

Mechanisms and Treatment of Resistant Hypertension

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Definition and prevalence

Resistant hypertension is defined as blood pressure (BP) that remains above goal in spite of use of three antihypertensive medications in effective doses, usually including a diuretic¹. Patients who are intolerant of diuretics and have uncontrolled BP on regimens of 3 drugs from other classes are also considered to have resistant hypertension. The BP goal is <140/90 mm Hg in the general population of hypertensives and <130/80 mm Hg in hypertensive patients with diabetes or chronic kidney disease (CKD) (glomerular filtration rate <60 ml/min/1.73m²; serum creatinine >1.5 mg/dl in men or >1.3 mg/dl in women; albuminuria >300 mg/24-hr or >200 mg/g creatinine)¹. Similarly, patients who require 4 or more medications to control their BP are considered to have resistant hypertension.

Factors that predispose to antihypertensive treatment resistance include population characteristics, such as increased life expectancy, higher obesity rates and decreased physical activity, as well as provider characteristics, including inadequate attention to systolic BP (SBP) elevations and the more aggressive BP goals recommended by recent guidelines. The various contributing factors (Table 1) and secondary causes related to resistant hypertension (Table 2) are discussed in this review.

Pseudoresistance

Pseudoresistance is the appearance of lack of BP control caused by inaccurate measurement of BP, inappropriate drug choices/doses, nonadherence to prescribed therapy, or white-coat effect. Pseudoresistance is commonly misdiagnosed as resistant hypertension. Careful assessment of pseudoresistance avoids overtreatment and expensive/excessive evaluation.

Suboptimal treatment

Suboptimal medical treatment is a major contributing factor to uncontrolled hypertension. Suboptimal treatment is frequently related to clinical inertia defined as the provider's failure to increase therapy when the treatment goal is not

Key words

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Table 1 - Contributing factors for resistant hypertension

Volume expansion
Excess sodium intake
Volume retention secondary to chronic kidney disease
Inadequate diuretic therapy
Obesity
Exogenous substances
Nonsteroidal anti-inflammatory agents
Oral contraceptives
Alcohol
Corticosteroids
Anabolic steroids
Sympathomimetic agents (nasal decongestants, diet pills, cocaine)
Caffeine
Cyclosporine
Erythropoietin
Chemotherapeutic agents
Antidepressants

Adapted from Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure¹.

Table 2 - Secondary causes of hypertension

Hyperaldosteronism
Obstructive sleep apnea
Chronic kidney disease
Renal artery stenosis
Pheochromocytoma
Central nervous system tumors
Coarctation of the aorta
Thyroid diseases

reached. A retrospective study conducted in 7,253 hypertensive patients found that in patients with uncontrolled hypertension, providers had frequently failed to begin new medications or increase dosages of current medications during previous visits². Lack of knowledge of treatment guidelines, underestimation of cardiovascular (CV) risk, and the use of spurious reasons to avoid

intensification of therapy, such as the physician's perception that the patient will not accept more medications, are related to clinicians failure to intensify treatment^{3,4}.

Nonadherence

Poor adherence to prescribed medications is a common problem in patients with high blood pressure and a common cause of uncontrolled hypertension⁵. Poor adherence is common at the primary care level, but may be less common among patients who are seen by specialists⁶⁻⁸. Cost of treatment, poor relations between doctor and patient, multiple pills, and adverse effects of medical therapy are additional causes of poor adherence.

White-coat effect

White-coat effect, the difference between office BP and ambulatory (ABPM) or home BP measurements, can be calculated as the mean office BP minus mean daytime ambulatory BP. Mean daytime BP <135/85 mm Hg is considered normal for both ambulatory and home BP monitoring methods. The prevalence of significant white-coat effect ranges from 20 to 40% of all hypertensive patients and may be even more common in resistant hypertension. White-coat effect is more prevalent in women and older persons, and should be suspected in patients with symptoms related to hypotension in the absence of low BP recordings at the clinic and in those with high office BP without related target organ damage⁹.

Ambulatory and home BP monitoring are important methods to evaluate patients with uncontrolled BP and rule out true treatment resistance in clinical practice. ABPM and home BP measurements can avoid overtreatment and excessive visits to the clinic in patients with white-coat effect.

Contributing factors

Volume expansion

Volume expansion related to excessive dietary sodium, sodium retention secondary to CKD and/or failure to use diuretics appropriately can cause resistant hypertension¹⁰⁻¹². Assessment of plasma volume status in patients with resistant hypertension may be useful in the selection and titration of more appropriate treatment, e.g. initiation or intensification of diuretic therapy in volume expanded patients; renin-angiotensin-aldosterone system (RAAS) inhibitors/vasodilators in euvoletic vasoconstricted patients. Measurement of thoracic impedance can be useful in this regard¹³. A prospective study that randomized 104 patients with resistant hypertension to drug selection based on hemodynamic measurements or drug selection defined by a hypertension specialist found that patients randomized to treatment based on hemodynamic parameters had significantly higher control rates than patients whose treatment was based on specialist decision (56% vs 33%)¹⁴.

Diuretics are the cornerstone of treatment in patients whose BP cannot be controlled with multiple agents from other drug classes. Dietary salt reduction is a useful adjunctive treatment

in patients with resistant hypertension, particularly because it enhances the potency of antihypertensive drugs¹⁵. Some demographic groups, including the elderly, the obese, African Americans and patients with CKD tended to be more salt-sensitive and benefit more from dietary salt reduction.

Obesity

Obesity is common in patients with resistant hypertension. Data from the Framingham Heart Study showed that persons with a body mass index (BMI) ≥ 30 kg/m² had a 50% higher probability of uncontrolled BP than patients with a normal BMI (<25 kg/m²).¹⁶ Furthermore, the HYDRA study, a cross-sectional study of 45,125 primary care patients, showed that those with a BMI ≥ 40 kg/m² had a higher prevalence of hypertension, as well as a 5.3 and 3.2 fold higher probability of requiring 4 or 3 antihypertensive drugs, respectively, to achieve BP control compared to patients with normal weight (BMI ≤ 25 kg/m²) (Figure 1)¹⁷. Increased sodium and fluid retention, sympathetic activation, and stimulation of the RAAS appear to contribute to high BP in obese subjects¹⁸.

Exogenous substances

Use of a variety of prescription drugs and other exogenous substances is commonly related to resistant hypertension (Table 1). A history of use of these agents should be queried in all patients with resistant hypertension. Withdrawal of these agents can reduce or even normalize BP in some patients with resistant hypertension.

Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase (COX-) 2 inhibitors, are a common cause of uncontrolled BP and renal impairment in hypertensive patients¹⁹⁻²¹. NSAIDs appear to increase BP through volume and sodium retention, likely due to inhibition of vasodilating prostaglandins in the kidney. Elderly and diabetic patients are particularly susceptible to these adverse effects. The Nurses' Health Study prospectively analyzed the BP effect of non-narcotic analgesics in 51,630 normotensive female nurses 44 to 69 years of age followed for 8 years²². Compared with nonusers, women who frequently used aspirin, acetaminophen or NSAIDs had a 21, 20, and 35% increased risk of developing hypertension, respectively. This study clearly demonstrated that aspirin and acetaminophen, as well as conventional NSAIDs, have important BP effects.

All NSAIDs appear to elevate mean BP and antagonize the BP lowering effects of antihypertensive drugs²³. Selective COX-2 inhibitors are also associated with BP elevation. A meta-analysis of 45,451 patients enrolled in 19 randomized controlled trials showed that COX-2 inhibitors elevate BP by $\sim 4/1$ mm Hg compared to placebo, and by $\sim 3/1$ compared to NSAIDs²⁴. The BP elevating effects of NSAIDs and COX-2 inhibitors are dose-related and some agents appear to have greater effects than others. For example, in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program which randomized 34,701 patients with osteoarthritis or rheumatoid arthritis to etoricoxib or diclofenac, patients assigned to etoricoxib discontinued the study due to hypertension more frequently than those assigned to diclofenac²⁵. Of the selective COX-2 inhibitors,

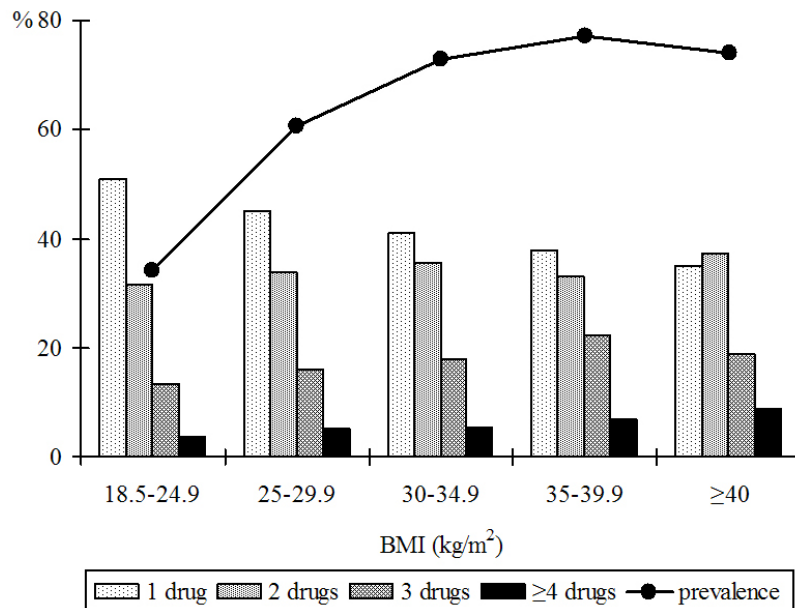


Fig. 1 - Increasing use of combination therapy and increase of prevalence of hypertension according to body mass index. Adapted from Bramlage P, et al. Am J Hypertens 2004; 17: 904-10.

rofecoxib is more likely to raise BP compared to celecoxib in both normotensive and hypertensive subjects²⁶. If analgesics are necessary in hypertensive patients, medications such as tramadol or hydrocodone and nerve block are useful alternatives to NSAIDs or COX-2 inhibitors. If NSAIDs or COX-2 inhibitors are needed, minimal effective doses should be prescribed. Providers must ask all hypertensive patients about use of pain control medications in order to avoid this form of iatrogenic resistant hypertension.

Oral contraceptives induce small increases in BP in the entire population of users, with frank hypertension occurring in a small number and resistant hypertension in an even smaller number of subjects^{27,28}. The Nurses' Health Study prospectively followed 68,297 normotensive premenopausal female nurses for development of hypertension over 4 years²⁹. Current oral contraceptive users had an 80% increased risk of developing hypertension compared with never-users, but this increased risk resolved almost completely with withdrawal of the medication (Figure 2). Furthermore, oral contraceptive use in persons with underlying hypertension is associated with uncontrolled BP. A cross-sectional study evaluating the association between oral contraceptives and BP control in 171 hypertensive women found that oral contraceptive users had poorer BP control and tended to have more severe hypertension than users of other contraceptive methods or nonusers³⁰. Combined (estrogen + progestin) oral contraceptives are more often associated with BP increases than progestin-only oral contraceptives. Progestins have mineralocorticoid receptor antagonist effects that may account for their BP neutral or BP lowering actions. The new 4th generation progestin, drospirenone, when combined with estradiol, has been shown to reduce BP³¹. Based on these and other data, progestin-only contraceptives are recommended

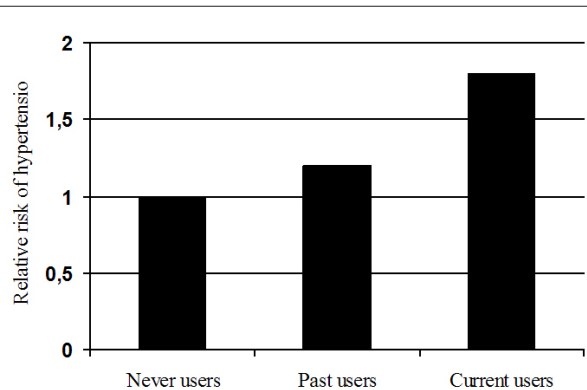


Fig. 2 - Relative risk for development of hypertension by current and past oral contraceptive users compared to never-users. Adapted from Chasan-Taber L, et al. Circulation 1996; 94: 483-9.

for women with established hypertension.

The World Health Organization³² and the American College of Obstetrics and Gynecology³³ recommend use of combined oral contraceptives containing low doses of estrogen for women who are free of CV disease and major CV risk factors, including hypertension. Progestin-only contraceptives, including intrauterine devices are recommended for women with established CV disease, at high CV risk, migraine headaches with focal neurologic signs or history of thromboembolic disease.

Menopausal hormone therapy has minimal effects on BP and is not contraindicated in either normotensive or hypertensive women. Nevertheless, all hypertensive women treated with menopausal hormone therapy should have

their BP measured initially and then at 3-6-month intervals depending on the difficulty of control³⁴.

Heavy alcohol ingestion increases the risk of uncontrolled hypertension. In a cross sectional analysis, men with excessive alcohol intake (≥ 4 glasses per day) had 50% higher probability of poor BP control³⁵. Alcohol cessation promotes BP reduction and improves adherence to treatment. A prospective study of the effect of 1 month of abstinence on 24-hr BP in heavy drinkers documented an average reduction of 7.2 mm Hg in 24-hr SBP and 6.6 mm Hg in 24-hr diastolic BP (DBP).³⁶ The prevalence of hypertension among study subjects decreased from 42% to 12%. Moderation in alcohol consumption (≤ 2 drinks per day) is recommended as a lifestyle modification in the general population, especially in patients with hypertension, and complete cessation should be advised in the case of heavy drinkers.

Other exogenous substances that contribute to hypertension, such as corticosteroids, sympathomimetic agents, erythropoietin, and antidepressants should be avoided in patients with high BP and should be discontinued if at all possible in those with uncontrolled BP. In subjects to whom these substances are essential, more frequent BP evaluations and increased doses and/or numbers of antihypertensive medications may be required.

Secondary hypertension

The prevalence of secondary hypertension is greater in patients with resistant hypertension than in the general hypertensive population. The most common secondary causes of resistant hypertension are hyperaldosteronism, chronic kidney disease, renal artery stenosis and obstructive sleep apnea (Table 2). The prevalence of secondary hypertension increases with age, mainly due to increases in chronic kidney disease, obstructive sleep apnea, and renal artery stenosis.

Hyperaldosteronism

The aldosterone excess syndrome was initially described by Jerome Conn in 1955 in a patient with prolonged hypokalemia, severe hypertension and adrenal tumor³⁷. However, the modern syndrome of hyperaldosteronism differs from classical primary aldosteronism. Hypokalemia and adrenal tumors are no longer required for the diagnosis of hyperaldosteronism. In fact, a substantial proportion of patients with hyperaldosteronism have normal potassium levels. In our experience 50% of patients with hyperaldosteronism and resistant hypertension have normal potassium levels or have never needed potassium supplementation³⁸.

Hyperaldosteronism is now recognized as the most common cause of secondary hypertension and is a common contributor to treatment resistance³⁹⁻⁴⁵. Among untreated patients, hyperaldosteronism prevalence increases with increasing hypertension severity, from 2% in patients with stage 1 hypertension to 8% in those with stage 2 hypertension and 13% in those with stage 3 hypertension³⁹. The prevalence of hyperaldosteronism is even higher in patients with resistant hypertension, approaching 17-22% in multiple studies⁴⁶⁻⁴⁹. In a prospective evaluation of patients referred to our own specialty clinic for resistant hypertension, defined as uncontrolled

hypertension despite use of three or more medications, 18 of 88 (prevalence of 20%) patients had hyperaldosteronism based on suppressed renin activity and high 24-hr urinary aldosterone excretion while consuming a high salt diet⁴⁶.

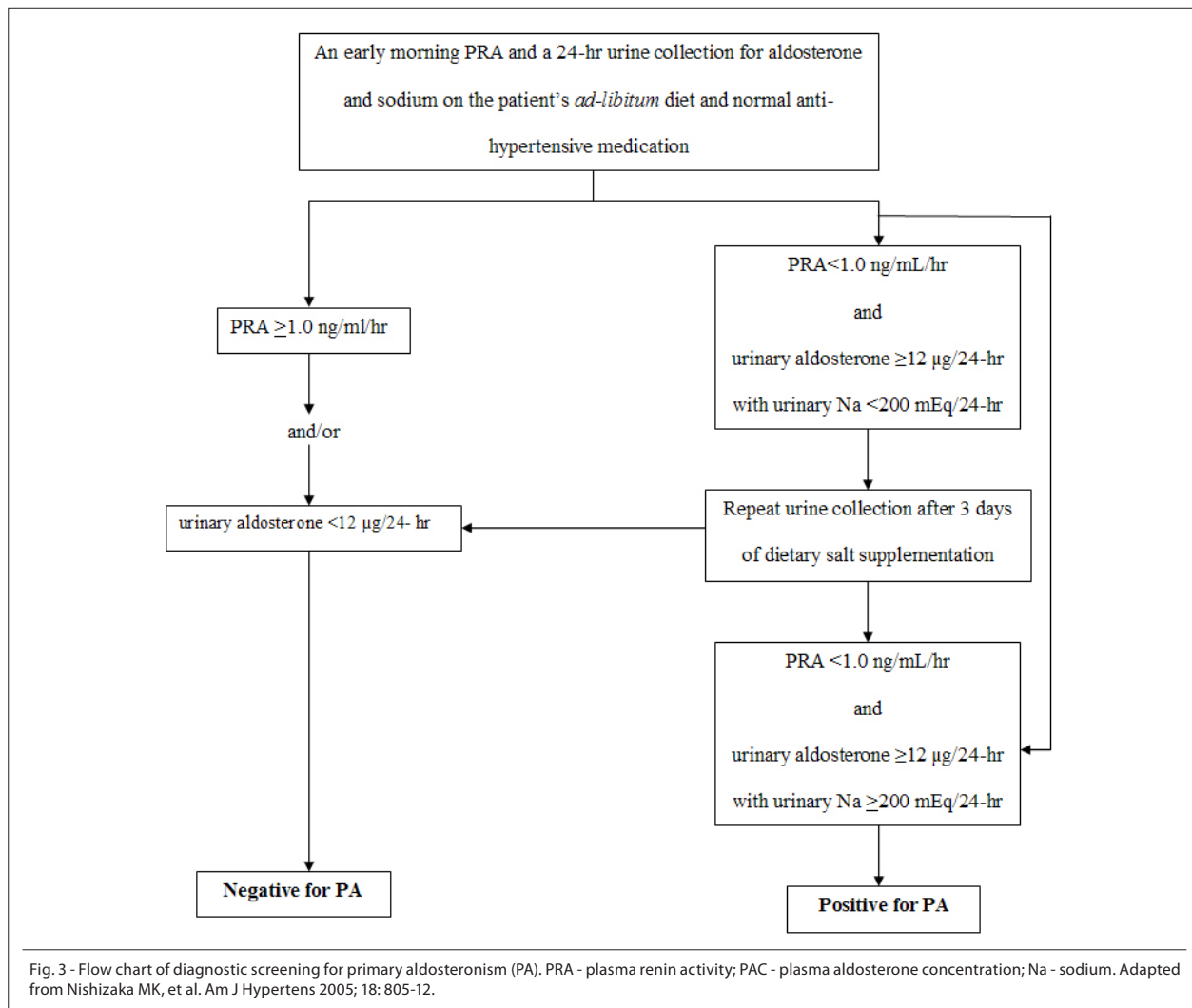
Because of its high prevalence in this patient group, all patients with resistant hypertension, even those with normokalemia, should be evaluated for hyperaldosteronism. A presumptive diagnosis of aldosterone excess can be made by documenting elevated aldosterone levels in plasma and urine in the setting of suppressed renin activity. Measurement of plasma aldosterone concentration (PAC) level/plasma renin activity (PRA) ratio (ARR) has been shown to have sufficient sensitivity and specificity to serve as an effective screening test for hyperaldosteronism. Although the exact test characteristics of the ARR have varied widely between studies, its negative predictive value has been such that a low ARR (< 20 when PAC is measured in ng/dl and PRA is measured in ng/ml/min) reliably excludes hyperaldosteronism. The specificity of ARR is less consistent insofar that a high ratio ($> 20-30$) is suggestive, but not diagnostic of hyperaldosteronism. Accordingly, a high ARR is suspicious of hyperaldosteronism, but the diagnosis must be confirmed.

Demonstration of increased 24-hr urinary excretion of aldosterone confirms the diagnosis of hyperaldosteronism in patients with resistant hypertension⁵⁰. As a first approach, PRA, 24-hr excretion of aldosterone and sodium can be measured in patients on their normal diets. (Measuring aldosterone and sodium from the same urine collection requires use of a non-salt preservative such as acetic acid). If the aldosterone excretion (≥ 12 $\mu\text{g}/24\text{-hr}$) and the sodium excretion are both high (≥ 200 mEq/24-hr), indicative of chronic high salt intake, it is not necessary to do additional salt loading to confirm hyperaldosteronism (Figure 3). If the aldosterone is high but the sodium is low (< 200 mEq/24-hr) in the first collection, we repeat the collection after oral salt supplementation sufficient to increase the sodium ≥ 200 mEq/24-hr.

After confirmation of biochemical hyperaldosteronism, thin-section abdominal CT imaging is recommended in an attempt to identify adrenal tumors. Even in the setting of confirmed biochemical hyperaldosteronism, CT imaging has a poor specificity for identifying adenoma and adrenal vein sampling can confirm or exclude lateralization of aldosterone excretion consistent with a unilateral adenoma. Laparoscopic adrenalectomy should be considered in patients with unilateral adenoma. For patients with contraindications to surgery or who do not have tumors, treatment with a mineralocorticoid receptor antagonist promotes BP reduction and regresses target organ damage.

Obstructive sleep apnea

Obstructive sleep apnea (OSA), characterized by preserved and increased respiratory effort despite partial or complete occlusion of the upper airway, is a common finding in patients with resistant hypertension^{51,52}. OSA is strongly related to resistant hypertension and can predict hypertension in normotensive subjects^{53,54}. A report of overnight polysomnographic studies in 41 unselected patients with resistant hypertension found OSA, defined as an apnea-hypopnea index of ≥ 10 events/hour in 83% of patients⁵⁵. The



prevalence and severity were significantly higher in men than in women with resistant hypertension. Our clinic reported that 85% of patients with resistant hypertension have OSA defined as an apnea-hypopnea index of ≥ 5 events/hour⁵².

There is an association between aldosterone excess, obesity and sleep apnea^{56,57}. Stimulation of aldosterone release by visceral fat, excessive sodium retention stimulated by sympathetic activation and hypoxemia are possible mechanisms related to this association⁵⁶. Sympathetic activity is increased in patients with hypertension and OSA, suggesting that intermittent hypoxemia could contribute to adrenergic activation⁵⁸. Obesity and/or sleep-disordered breathing also may stimulate the adrenal gland to produce inappropriately large amounts of aldosterone. However, the mechanisms by which OSA could lead to hypertension are not completely elucidated (Figure 4).

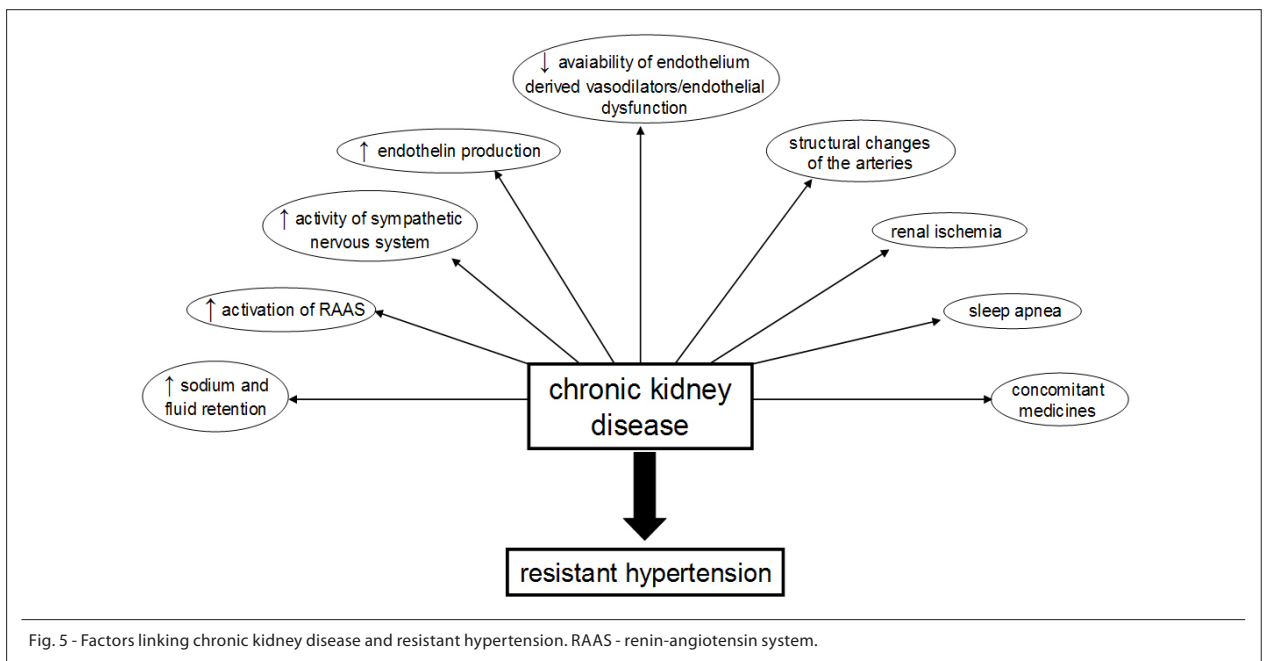
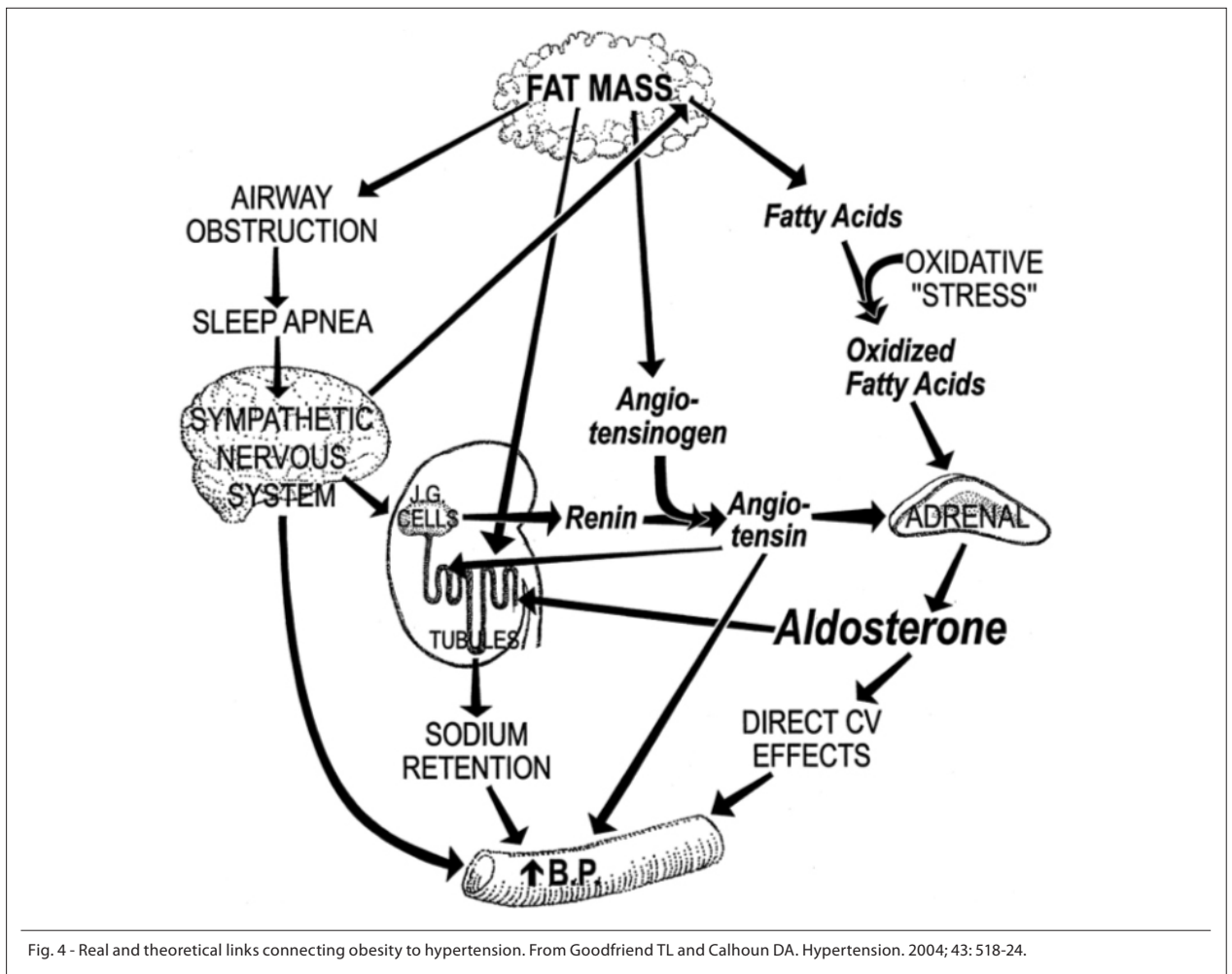
Continuous positive airway pressure (CPAP) treatment is the gold standard for management of OSA. However, the role of CPAP in the treatment of hypertension is not well established. While cause and effect between OSA and resistant hypertension cannot be inferred, patients with resistant

hypertension and OSA should be treated with CPAP and encouraged to lose weight. Oropharyngeal surgery has proved disappointing as a treatment for obstructive sleep apnea.

Chronic kidney disease

CKD is a common cause of resistant hypertension and a consequence of poor BP control over time. Fluid retention, excessive activation of the RAAS and concomitant medicines are related to treatment resistance in patients with impaired renal function (Figure 5)⁵⁹.

All patients with resistant hypertension should have their glomerular filtration rate estimated by use of the Modification of Diet in Renal Disease (MDRD) Study or Cockcroft-Gault equation⁶⁰, since serum creatinine is an unreliable marker of CKD, particularly in elderly patients. Albuminuria should also be assessed. Dietary salt reduction plays an important role in order to decrease the volume expansion. Loop diuretics are indicated to effectively reduce volume and facilitate BP control in patients with creatinine clearance < 30 ml/min. Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are indicated in patients with mild



to severe CKD, particularly in the presence of micro- or macroalbuminuria. Blockade of the RAAS in patients with CKD reduces cardiovascular risk, improves BP control, and reduces proteinuria and progression to end stage renal disease⁶¹. Transitory and usually limited decreases in glomerular filtration rate can occur after instituting ACE inhibitors or ARBs and are not an indication for cessation of therapy.

Renal artery stenosis

Renovascular disease is a common finding in hypertensive patients with multiple risk factors and extra-renal atherosclerotic disease, particularly among patients with resistant hypertension^{62,63}. Approximately 10% of cases of renal artery stenosis are attributable to fibromuscular dysplasia. Those patients are more likely to be women, to be younger than 50 years of age, and to be successfully treated with renal revascularization⁶⁴.

The vast majority (90%) of renal artery lesions are atherosclerotic in etiology, and this prevalence increases with age^{65,66}. Patients with resistant hypertension and known atherosclerotic disease, declining renal function, or a history of flash pulmonary edema have an increased likelihood of atherosclerotic renal arterial disease and should be evaluated with Doppler or magnetic resonance angiography of the renal arteries. The choice of treatment for atherosclerotic renal lesions is controversial due to a lack of strong evidence in favor of either medical treatment or revascularization for BP control and preservation of renal function^{67,68}. CORAL is a large ongoing randomized clinical trial that is comparing the effects of optimal medical treatment alone to stent revascularization plus optimal medical treatment on a composite cardiovascular and renal end point in hypertensive patients with atherosclerotic renal artery stenosis⁶⁹. Patients with resistant hypertension should be screened for renal artery stenosis and considered for revascularization if the anatomy of the lesion(s) is appropriate and if the BP cannot be controlled with optimal medical treatment. Stent therapy is superior to balloon angioplasty for atherosclerotic renal arterial lesions⁷⁰.

Pheochromocytoma

The prevalence of pheochromocytoma in general hypertensive population is low (0.1-0.6%)^{71,72}, but diagnosis and treatment are extremely important due to difficult-to-control hypertension, the possibility of precipitating hypertensive crisis if the tumor is stimulated and the possibility that the tumor could be malignant. Headaches, palpitations, and sweating are the most common findings, but the clinical presentation of pheochromocytoma is widely variable⁷³. Pheochromocytoma is associated with increased BP variability due to fluctuations in the levels of norepinephrine secreted by the tumor.

All patients with resistant hypertension and symptoms typical of pheochromocytoma should be screened. Pheochromocytoma should be ruled out in pregnant women with symptoms and signs of pheochromocytoma before 20 weeks gestation, because pheochromocytoma is related to increased maternal and fetal morbidity and mortality⁷⁴. Plasma free metanephrine is the best screening test for

pheochromocytoma, with high sensitivity (99%) and specificity (82%)⁷³. Surgical removal is the appropriate treatment.

Treatment of resistant hypertension

Treatment of a patient with resistant hypertension includes removal of contributing factors, appropriate treatment of secondary causes and use of effective multi-drug regimens. Nonpharmacologic therapies, such as weight loss, exercise, dietary salt reduction, and moderation of alcohol intake should be encouraged in all patients. Interfering substances should be withdrawn or down-titrated as much as possible and obstructive sleep apnea should be treated.

Factors related to poor adherence need to be assessed. Discussing the cost and adverse effects of medications, number of pills, and objectives of treatment can improve patient adherence. Multidisciplinary teams, including nurses, pharmacists, nutritionists, psychology, and fitness trainers can improve treatment results⁷⁵.

Pharmacologic treatment

Full doses of appropriate combinations such as an ACE or ARB, calcium channel blocker, and a thiazide diuretic are generally very effective and well tolerated. Patients with resistant hypertension often have occult volume retention and effective diuretic therapy is essential for BP control^{6,13}. Long-acting thiazide diuretics are effective in most patients with resistant hypertension. Loop diuretics are preferable in patients with CKD if creatinine clearance is <30 ml/min. Furosemide is relatively short-acting and it should be prescribed at least twice-daily. Serum potassium needs to be monitored closely.

Mineralocorticoid receptor antagonists promote significant additional BP reduction independent of aldosterone/renin levels in patients with resistant hypertension (Figure 6)^{38,76-78}. Our group has described the effect of low-dose (12.5 to 25 mg/day) spironolactone in patients with uncontrolled BP on an average of four medications, including ACE inhibitor or ARB, and a diuretic³⁸. After 6 months of follow-up SBP was reduced by 25 mm Hg and DBP by 12 mm Hg. BP reductions were similar in patients with and without hyperaldosteronism, and the BP response to spironolactone was not predicted by baseline PAC or PRA or by 24-hr urinary aldosterone excretion. The benefit

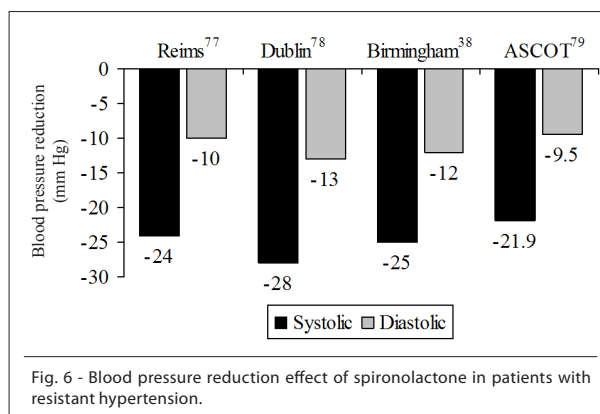


Fig. 6 - Blood pressure reduction effect of spironolactone in patients with resistant hypertension.

was similar in African-American and Caucasian subjects. Data from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT) also demonstrated a significant BP lowering effect of spironolactone as fourth-line therapy. SBP and DBP were reduced by 21.9 and 9.5 mm Hg, respectively, with spironolactone treatment in 1,411 participants⁷⁸.

Spironolactone was generally well tolerated in these studies, although breast tenderness occurred in about 10% of the men. The more selective mineralocorticoid receptor antagonist eplerenone is better tolerated than spironolactone, with a lower incidence of breast tenderness, gynecomastia, sexual dysfunction, and menstrual irregularities, and has been shown to effectively reduce BP⁷⁹.

Hyperkalemia, with or without acute renal insufficiency was uncommon in spite of concomitant using of an ACE inhibitor or ARB, but older patients and those with CKD or diabetes are at increased risk of developing hyperkalemia. Serum potassium and creatinine levels should be monitored in patients treated with mineralocorticoid receptor antagonists, particularly if they are receiving concomitant ACE inhibitor or ARB therapy. Potassium supplementation or salt substitutes that contain potassium should be discontinued or reduced in patients who are started on mineralocorticoid receptor antagonists.

Conclusion

Resistant hypertension defined as uncontrolled BP despite use of at least 3 antihypertensive medications is an increasingly common problem. Hyperaldosteronism, obesity, volume expansion, and OSA are common findings in patients with resistant hypertension. Mineralocorticoid receptor antagonists are an effective therapeutic option for treatment of resistant hypertension even in the absence of demonstrable aldosterone excess.

Potential conflict of interest

Disclosures: Dr. Pimenta has no conflicts. Dr. Calhoun has served as a consultant for Novartis; has received grant support from Novartis, Merck, Astra-Zeneca and Encysive Pharmaceuticals. Dr. Oparil has received grants-in-aid from Abbott Laboratories, Astra-Zeneca, Aventis, Biovail, Boehringer Ingelheim, Bristol Myers-Squibb, Forest Laboratories, GlaxoSmithKline, Novartis, Merck & Co, Pfizer, Sankyo Pharma, Sanofi-Synthelabo, Schering-Plough; has served as consultant for Bristol Myers-Squibb, Daiichi Sankyo, Merck & Co, Novartis, Pfizer, Sanofi Aventis, and The Salt Institute, and is a member of Board of Directors for Encysive Pharmaceuticals.

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