hypertension. The former is usually a result of inaccurate blood pressure recordings due to improper sizing of the blood pressure cuff. The width of the cuff bladder should cover 40–46% of the arm circumference and the length should encircle 80% of the arm's circumference [18, 19]. Blood pressure cuffs that are inappropriately small can result in falsely elevated blood pressure recordings due to inadequate compressive occlusion of the brachial artery. The error of underestimation of pressure resulting from "overcuffing" is less than the error of overestimation of blood pressure from a cuff bladder that is too small. In patients with morbid obesity in whom a short upper arm length is coupled with a very large arm circumference, the cuff can be placed on the forearm with the systolic pressure alone palpated or Korotkoff sounds ausculted over the radial artery. As with any measurement of blood pressure, the sphygmomanometer and thus the part of the arm where blood pressure is being measured must be at the level of the heart.

Conversely, labile hypertension refers to real increases in blood pressure usually driven by anxiety-mediated augmentation in central sympathetic nervous traffic. Blood pressures return to normal or significantly lower levels in non-stressful situations. Exclusion of this phenomenon can only be done using out-of-office blood pressure measurements such as home or ambulatory blood pressure monitoring.

Ascertaining the possible cause(s) for resistant hypertension is a challenge to all clinicians, but critical in eventual determination of a therapeutic solution. The following review will hopefully help guide clinicians in their discernment of causes and potential treatments for resistant hypertension.

Causes and treatment of resistant hypertension

In general, the causes of resistant hypertension can be divided into four categories. These include endocrine disorders, kidney-related disorders, lifestyle-related disorders, and drug-related issues (Table 1). Treatment is directed at the specific contributing cause.

Critically important in any work up of refractory hypertension are historical and physical exam findings that may lead one to a diagnosis. Additionally, an initial battery of routine laboratory tests frequently provides clues to the potential cause for poor blood pressure control (Table 2). These diagnostic clues can increase the pretest sensitivity during further screening for endocrine and kidney-related cause for hypertension.

Endocrine disorders

The major endocrine causes of resistant hypertension include hyperaldosteronism, Cushing's syndrome and pheochromocytoma.

In addition to severe hypertension, clinical clues to the possible presence of hyperaldosteronism or "Conn's syndrome" include spontaneous or diuretic-induced hypokalemia and metabolic alkalosis. The absence of either of these laboratory findings does not exclude the diagnosis, however. Currently, the best screening test for hyperaldosteronism is the morning ambulatory plasma aldosterone concentration (PAC) to plasma renin activity (PRA)

Table 1. Causes for resistant hypertension.

Endocrine disorders
Primary hyperaldosteronism
Cushing's syndrome
Pheochromocytoma
Hyper-/hypothyroidism
Hyperparathyroidism
Hypercalcemia (non-parthyroid-related)
Kidney-related causes
Renal artery stenosis
Chronic kidney disease
Aortic coarctation
Drug-related causes
Inappropriate drug combinations
Insufficient diuresis
Offsetting-drugs
NSAIDS
Pseudoephedrine/ephedrine
St. John's Wort
Gingko biloba
Estrogen
Prednisone
Antidepressants (tricyclics/MAOs)
Erythropoietic stimulating agents
Illicit drugs (cocaine, amphetamines)
Lifestyle-related causes
Medication non-adherence
Dietary non-adherence
Obesity
Obstructive sleep apnea
Alcohol excess
Caffeine excess

ratio. If the ratio is greater than 20 ng/dL per ng/mL per hour in the setting of a PAC level greater than 15 ng/dL, then hyperaldosteronism is suggested [20]. This has been demonstrated in some studies to have a 90% sensitivity and specificity.

Ideally, the patient should be off angiotensin converting enzyme inhibitors (CEI) and angiotensin receptor blockers (ARB), both of which can increase plasma renin activity, as well as beta-blockers (which can decrease PRA) when the test is performed. However, the PAC/PRA ratio has been shown to be valid even with sodium loading/diuresis or ongoing antihypertensive therapy, save for aldosterone antagonists or high dose amiloride [21, 22]. If the patient is on an aldosterone receptor antagonist, it should be discontinued for six weeks prior to performing any studies on plasma or urinary aldosterone levels. Given the expected increase in PRA induced with either of a CEI or ARB, an increased PAC/PRA ratio on either agent in the setting of an elevated PAC deserves further evaluation.

As hypokalemia can suppress aldosterone secretion, it should be corrected before any aldosterone testing. PAC and PRA levels should ideally be drawn in the morning. In the presence of a suggestive PAC/PRA screening test, the clinician should obtain a 24-hour urine for creatinine (as a benchmark of collection adequacy), aldosterone, sodium, and potassium. The test should be done after the patient has been on a high salt diet (or sodium chloride tablets 2 g TID) for three days documented by a total urinary sodium of > 200 mEq/day in the 24 hour collection [20, 21]. Ideally, patients should

Table 2. Classic clinical clues to secondary hypertension*.

Cause	History	Physical	Laboratory
Hyperaldosteronism	Fatigue	NA	Potassium < 3.5 meq/L and metabolic alkylosis especially if spontaneous > diuretic-induced
Cushing's syndrome	Muscle weakness; menstrual irregularities	Striae, trunkal obesity, cervical and supra-clavicular fat pads	Glucose intolerance (diabetes mellitus)
Pheochromocytoma	Headaches; episodic palpitations, clamminess; weight loss	NA	NA
Chronic kidney disease	NA	NA	Estimated GFR < 60 cc/min
Renal artery stenosis	Episodes of flash pulmonary edema; smoking; diffuse vascular disease	Bruits over multiple vessels (carotid, subclavian, epigastric, femoral)	Reduced GFR or its unexplained accelerated decline; spontaneous hypokalemia

*Patients may have these secondary causes of hypertension without necessarily manifesting *any* of these findings

be off diuretic therapy to enhance volume expansion. A urinary aldosterone level in excess of 14 mcg/day with a urinary potassium > 30 mEq/day in the salt loaded state is virtually diagnostic. A plasma aldosterone concentration > 10 ng/dL obtained after a two-liter infusion of normal saline administered over four hours while the patient is supine is an alternative diagnostic test [22].

After biochemical confirmation of non-suppressible aldosterone secretion, anatomic localization should be attempted using thin-cut computed tomography (CT) imaging. Presence of a unilateral adenoma should result in laparoscopic resection in younger hypertensive patients (< 40 years old), whenever the gland is large (> 4 cm) and dense, or when ther are findings suggestive of possible malignancy, irrespective of age. Failure to discern an adenoma by CT imaging does not exclude the presence of a microadenoma and should prompt long-term treatment with specific aldosterone antagonism with either spironolactone or eplerenone [23, 24]. Adrenal vein sampling can provide direct evidence of anatomic and biochemical correlation that should ideally be performed in any individual prior to anticipated surgical resection. It may be particularly valuable when bilateral adrenal masses are found on imaging studies; however, it is technically difficult and should only be performed by an experienced radiologist.

The presence of Cushing's syndrome is suggested on history and physical exam by the presence of easy bruisability, striae, post-cervical and supraclavicular fat pads, menstrual irregularities, and hyperglycemia. Again, presence of these findings increases the pre-test odds of any screening tests. Screening for this disorder depends upon demonstration of high cortisol levels at a time when one would expect the levels to be low. A normal circadian rhythm results in a serum cortisol level that is highest in the morning, but which is virtually immeasurable after midnight [25]. As it is logistically difficult to obtain plasma samples on patients at this late hour unless they are hospitalized, alternative diagnostic tests are necessary. Salivary levels of cortisol have demonstrated excellent sensitivity and specificity [26]. The patient should be instructed to assume a recumbent posture and not to eat, drink, or brush their teeth for at least one hour prior to specimen collection. The patient collects at least 1 cc of saliva into a sterile container after midnight. The specimen should be refrigerated and dropped off at the lab the following morning. When the salivary cortisol level exceeds 550 ng/dL, the sensitivity and specificity of this test are 92–100% and 96–100%, respectively [27]. In a hospitalized patient, serum cortisol levels obtained after midnight exceeding 2 mcg/dL are also strongly suggestive of the diagnosis with a 100% sensitivity and specificity [28].

A confirmatory test for Cushing's is a 24-hour urine for creatinine and free cortisol. Cortisol excretion greater than three times the upper limit of normal provides strong evidence of Cushing's syndrome. The overnight 1 mg dexamethasone suppression test provides another strong screening tool. An 8 AM cortisol value > 1.8 mcg/dL after a 1 mg dexamethasone dose the previous night is highly suggestive of the diagnosis [29, 30]. Adrenocorticotropic hormone (ACTH) levels then allow differentiation between cortisol produced from an autonomous adrenal neoplasm (ACTH concentration suppressed to < 1.1 pmol/L) and either a pituitary (Cushing syndrome) or non-pituitary tumor (ACTH-dependent). These findings should lead to further biochemical testing and imaging studies to confirm the diagnosis and localize the lesion [31].

Pheochromocytoma is a rare cause of resistant or secondary hypertension. Its presence is suggested by a history of frequent headaches, diaphoresis, paroxysmal tachycardia, and a family history of pheochromocytoma, von-Hippel-Lindau disease, or Multiple Endocrine Neoplasia Type II. The classic means of screening for this has been a 24-hour urine for creatinine and metanephrines. Plasma metanephrine and normetanephrine levels, however, provide better sensitivity and nearly equal specificity (99% sensitivity and 89% specificity, respectively) to the time honored 24-hour collection [32]. The advantage of assaying metanephrines is that they are produced continuously by pheochromocytomas, resulting in steady-state levels, whereas catecholamines are released only sporadically. A negative test effectively excludes the diagnosis. Exceptions include patients (usually encountered during screening because of hereditary predisposition or a previous history of pheochromocytoma) with microscopic (< 1 cm) pheochromocytomas that produce only small amounts of catecholamines. Plasma levels of free metanephrines are also relatively independent of renal function, making this a good screening test for individuals with kidney failure [33]. Prior to any screening for pheochromocytoma, beta-adrenoreceptor blocking drugs, phenoxybenzamine, diuretics, tricyclic antidepressants, and monoamine oxidase inhibitors should be discontinued. Acetaminophen should also be avoided for several days prior to testing as it can lead to false positive results [33].

As with any plasma tests to work up hypertension, the patient should be maintained in the supine position and an intravenous indwelling venous catheter should be placed 30 min prior to collection of samples, thereby reducing the likelihood that pain or stress will cause an elevation in catecholamine levels. Plasma metanephrine levels > 1.4 pmol/mL (> 2.5 fold above normal) and normetanephrine levels > 2.5 pmol/mL (> 4 fold above normal) are highly suggestive of the diagnosis. Patients with equivocally elevated plasma metanephrine and normetanephrine levels should undergo a clonidine suppression test [34]. This will distinguish weather elevated catecholamine levels are a result of augmented central sympathetic outflow ("nervous") or a pheochromocytoma. A decrease in plasma normetanephrine to more than 50% below baseline or a level less than 2.96 nmol/L three hours after an oral clonidine dose of 0.3 mg suggests a centrally driven catecholamine elevation, not a pheochromocytoma. A 24-hour urine sample for creatinine, metanephrines, free catecholamines, and vanillylmandelic acid, when done, are best obtained within 24 hours after a crisis to catch the surge in catecholamines secreted. However, this test suffers from lack of sensitivity and specificity [32].

Marked elevation in plasma metanephrines or normetanephrines, with a confirmatory clonidine suppression test, if necessary, should lead to imaging studies for localization of the tumor.

Kidney-related causes

Renal artery stenosis (RAS) is the most common and well-recognized cause of resistant hypertension. While renal artery stenosis can be caused by fibromuscular dysplasia, the vast majority of renal artery lesions are due to atherosclerosis. Atherosclerotic RAS occurs more commonly in elderly patients with a history of diffuse atherosclerotic cardiovascular disease, declining kidney function, a history of smoking, and hypercholesterolemia [35]. Other clinical clues to its presence include unexplained kidney impairment in the setting of a bland urinalysis, sudden onset of hypertension in an individual less than 30 years old or an acute exacerbation of previously well controlled hypertension in a patient older than 55. Recurrent episodes of "flash" pulmonary edema should also raise clinical suspicion. For reasons that are poorly understood, RAS is less likely to occur in the African-American population [36].

Acute renal failure (ARF) defined by a > 30% decrease in renal excretory function in response to CEI or ARB can also provide a clinical clue to the diagnosis [37]. While this occurs most commonly in patients who have high-grade bilateral disease, the clinician has to be aware of the possibility of a stenosis in a dominant or a single kidney. ACEI- or ARB-induced-ARF is not specific for RAS, however. Atherosclerotic disease in small pre-glomerular vessels or afferent arteriolar narrowing due to hypertension or chronic use of vasoconstrictive agents like cyclosporine can also cause ARF in the setting of renin-angiotensin blockade. While a bruit may not always be heard over the renal arteries, bruits over other central vessels including subclavian, carotid, and femoral arteries suggests diffuse vascular disease and increases the likelihood of a renal artery lesion.

As CEI and ARB therapy used in conjunction with a diuretic can effectively control hypertension in the majority of patients with unilateral RAS [38], diagnostic screening is only recommended if intervention to correct a stenotic lesion is planned. Resistance to antihypertensive therapy or progressive renal functional impairment due to bilateral disease are reasons to intervene. Diagnostic screening for renal artery stenosis is best accomplished with either magnetic resonance angiography (MRA) or Doppler ultrasound [39–41], both of which can provide sensitivity and specificity exceeding 90% though the diagnostic accuracy of the latter is markedly operator dependent and limited in obese patients. Spiral CT angiography is another reasonably accurate method of screening for RAS [42]. It is less invasive than standard angiography, but also places the patient with kidney impairment at risk for contrast nephropathy. As such, until recently, both MRA and Doppler ultrasound have been considered the screening test of choice in patients with significant impairment in renal excretory function. However, the safety of MRA has come into question with recognition of a condition called nephrogenic fibrosing dermopathy (NFD), a scleroderma-like condition that can develop on the skin of the extremities [43]. NFD is a rare, but potential complication of the gadolinium-based MRA contrast agents when used in patients with an estimated glomerular filtration rate (GFR) less than 30 mL/min/1.73 m^2. Its use in patients with kidney function > 60 mL/min/1.73 m^2 appears to be safe, however.

Prophylactic measures to reduce the likelihood of contrast-induced nephropathy are well described [44] and should be taken in patients with renal impairment prior to CT or conventional angiography. Again, the sensitivity and specificity of any of these tests is influenced by pre-test probability of the disease. Angiography should be

reserved for patients in whom simultaneous endovascular intervention is also planned.

Fibromuscular dysplasia should be suspected in a younger hypertensive patients, particularly women. Successful correction of a stenotic lesion can obviate need for lifelong antihypertensive therapy in these patients. If fibromuscular dysplasia is suspected, angiography should be the primary diagnostic step as simultaneous angioplasty is curative, and both CT angiography and MRA have limited diagnostic value [45, 46]. Low sensitivity and specificity of these non-invasive tests is attributable to the majority of fibromuscular lesions being located in the mid and distal main renal artery at times extending into intrarenal branches, which may be less well visualized.

Coarctation of the aorta is an infrequent cause of resistant hypertension in the adult population, but is easy screened for during physical exam. Renal ischemia caused by narrowed aortic lumen is usually amenable to blockade of the renin-angiotensin system.

Chronic kidney disease (CKD) or reduced renal excretory function can also be a cause for resistant hypertension, mainly due to reduced filtration of sodium and resulting extracellular volume expansion [47]. Despite the latter, edema may be absent. An adequate challenge of diuretic therapy is therefore imperative in patients with an estimated GFR less than 60 mL/min. Careful monitoring of renal excretory function is imperative, however, as diuretic-induced decrease in renal preload to afferent arterioles stiffened by chronic hypertensive vascular changes can result in significant deterioration in GFR. Both increased activity of the renin-angiotensin system mediated by regional ischemia in segments of kidney scarred by various disease processes and renal-derived increases in sympathetic nervous activity may also contribute to resistant hypertension in this CKD [48].

Medication-related

Drug-drug interactions are another cause for failed antihypertensive therapy. A plethora of prescription and non-prescription agents can also offset the salutary effects of antihypertensive drugs. Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDS) may confound the antihypertensive effects of medications by their sodium retentive properties [49]. Additionally, they may antagonize the vasodilatory effects of prostaglandins. Pseudoephedrine, Ephedra, St. John's Wort, and Ginseng are all agents that may be vasoconstrictive via different mechanisms, thereby attenuating the effects of antihypertensive medications [50].

Lifestyle factors

Non-adherence to medications, excessive intake of dietary sodium, excessive alcohol intake, obstructive sleep apnea, and obesity are all patient-related factors that can cause or contribute to resistant hypertension.

While non-adherence is difficult to assess historically, absence of known side effects to specific antihypertensive therapy should raise suspicion about compliance with medications. For example, one would expect development of some hirsuitism or increasing weight and edema after treatment with minoxidil. Normokalemia on loop or thiazide diuretic therapy in the absence of potassium supplementation, CEI or ARB therapy should raise the suspicion of non-compliance, especially in a setting of poorly controlled hypertension. Volume depletion driven both by diuretic- and pressure-induced natriuresis would be expected to enhance aldosterone-mediated kaliuresis.

As demonstrated in the ALLHAT study, diuretic therapy is important to the success of any antihypertensive regimen [51]. This is particularly true in the treatment of resistant hypertension [52]. Ingestion of a diet high in sodium will offset most antihypertensive regimens. Examination of a 24-hour urine for creatinine (as a marker of collection adequacy) and sodium will inform the clinician about dietary compliance. Barring initiation of or a recent change in dose of either a diuretic or an NSAID, and assuming an otherwise steady physiologic state, patients are generally in sodium balance. As such, the amount of sodium ingested by a patient is a very close approximate of what is excreted in the urine. The total urinary sodium (reported as mmol of sodium and converted to mg of sodium by multiplication by 23, the gram molecular weight of sodium) thus gives the clinician a close estimate of the intake of dietary sodium.

One frequently needs to depend upon family members to get more accurate history with regard to alcohol intake. Alcohol abuse is an important factor contributing to elevated blood pressure, although the relationship between quantities of alcohol imbibed and degree of blood pressure elevation.is unclear. The mechanism through which alcohol elevates blood pressure also remains unclear, although increased vascular contractility, perhaps due to increased vascular smooth muscle cell calcium content, may play a role [53]. These changes may be mediated by augmented sympathetic

discharge driven by alcohol-induced corticotrophin-releasing hormone release [54].

Likewise, a history of obstructive sleep apnea (OSA) is best obtained from the bed partner. Obstructive sleep apnea is diagnosed by demonstration of apnea and hypoxemia during a sleep study. Hypertension in this disorder is driven by hypoxia-induced activation of sympathetic nervous pathways [55]. Treatment with BIPAP has been shown in some studies to reduce systolic blood pressure by as much as 10 mm Hg [56]. Other studies have not demonstrated similar success [57].

Obesity is reaching epidemic proportions in the United States and around the world [58]. To a large extent, its preponderance has accrued as a result of decreased physical activity and increased caloric intake. While obesity and associated insulin resistance contribute to hypertension by multiple mechanisms, one of the main effects is to increase sympathetic nervous system traffic [59]. Renin-angiotensin activity is augmented both by downstream effects from the sympathetic nervous system (SNS) activation and by adiposity itself. Sodium retention then occurs as a result of enhanced SNS and RAS effects on the kidney. While antihypertensive therapy simultaneously directed at blocking the sympathetic nervous system, the RAS and extracellular volume expansion can be implemented, the antihypertensive response is at times ineffective. Visceral obesity has also been associated with increased aldosterone levels [60]. Successful treatment of obesity-related hypertension with aldosterone antagonists suggests that mineralocorticoid may also play a pathogenic role.

Treatment of resistant hypertension

If no apparent lifestyle, endocrine, kidney, or medication-related cause for resistant hypertension can be identified, the appropriateness of the failed medical regimen should be examined. A rational regimen of antihypertensive agents is important when dissecting potential causes for treatment failure. The major contributors to hypertension include the renin-angiotensin axis SNS, and sodium-intracellular calcium metabolism (Fig. 1). The first two contribute to vasoconstriction while sodium-calcium dysmetabolism acts on the volume component [61]. Any or all of these components may contribute to blood pressure elevation in a particular patient. Clues to their individual contributions can frequently be gleaned from demographic, historical and physical exam findings (Table 3). For example, resting tachycardia may indicate overactivity of the SNS, and the addition of a sympatholytic (i.e. clonidine) may be in order. African-Americans, as a demographic group, may have low renin hypertension perhaps due to metabolic abnormalities that result in both excess total extracellular sodium and intracellular calcium levels [62]. This population is more likely to respond to diuretics and calcium channel blockers (CCB) [63].

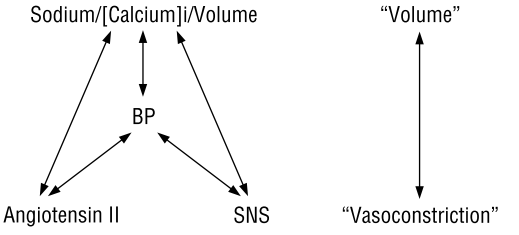

Figure 1. Factors influencing blood pressure (BP). Modified from Izzo JL et al. [61].

When considering a reasonable regimen of antihypertensive medications for individuals already on a multi-drug regimen, one must consider whether all limbs of the hypertension axis have been adequately blocked. For example, a potent vasodilator like minoxidil will cause reactive increases in both SNS traffic and renal sodium retention. As such, complementary use of a sympatholytic and a diuretic would be indicated. Sufficient diuretic therapy is imperative and is a frequently under-appreciated cause of resistant hypertension especially where vasodilator therapy is used predominantly or exclu-

Table 3. Clinical clues to causes of resistant hypertension.

Clinical clue	Finding	Possible association	Possible treatment
Demographics	Black/elderly	Low renin state/intracellular calcium dysmetabolism	Diuretic/CCBs
History	Type A personality	Sympathetic nervous system activation	Sympatholytics/ /beta-blockade
Physical exam	Tachycardia	Sympathetic nervous system activation	Sympatholytics/ /beta-blockade
	Bruits/vascular disease	Renal artery stenosis activation	CEI/ARB
	Edema	Sodium/volume excess	Diuretics

sively. Utilization of multiple diuretics that effect different limbs of sodium retention in the kidney (loop and thiazide diuretics) may be necessary in some patients. Close follow up of renal excretory function, plasma bicarbonate, and potassium values is imperative in these cases. Conversely, diuretic use with concomitant volume depletion augments activation of the SNS and the renin-angiotensin system. The resulting vasoconstriction can offset the diuretic effect, increasing blood pressure. Addition of specific vasodilator agents in this circumstance can result in improved blood pressure control.

Duplicative therapy directed at any one particular limb of the blood pressure axis (i.e. use of both an ACE-inhibitor and an ARB) should usually be considered unreasonable therapy if other limbs have not been addressed. Combined ACE-inhibitor-ARB therapy provide utility only for synergy to attenuate proteinuria in nephrotic patients and to improve survival in congestive heart failure [64, 65]. Conversely, because of the different binding and pharmacologic characteristics, combining different subclasses of CCB has been shown to be efficacious in some hypertensive patients [66].

The use of treatment algorithms for managing hypertension and rapid titration of therapy over a short period of time may also be of benefit. Increasing the frequency with which patients are seen in follow up has been shown to correlate with better blood pressure control [67]. Other factors that have been shown to improve hypertension control include referral to a specialist in clinical hypertension, or management in a nurse-led clinic where more frequent patient visits can often be accommodated [68]. Changes instituted in the management of resistant hypertension have included the up-titration of CCB to higher doses, and the initiation of moderate doses of longer-acting thiazide diuretics. Resistant hypertension can usually be controlled on standard therapy with 4 to 5 medications, and appropriate titration of doses.

A trial of therapy with aldosterone receptor antagonists may also be of benefit, particularly in a setting of obesity-related hypertension. Visceral obesity has been associated with increased aldosterone levels, the metabolic syndrome and hypertension [69]. Aldosterone may play a greater role in resistant hypertension than might be indicated by either plasma or urinary aldosterone levels [70].

Novel approaches to treatment

Endothelin antagonists have been shown to reduce systolic blood pressure in animal and human models [71]. Endothelin is an endogenous peptide that is mostly secreted by endothelial cells. It is responsible for vasoconstriction and hypertrophy of vascular smooth muscle. The endothelin antagonists, however, are still not clinically used in systemic hypertension for concern of teratogenicity, but they do have a role in the management of advanced heart failure and pulmonary hypertension. The exciting feature about this group of drugs is the fact that there is no rebound increase in heart rate despite their vasodilator effect, a significant advantage over the traditional vasodilators. There may be a role for these drugs in resistant hypertension in the future once their side effect profile is better characterized. They may turn out to be especially useful in obesity, renal failure and calcineurin-induced hypertension [72].

Carotid stimulators [73, 74] provide an elegant method for using the baroreceptor reflex to reduce blood pressure. Electrical stimulation of the carotid baroreceptors reduces sympathetic tone via centrally mediated reflexes. This leads to a reduction in both systolic and diastolic blood pressure as well as the resting heart rate. The newer devices are adjustable via radiofrequency signals and are free of the side effects of the more archaic models used in the 1960's. Thus far, this method has been used only in limited situations involving markedly resistant hypertension at academic centers with experience in inserting the device. However, the results have been impressive with an average drop in systolic and diastolic pressures of over 22 mm Hg and 18 mm Hg, respectively [71, 72]. It is foreseeable that these devices and similar technology will be increasingly relevant as the prevalence of resistant hypertension increases and blood pressure targets decrease.

The device *RESPeRATE* is another new entry into the field of mechanical approaches to hypertension [75–78]. It consists of a control box containing a microprocessor, a belt-type respiration sensor, and headphones, which provide feedback to the patient during breathing. The device analyzes the patient's breathing pattern and creates a personalized melody composed of 2 distinct tones — one tone for inhalation and one for exhalation. As the patient synchronizes breathing with the tones, the device gradually prolongs the exhalation tone (primarily) and slows the breathing rate to < 10 breaths/minute ("slow deep breathing"). The device is indicated by the US Food and Drug Administration (FDA) for the reduction of stress and as an adjunctive therapy in hypertension. It can be combined with standard antihypertensive drugs and other nonpharmacologic

interventions. It has been shown to reduce systolic pressure by 10–15 mm Hg and diastolic pressure by 5–10 mm Hg [79]. The mechanism of action is related to increased tidal volume and stimulation of pulmonary mechanoreceptors with slow, deep breathing. These pulmonary mechanoreceptors in turn activate central pathways to reduce sympathetic tone, cause arteriolar dilation, and reduce heart rate and blood pressure The barriers to use are cost (average $250 per device) and lack of insurance coverage.

Lastly, dark chocolate which is high in flavonoid content [80], appears to have a cardiovascular protective effect through its effects on nitric oxide. In a crossover study, investigators demonstrated that dark but not white chocolate significantly reduced systolic pressure by an average of 12 mm Hg and diastolic pressure by over 8 mm Hg. There also seemed to be a positive effect on insulin resistance and LDL levels. The high flavonoid content and the procyanidin oligomers in red wine, tea and dark chocolate may contribute to some of their putative cardiovascular benefits.

Summary

Control of hypertension is perhaps the most important physician-directed modifiable factor in preventing stroke, heart, and kidney disease. As blood pressure targets continue to be lowered, clinicians need a reasonably accurate and streamlined approach to ruling out secondary causes of hypertension. In the absence of an apparent secondary cause for hypertension, attention to individual patient characteristics, demographics, and physical exam findings coupled with rational, targeted pharmacotherapy and earnest attention to lifestyle modifications usually results in improved blood pressure control.

References

1. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment and control of hypertension in the United States, 1988–2000. JAMA, 2003; 290: 199–206.
2. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970––2002. JAMA, 2005; 294: 1255–1259.
3. Lewington S, Clarke R, Qizilbash N et al. Age-specific relevance of usual BP to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet, 2002; 360: 1903–1913.
4. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and the risk of end stage renal disease in subjects without baseline kidney disease. Arch Intern Med, 2005; 165: 923–928.
5. United States Renal Data System, 2005.
6. Cooper RS, Liao Y, Rotimi C. Is hypertension more severe among U.S. blacks, or is Severe hypertension more common? Ann Epidemiol, 1996; 6: 173–180.
7. Burt VL, Whelton P, Roccella EJ et al. Prevalence of Hypertension in the US Adult Population: Results From the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertens, 1995; 25: 305–313.
8. Berenson GS, Voors AW, Weber LS et al. Racial differences of parameters associated with blood pressure levels in children: the Bogalusa Heart Study. Metabolism, 1979; 28:1218–1228.
9. Law CM, Shiell AW. Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. J Hypertens, 1996; 14: 935–941.
10. Profant J, Dimsdale JE. Race and diurnal blood pressure patterns: a review and meta-analysis. Hypertension, 1999; 33: 1099–1104.
11. Wilson DK, Sica DA, Miller SB. Ambulatory blood pressure nondipping status in salt-sensitive and salt-resistant black adolescents. Am J Hypertens, 1999; 12: 159–165.
12. Chobanian AV, Bakris GL, Black HR et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC Report. JAMA, 2003; 289: 2560–2572.
13. American Diabetes Association. Standards of medical care in diabetes-2006. Diabetes Care, 2006; 29 (suppl. 1): S4–S42.
14. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. AJKD, 2004; 43 (suppl. 1): 65–230.
15. Gifford RW Jr. Resistant hypertension: Introduction and definitions. Hypertension, 1988; 11: 65–66.
16. Swales JD, Bing RF, Heagerty A. Treatment of refractory hypertension. Lancet, 1982; 1: 894–896.
17. Muxfeldt ES, Bloch KV Nogueira AR et al. Twenty four hour ambulatory blood pressure monitoring pattern of resistant hypertension. Blood Press Monit, 2003; 8: 181–185.
18. Beevers G, Lip GY, O'Brien E. ABC of Hypertension. Blood press measurement. Part I. Sphygmomanometry: Factors common in all techniques. BMJ, 2001; 322: 981–985.
19. Pickering TG, Hall JE, Appel LJ et al. Recommendations for blood pressure measurement in humans and experimental animals: blood pressure measurement in humans: A statement for professionals from the subcommittee of professional and public education of the American Heart Association council on high blood pressure research. Hypertension, 2005; 45: 142–161.

20. Mulatero P, Dluhy RG, Giacchetti G, Boscaro M, Veglio F, Stewart PM. Diagnosis of primary aldosteronism: from screening to subtype differentiation. Trends Endocrinol Metab, 2005: 16: 114–119.
21. Schwartz GL, Turner ST. Screening for primary aldosteronism in essential hypertension: diagnostic accuracy of the ratio of plasma aldosterone concentration to plasma renin activity. Clin Chem 2005; 51: 386–394.
22. Schwartz GL, Turner ST. Screening for primary aldosteronism in essential hypertension: Diagnostic accuracy of the ratio of plasma aldosterone concentration to PRA. Clin Chem, 2005; 51: 386–394.
23. Pimenta E, Calhoun DA. Primary Aldosteronism: Diagnosis and treatment. J Clin Hypertens, 2006; 8: 887–893.
24. Mattsson C, Young WF. Primary aldosteronism: Diagnostic and treatment strategies. Nature Clin Pract, 2006; 2: 198–208.
25. Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. J Clin Endocrinol Metab, 1971; 33: 14–22.
26. Yaneva M, Mosnier-Pudar H, Duque MA, Grabar S, Fulla Y, Bertagna X. Midnight salivary cortisol for the initial diagnosis of Cushing's syndrome of various causes. J Clin Endocrinol Metab, 2004; 89: 3345–3351.
27. Papanicolaou DA, Mullen N, Kyrou I, Nieman LK. Nighttime salivary cortisol: a useful test for the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab, 2002; 87: 4515–4521.
28. Newell-Price J, Trainer P, Perry L, Wass J, Grossman A, Besser M. A single sleeping midnight cortisol has 100% sensitivity for the diagnosis of Cushing's syndrome. Clin Endocrinol, 1995; 43: 545–550.
29. Blethen SL, Chasalow FI. Overnight dexamethasone suppression test: normal responses and the diagnosis of Cushing's syndrome. Steroids, 1989; 54: 185–193.
30. Wood PJ, Barth JH, Freedman DB, Perry L, Sheridan B. Evidence for the low dose dexamethazone suppression test to screen for Cushing's syndrome: Recommendations for a protocol for biochemistry laboratories. Ann Clin Biochem, 1997; 34: 222–229.
31. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. Ann Intern Med, 2003; 13: 980–991.
32. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS. Recent advances in genetic, diagnostics, localization, and treatment of pheochromocytoma. Ann Intern Med, 2001; 134: 315–329.
33. Eisenhofer G, Huysmana F, Pacak K, Walther MM, Sweep FC, Lenders JW. Plasma metanephrines in renal failure. Kidney Int, 2005; 67: 668–677.
34. Eisenhofer G, Goldstein DS, Walther MM et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. J Clin Endocrinol Metab, 2003; 88: 2656–2666.
35. Vasbinder GBC, Nelemans PJ, Kessels AGH et. al. Accuracy of computer angiography and magnetic resonance angiography for diagnosing renal artery stenosis. Ann Intern Med, 2004; 141: 674–682
36. Alhaddad IA, Blum S, Heller EN et al. Renal artery stenosis in minority patients undergoing diagnostic cardiac catheterization: Prevalence and risk factors. J Cardiovasc Pharmacol Ther, 2001; 6: 147–153.
37. Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS. Renal considerations in angiotensin converting enzyme Iinhibitor therapy. Circulation, 2001; 104: 1985–1991.
38. Tullis MJ, Caps MT, Zierler RE et al. Blood pressure, antihypertensive medication, and atherosclerotic renal artery stenosis. Am J Kidney Dis, 1999; 33: 675–681.
39. Schoenberg SO, Rieger J, Johannson LO, Dietrich O, Prince MR, Reise MF. Diagnosis of renal artery stenosis with magnetic resonance angiography: update 2003. Nephrol Dial Transplant, 2003; 18: 1252–1256.
40. Riehl J, Schmitt H, Bongartz D, Bergmann D, Sieberth HG. Renal artery stenosis: Evaluation with color duplex ultrasound. Nehrol Dial Transplant, 1997; 12: 1608–1614.
41. Garovic VD, Kane GC, Schwartz GL. Renovascular hypertension: Balancing the controversies in diagnosis and treatment. Cleveland Clin J Med, 2005; 72: 1135–1147.
42. Elkohen M, Beregi JP, Deklunder G et al. A prospective study of helical computed tomography angiography versus angiography for the detection of renal artery stenosis in hypertensive patients. J Hypertens, 1996; 14; 525–528.
43. www.fda.gov/cder/drug/advisory/gadolinium_agents (Dec 2006).
44. Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. N Eng J Med, 2006; 354: 379–386.
45. Slovut DP, Olin JW. Fibromuscular dysplasia. N Engl J Med, 2004; 350: 1862–1871.
46. Prisant LM, Szerlip HM, Mulloy LL. Fibromuscular dysplasia: An uncommon cause of secondary hypertension. J Clin Hypertens, 2006; 8: 894–898.
47. Galla JH, Luke RG. Hypertension in renal parenchymal disease. In: Brenner BM ed. Brenner and Rector's the kidney. 6th ed. W.B. Saunders, Philadelphia 2000: 2035–2058.
48. Joles JA, Koomans HA. Causes and consequences of increased sympathetic activity in renal disease. Hypertension, 2004: 43: 699–706.
49. Oates JA. Antagonism of antihypertensive drug therapy by nonsteroidal anti-inflammatory drugs. Hypertension, 1988; 11 (suppl. II): 4–6.
50. Mansoor GA. Herbs and alternative therapies in the hypertension clinic. Am J Hypertens, 2001; 14: 971–975.

51. The ALLHAT Officers and coordinators for the ALLHAT collaborative research group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA, 2002; 288: 2981–2997.
52. Graves JW, Bloomfield RL, Buckalew VM. Plasma volume in resistant hypertension: Guide to pathophysiology and therapy. Am J Med Sci, 1989; 298: 361–365.
53. Altura BM, Altura BT Peripheral and cerebrovascular actions of ethanol, acetaldehyde, and acetate: Relationship to divalent cations. Alcoholism Clin Exper Res, 1987; 11: 99–111.
54. Randin D, Vollenweider P, Tappy L, Jequier E, Nicod P, Scherrer U. Suppression of alcohol-induced hypertension by dexamethasone. NEJM, 1995; 332: 1733–1738.
55. Richert A, Anasarin K, Baran AS. Sleep apnea and hypertension: pathophysiologic mechanisms. Semin Nephrol, 2002; 22: 71–77.
56. Pickering TG. Sleep apnea and hypertension. J Clin Hypertens, 2002; 4: 437–440.
57. Campos-Rodriguez F, Grilo-Reina A, Perez-Ronchel J et al. Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: a placebo-controlled trial. Chest, 2006; 129: 1459–1467.
58. James PT, Leach R, Kalamara E, Shayegi M. The worldwide obesity epidemic. Obes Res, 2001; supl. 9: 228S–233S.
59. El-Atat FA, Stas SN, McFarlane SI, Sowers JR. The relationship between hyperinsulinemia, hypertension, and progressive renal disease. J Am Soc Nephrol, 2004; 15: 2816–2827.
60. Rahmouni K, Correia LG, Haynes WG, Mark AL. Obesity-associated hypertension: new insights into mechanisms. Hypertension, 2005; 45: 9–14.
61. Izzo JL. Sympathoadrenal activity, catecholamines, and the pathogenesis of vasculopathic hypertensive target-organ damage. Am J Hypertens, 1989; 2: 305S–312S.
62. Gareth B, Lip GYH, O'Brien E. The ABC of Hypertension: The pathophysiology of hypertension. BMJ, 2001; 322: 912–916.
63. Materson BJ, Reda DJ, Cushman WC et al. Single--drug therapy for hypertension in men: A comparison of six antihypertensive agents with placebo. NEJM. 1993; 328: 914–921.
64. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. Lancet, 2003; 361: 117–124.
65. Pfeffer MA, Swedberg K, Granger CB et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-overall programme. Lancet, 2003; 362: 759–766.
66. Sica D. Combination calcium channel blocker therapy in the treatment of hypertension. J Clin Hypertens, 2001; 3: 322–327.
67. Stason WB, Shepard DS, Perry HM et al. Effectiveness and costs of veterans affairs hypertension clinics. Med Care, 1994; 32: 1197–215.
68. Wang TJ, Vasan RS. Epidemiology of uncontrolled hypertension in the United States. Circulation, 2005; 112: 1651–1662.
69. Lamounier-Zepter V, Ehrhart-Bornstein M, Bornstein SR. Mineralocorticoid-stimulating activity of adipose tissue. Best Pract Res Clin Endocrinol Metab, 2005; 19: 567–575.
70. Calhoun DA. Aldosterone and hypertension. Clin J Am Soc Nephrol, 2006; 1: 1039–1045.
71. Kirchengast M, Luz M. Endothelin receptor antagonists: Clinical realities and future directions. J Cardiovasc Pharmacol, 2005;45: 182–191.
72. Vorobiof G, Blaxall BC, Bisognano JD. The future of endothelin-receptor antagonism as treatment for systemic hypertension. Curr Hypertens Rep, 2006; 8: 35–44.
73. Filippone JD, Sloand JA, Illig KA, Bisognano JD. Electrical stimulation of the carotid sinus for the treatment of resistant hypertension. Curr Hypertens Rep, 2006; 8: 420–424.
74. Bisognano J, Sloand J, Papademetriou V et al. An implantable carotid sinus baroreflex activating system for drug-resistant hypertension: interim chronic efficacy results from the multi-center Rheos Feasibility Trial. Circulation, 2006; 575 (suppl. II): 2751.
75. Grossman E, Grossman A, Schein MH, Zimlichman R, Gavish B. Breathing control lowers blood pressure. J Human Hypertens, 2001; 15: 263–269.
76. Rosenthal T, Alter A, Peleg E, Gavish B. Device--guided breathing exercises reduce blood pressure: Ambulatory and home measurements. Am J Hypertens, 2001; 14: 74–76.
77. Viskoper R, Shapira, Priluck I et al. Non-pharmacological treatment of resistant hypertensives by device-guided slow breathing exercises. Am J Hypertens, 2003; 16: 484–487.
78. Schein M, Gavish B, Herz M et al. Treating hypertension with a device that slows and regularizes breathing: A randomized double-blind controlled study. J Human Hypertens, 2001; 15: 271–2780
79. Elliott WJ, Izzo JL Jr, White WB et al. Graded blood pressure reduction in hypertensive outpatients associated with use of a device to assist with slow breathing. J Clin Hypertens, 2004; 6: 553–559.
80. Grassi D, Necozione S, Lippi C et al. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. Hypertension, 2005; 46: 398–405.