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Review Article

Role of the Kidneys in Resistant Hypertension

Z. Khawaja and C. S. Wilcox

Division of Nephrology and Hypertension, Georgetown University Medical Center, 3800 Reservoir Road NW, PHC F6003, Washington, DC 20007, USA

Correspondence should be addressed to C. S. Wilcox, wilcoxch@georgetown.edu

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Resistant hypertension is a failure to achieve goal BP (<140/90 mm Hg for the overall population and <130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) in a patient who adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic. The kidneys play a critical role in long-term regulation of blood pressure. Blunted pressure natriuresis, with resultant increase in extracellular fluid volume, is an important cause of resistant hypertension. Activation of the renin-angiotensin-aldosterone system, increased renal sympathetic nervous system activity and increased sodium reabsorption are important renal mechanisms. Successful treatment requires identification and reversal of lifestyle factors or drugs contributing to treatment resistance, diagnosis and appropriate treatment of secondary causes of hypertension, use of effective multidrug regimens and optimization of diuretic therapy. Since inappropriate renal salt retention underlies most cases of drug-resistant hypertension, the therapeutic focus should be on improving salt depleting therapy by assessing and, if necessary, reducing dietary salt intake, optimizing diuretic therapy, and adding a mineralocorticoid antagonist if there are no contraindications.

1. Introduction

The Joint National Committee (JNC) 7 defined resistant hypertension as failure to achieve goal blood pressure (BP) (<140/90 mm Hg for the overall population and <130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) in a patient who adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic. An increasing number of patients, especially the aged, those with diabetes or who are African American, meet this definition. However, it is important to rule out white coat hypertension by asking the patient to record their own home blood pressures and undertaking an ambulatory blood pressure monitor if the results are equivocal. A careful enquiry about whether the patient is taking the prescribed medications and if there are adverse effects that are causing concern may give clues to noncompliance. In some cases, it may be useful to measure blood or urine drug levels, for example of diuretics, to check for noncompliance. A recent study of African Americans with hypertensive focal segmental glomerulosclerosis [1] has linked a single nucleotide polymorphism for the apolipoprotein L1 gene to the disease but this is not yet available as a diagnostic test. Since aging increases the burden of vascular disease, resistant hypertension and its consequences are more common in elderly people. The kidneys play a critical role in long term regulation of blood pressure. In this paper, we discuss the renal mechanisms which contribute to the development of resistant hypertension, which are summarized in Table 1, and their management.

2. Blunted Pressure Natriuresis

Pressure natriuresis [2] describes the increased sodium excretion that occurs with elevated blood pressure. A normal pressure natriuresis should prevent hypertension because any elevation of blood pressure would elicit an increased sodium and water excretion that would reduce the blood volume and venous return and retain a normal level of blood pressure. Patients with hypertension have a defective pressure natriuresis. The relationship between sodium excretion and blood pressure is shifted to higher levels of blood pressure, which implies an abnormal response in the kidney that

Table 1: Renal mechanisms of drug-resistant hypertension.

(1) Blunted pressure natriuresis
(a) Chronic kidney disease
(b) Renal artery stenosis
(2) Renal nerve activation
(3) Renal nitric oxide deficiency
(4) Medications acting adversely on the kidney
(a) Non steroid anti inflammatory drugs (NSAIDs)
(b) Cox-2 inhibitors
(c) Corticosteroids
(d) Cyclosporine
(e) Erythropoietin
(f) Licorice
(5) Extra renal factors causing salt retention
(a) Hyperaldosteronism
(b) Vasodilator medications
(c) Obstructive sleep apnea (OSA)
(d) Endothelin type A receptor antagonists.
(6) Inappropriately high salt intake
(7) Ineffective diuretic usage

maintains hypertension. Salt retention occurs when intake exceeds excretion. This leads to extracellular fluid (ECF) volume expansion which is common in chronic kidney disease (CKD) and is an important cause of resistant hypertension. The salt retention is typically subtle and does not lead to edema. Even a normal rate of sodium excretion in a patient with hypertension is inappropriate and implies a renal mechanism of hypertension since a normal kidney increases the sodium excretion above intake and reduces ECF volume when blood pressure is increased to restore a normal level of BP. The mechanism of renal sodium retention usually entails a combination of reduced glomerular filtration rate (GFR) and increased tubular sodium reabsorption. Since the GFR may be normal or only reduced modestly, the renal defect in resistant hypertension is predominantly a failure to appropriately suppress tubular sodium reabsorption [3].

Large increases in ECF volume may arise if sodium intake is very high or reduction in GFR is severe (e.g., chronic kidney disease stage 4-5). Patients with resistant hypertension had higher brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) levels confirming that they had increased intrathoracic blood volume [4].

Heart failure may aggravate sodium retention. Drugs that include fludrocortisone (mineralocorticoid receptor agonist), estrogens, and nonsteroidal antiinflammatory drugs (NSAIDS) [5] cause sodium retention and therefore are important renal causes of resistant hypertension.

Other renal mechanisms implicated in the pathogenesis of resistant hypertension include: increased renin-angiotensin-aldosterone system (RAAS) activity, increased renal sympathetic nervous system (SNS) activity, nitric oxide (NO) deficiency, oxidative stress, renal artery stenosis, hyperaldosteronism, obstructive sleep apnea and vasodilator medications (Table 1).

An important renal mechanism of resistant hypertension is renal artery stenosis. As first described by Goldblatt [6] in animal models, the reduction in renal perfusion pressure increases renin release by the kidney perfused by the stenosed artery. The ensuing increases in angiotensin II and aldosterone cause vasoconstriction and inappropriate renal salt retention. Moreover, the kidney downstream from the stenosis has a reduced renal perfusion pressure which is a further potent mechanism for salt retention. Numerous studies established the causal relationship between angiotensin II–mediated vasoconstriction and hypertension in the early phase of experimental renovascular hypertension [7, 8]. The high levels of angiotensin II stimulate the adrenal cortex to produce excessive aldosterone (secondary aldosteronism), promoting renal sodium retention by both kidneys. Moreover, angiotensin directly enhances renal salt and fluid reabsorption. Both the direct pressor effects of angiotensin II and the sodium retention restore the renal perfusion pressure at the stenosed kidney at the expense of systemic hypertension. However, during the chronic phase of experimental renovascular hypertension, which may be a better model for many patients with prolonged renal artery stenosis, plasma renin activity returns to baseline levels. The hypertension is sustained by hypertensive damage in the contralateral kidney. This may explain the disappointing results of controlled trials of renal revascularization of the stenosed kidney [9, 10]. The recently published STAR [11] trial, reported no overall benefit in renal function in patients with renal artery stenosis randomized to intervention, compared to the control group that received medication only. However, the number of antihypertensive medications taken by the patients was reduced after intervention. The CORAL [12] study is testing the effect of intervention for patients with renal artery stenosis on cardiovascular events, but it is not yet completed. Another trial, RAS-CAD [13] is studying the effect of medical therapy alone versus medical therapy plus renal artery stenting on left ventricular hypertrophy progression (primary end point) and cardiovascular morbidity and mortality (secondary end points) in patients affected by ischemic heart disease and renal artery stenosis.

Patients with bilateral renal artery stenosis are at an increased risk for developing severe renal salt retention. If the stenosis is unilateral, the unaffected kidney can eliminate the salt and water retained by the stenosed kidney via the pressure natriuresis mechanism. However, if both kidneys have a functional stenosis, the pressure natriuresis may be curtailed sufficiently to lead to episodic fluid retention that causes flash pulmonary edema.

Clues to the presence of bilateral renal artery stenosis in resistant hypertension include an abdominal bruit, atherosclerosis elsewhere, pulmonary edema with preserved ejection fraction and worsening renal function during therapy with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Recurrent flash pulmonary edema due to bilateral renal artery stenosis

is dangerous for the patient and should prompt consideration of renal revascularization by angioplasty and stenting [14].

3. Renal Nerve Activation

Intense renal efferent nerve stimulation causes renal vasoconstriction with decreases in renal blood flow (RBF) and increases in renal vascular resistance (RVR). However, more subtle increases in renal nerve activity increase renal tubular sodium reabsorption and increase renin secretion without changes in renal hemodynamics [15]. Renal nerves make functional contact with many parts of the nephron including the tubules and the juxtaglomerular apparatus, where these effects are manifest. The effects of renal nerve stimulation on renin secretion are direct and not secondary to volume depletion or hemodynamic changes.

Renal denervation decreased blood pressure in many animal models of hypertension. But this may be a response to preventing renal nerve traffic from the kidney (deafferentation) and/or to the kidney (deefferentation).

The renal afferent sensory nerves are located primarily in the renal pelvic wall where they exhibit mechanosensitive (responding to increases in renal pelvic pressure) or chemosensitive (responding to changes in chemical composition of the urine) properties. Physiological stimulation of renal afferent mechanosensitive nerves by increasing ureteropelvic pressure increased afferent renal nerve activity and decreased efferent renal sympathetic nerve activity, resulting in a diuresis and natriuresis. This was termed the renorenal reflex [16]. Selective interruption of the afferent pathway has been achieved by removal of the kidney (presumed source of the signal) or section of the dorsal roots conveying afferent renal nerve input to the neuraxis (T9-L1). Dorsal root section reduced the blood pressure in rat models of renovascular hypertension, which testifies to the importance of the renal afferent nerves in maintaining hypertension in this setting.

Muscle sympathetic nerve activity and calf muscle vascular resistance were increased in patients with hypertension receiving hemodialysis therapy [17]. Bilateral nephrectomy abolished these changes. This important study identified the chronically diseased kidney as the source of afferent renal input resulting in increased muscle sympathetic nerve activity, calf vascular resistance, and hypertension.

A proof of concept study in 45 patients with resistant hypertension reported that renal sympathetic denervation by renal artery radiofrequency ablation reduced the BP by 24/10 mm Hg at 3 months and 29/16 mm Hg at 12 months [18]. It is not clear whether this remarkable effect of renal nerve ablation on reducing BP is due to deafferentation or deefferentation of the renal nerves, or a combination of those. Symplicity HTN-2 trial [19] assessed 106 patients with treatment-resistant hypertension (i.e., systolic blood pressure $\geq$160 mm Hg or $\geq$150 mm Hg for patients with diabetes despite the use of three or more antihypertensive drugs). Patients were randomly assigned to renal sympathetic denervation (52) or control (54) groups. Renal denervation resulted in impressive reductions in mean office-based measurements of blood pressure (32/12 mm Hg at 6 months), whereas blood pressure remained almost unchanged in the control group. Home and ambulatory measurements of blood pressure followed a similar pattern; the corresponding reductions were 20/12 mm Hg and 11/7 mm Hg with renal denervation, whereas no significant reductions were observed in the control group. However, there were several limitations of the study design. The control group could not undergo sham operation, which would have provided double-blinding and reduced potential bias. Furthermore, secondary and white-coat hypertensions were not defined as exclusion criteria.

The increase in renin secretion with renal nerve stimulation is mediated via beta-1 receptors and is therefore blocked by cardioselective and noncardioselective beta blockers. The increase in tubular reabsorption and renal vascular resistance are mediated via alpha receptors and are diminished by alpha blockers. Central agents such as clonidine reduce renal nerve activity and renin secretion. Thus, several drugs used to treat hypertension interrupt some of the renal mechanisms that underlie resistant hypertension.

4. Nitric Oxide Deficiency

Studies in rodents have established that inhibition of nitric oxide synthase (NOS) causes systemic and glomerular hypertension, glomerular ischemia, glomerulosclerosis, tubulointerstitial injury, and proteinuria [20].

Most evidence suggests a decreased total nitric oxide (NO) production in human renal disease and hypertension. NO deficiency occurs in the presence of oxidative stress, due both to inactivation of NO by superoxide anion and to uncoupling of nitric oxide synthase, which then produces superoxide rather than NO. There is evidence that oxidative stress occurs early in the course of CKD and hypertension and is amplified as the disease progresses [21].

Oxidative stress can precede the development of hypertension and cause nitric oxide (NO) deficiency [22]. In a study of patients with early essential hypertension, Wang et al. [21] reported severe endothelial dysfunction and inhibition of microvascular nitric oxide synthase accompanied by elevated plasma reactive oxygen species and elevated plasma levels of asymmetric dimethyl arginine that can inhibit and uncouple nitric oxide synthase [23].

In almost all rodent models of hypertension, there is oxidative stress that if corrected, lowers BP, whereas creation of oxidative stress in normal animals can cause hypertension. Reactive oxygen species (ROS) can enhance afferent arteriolar tone and reactivity both indirectly via potentiation of the tubuloglomerular feedback mechanism [24] and directly by microvascular mechanisms that diminish endothelium-derived relaxation factor/nitric oxide responses, generate a cyclooxygenase-2-dependent endothelial-derived contracting factor that activates thromboxane-prostanoid receptors, [25] and enhance vascular smooth muscle cells reactivity [26]. Drugs that improve NO activity in blood vessels include nebivolol, nitrates and bidil. The hydralazine component in

bidil may act as a vascular antioxidant that preserves the NO generated by the nitrate component. It has been used primarily to treat resistant heart failure in African Americans. In a randomized, placebo-controlled, double blind study involving six subjects, Oliver et al. [27] showed that the combination of phosphodiesterase type 5 inhibitor, sildenafil and isosorbide mononitrate decreased BP by 26/18 mm Hg as compared with placebo. However, it should not be forgotten that sildenafil has been considered to be contraindicated in patients taking nitrates. Therefore, further evidence will be needed before this new therapeutic combination can be recommended for treatment of hypertension.

5. Medications Acting Adversely on the Kidney

5.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). NSAIDs are an important remediable cause of drug-resistant hypertension. They increase BP by an average of 5 mm Hg, but the effect can be more pronounced in resistant hypertension. They inhibit renal prostaglandin production, decrease renal blood flow and retain sodium [28]. They diminish the BP-lowering effect of all antihypertensive drug classes except calcium antagonists [29]. The effect of NSAIDs on BP is more pronounced in patients with CKD. Selective cyclo-oxygenase-2 inhibitors have effects generally similar to those of NSAIDs [30].

5.2. Glucocorticoids. Glucocorticoids such as prednisone induce a modest sodium and water retention but the mechanism by which they increase BP is uncertain [31]. Corticosteroids with mineralocorticoid effect (e.g., hydrocortisone, cortisone) produce significant fluid retention, but even agents without mineralocorticoid activity (e.g., dexamethasone, betamethasone, and triamcinolone) can exacerbate hypertension in susceptible subjects. Licorice, a common ingredient in oral tobacco products, can raise blood pressure by suppressing the metabolism of cortisol by beta hydroxysteroid dehydrogenase resulting in increased stimulation of the mineralocorticoid receptor [32].

5.3. Erythropoietin Stimulating Agents (ESA). Erythropoietin stimulating agents increased blood pressure in both normotensive and hypertensive patients with CKD. Epogen may raise BP by expanding blood volume, increasing the hematocrit and hence the viscosity of the blood and increasing vascular production of the vasoconstrictor prostaglandin, thromboxane. However, in studies in rats these prohypertensive effects of epogen were offset by increased NO generation in the endothelial cells of the kidney [33]. Since CKD impairs NO generation, this offsetting effect may be diminished and this may explain why the hypertensive effects of epogen are more pronounced in patients with CKD and hypertension [34].

5.4. Cyclosporine. As summarized in a Cochrane review, [35] cyclosporine, in lower doses (1–4 mg/kg/d) increases BP by an average of 5 mm Hg and in higher doses (>10 mg/kg/d) by 11 mm Hg. The mechanisms are not established and may include enhanced sympathetic nervous system activity, renal vasoconstriction, sodium/water retention, [36] impaired peripheral vasodilatation and decreased vascular compliance. Calcium channel blockers (CCBs) attenuate cyclosporine induced vasoconstriction [37]. Verapamil, diltiazem and the dihydropyridine nicardipine reduce the hepatic metabolism of cyclosporine, thereby increasing its blood level by 40–50%. Although some investigators have found this interaction beneficial as it leads to a reduction in the dose of cyclosporine, other investigators prefer nifedipine or isradapine, which have little effect on blood levels of cyclosporine or tacrolimus. Amlodipine has an intermediate effect on cyclosporine metabolism, and the dose does not usually need adjustment [38].

6. Extra Renal Factors Causing Salt Retention

6.1. Aldosterone. Aldosterone is secreted by the zona glomerulosa of the adrenal cortex under the influence of angiotensin II, potassium, metabolic acidosis and adrenocorticotropic hormone (ACTH). The genomic pathway for aldosterone action in tubular cells regulates the transport of sodium and potassium. Aldosterone binds to mineralocorticoid receptors in the cytoplasm of the principal cells of the collecting duct, which activate genes for specific protein synthesis. This results in an increase in apical epithelial sodium entry channels, basolateral sodium/potassium ATPase for cellular sodium extrusion and potassium entry, and apical ROMK channels for passive movement of cellular potassium into the lumen that facilitates K^+ secretion.

Thus, aldosterone promotes sodium reabsorption and potassium secretion by the collecting ducts. Recent studies have shown that aldosterone is important in resistant hypertension. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [39] of 1141 patients with resistant hypertension, 25 mg daily of spironolactone over 1.3 years decreased the mean systolic BP by 21.8 mm Hg and the diastolic BP by 9.5 mm Hg. Adverse effects included gynecomastia or breast tenderness (6%) and hyperkalemia (2%). In another study of patients with resistant hypertension (mean baseline BP 163/91 mm Hg), spironolactone decreased BP to a similar degree as the ASCOT trial. The decrements in systolic and diastolic BP were similar to patients with primary hyperaldosteronism [40] and were comparable in black and white patients. Although much of the antihypertensive effect is likely secondary to reduced sodium reabsorption, there is a nongenomic effect mediated through the action of spironolactone to block mineralocorticosteroid receptors on the cell membranes of blood vessels. Evidence for a nonrenal action comes from a study in which spironolactone (50 mg) twice daily reduced pre-dialysis systolic BP from 142 to 131 mm Hg in patients who had end stage renal disease (ESRD) [41]. These patients had anuria and therefore the effect of spironolactone must have been independent of changes in sodium balance by the kidneys. Moreover, aldosterone can injure the vascular endothelium, which could contribute to elevated BP. Amiloride is a potassium-sparing diuretic that can reduce BP and combat hypokalemia

in patients with resistant hypertension. Eplerenone is a more selective aldosterone antagonist than spironolactone and is a good choice for patients who have responded to spironolactone, but developed adverse effects of breast enlargement or loss of libido.

6.2. Vasodilatory Edema. Drug-induced edema with vasodilatory drugs can involve nonrenal mechanisms, including direct arteriolar dilatation (causing an increase in intracapillary pressure) in addition to stimulation of the RAAS and renal fluid retention. Vasodilatory edema is most commonly encountered with direct arteriolar dilators such as minoxidil or hydralazine, but also with dihydropyridine calcium antagonists and alpha-blockers. The addition of an ACE inhibitor or an ARB to a dihydropyridine calcium antagonist reduced vasodilatory edema, whereas the addition of a diuretic had little effect [42].

6.3. Obstructive Sleep Apnea (OSA). OSA causes intermittent hypoxemia and increased upper airway resistance that can increase sympathetic nervous system activity, [43] raise blood pressure and increase fluid retention. OSA has been associated with increased reactive oxygen species with concomitant reduction in nitric oxide bioavailability and with an increase in serum aldosterone [44]. A recent open-label study provided preliminary evidence that treatment with a mineralocorticoid receptor antagonist substantially reduced the severity of OSA [45]. Importantly this treatment also reduced the BP of these patients.

6.4. Endothelin Type A (ET-A) Receptor Antagonists. Circulating endothelin-1 is elevated in patients with essential hypertension [46]. The selective ET-A antagonist darusentan reduced mean office blood pressure (systolic/diastolic) by 18/10 mm Hg [47]. Adverse events of fluid retention and edema occurred in 14% of patients in the placebo group, 25% in the 50-mg group, 32% in the 100-mg group, and 25% in the 300-mg group. The mechanism of fluid retention is unclear, but may involve renal sodium retention. In a recent trial [48], darusentan decreased clinic systolic BP at 14 weeks by 15 mm hg ± 14 mm Hg as compared to guanfacine (12 ± 13 mm Hg; $P < .05$). However, analysis of ambulatory blood pressure concluded that darusentan reduced mean 24-hour systolic BP (9 ± 12 mm Hg) more than placebo (2 ± 12 mm Hg) or guanfacine (4 ± 12 mm Hg). Unfortunately, the study was considered to be negative because it did not meet the prespecified goal of reducing office blood pressure, although the drug did have a clear-cut effect in reducing ambulatory blood pressure, whether compared to placebo or to active control.

7. Excessive Salt Intake

Excessive dietary salt intake contributes to the development of resistant hypertension both by increasing blood pressure and by blunting the blood pressure lowering effects of most classes of antihypertensive agents, [49] including diuretics. These effects are more pronounced in some subjects who are termed salt-sensitive. Salt sensitivity is more common in the elderly, African Americans and in patients with CKD. Among patients referred to a university hypertension center for resistant hypertension, the average dietary salt ingestion based on 24-hour urinary sodium excretion exceeded 10 g or (230 mmol of sodium) a day [50].

Sodium intake should be assessed from sodium excretion in a 24-hour urine collection. Urine sodium: creatinine ratio is inaccurate since sodium excretion varies during the day. Dietary sodium reduction to less than 3 g/day is associated with modest BP reductions, which are larger in African-American and elderly patients. Current guidelines suggest that dietary sodium for a hypertensive patient should be less than 100 mmol/day (2.4 g sodium or 6 g sodium chloride) [51]. This guideline is applicable to all patients with resistant hypertension. Pimenta et al. [52] randomized twelve subjects with resistant hypertension to low versus high sodium diet (50 versus 250 mmol daily for 7 days). The low compared to the high salt diet decreased office systolic and diastolic blood pressure by 22.7 and 9.1 mm Hg, respectively. Further reductions in dietary salt can produce further antihypertensive effects, but are not usually practicable.

8. Ineffective Diuretic Usage

The correct use of diuretics is a critical step in the management of resistant hypertension. Diuretics not only reduce ECF volume but also potentiate the effects of ACE inhibitors, ARBs, and other antihypertensive agents. Based on the results of the ALLHAT trial, JNC 7 recommended thiazide diuretics as preferred agents in the general population with essential hypertension to lower blood pressure and reduce CVD risk [51].

There are three major classes of diuretics: thiazides, loop diuretics, and potassium-sparing agents. The choice of diuretic agents depends on the level of GFR, electrolyte status and the degree of ECV expansion [53].

Thiazide diuretics inhibit the apical Na^+-Cl^- cotransport system in the first part of the distal tubule. Thiazides given once daily are recommended in patients with GFR ≥ 30 mL/min/1.73 m^2. Chlorthalidone was used in a dose range of 12.5 to 25 mg/d in the ALLHAT trial. It is longer-acting than hydrochlorothiazide (HCTZ), resulting in better blood pressure control, but also a higher incidence of hypokalemia. A small study of patients with resistant hypertension demonstrated that switching from the same dose of hydrochlorothiazide to chlorthalidone resulted in an additional 8 mm Hg drop in systolic BP and increased the number of subjects at goal [54]. Chlorthalidone in a daily dose of 25 mg provided greater ambulatory BP reduction, with the larger difference occurring overnight compared with hydrochlorothiazide 50 mg [55].

Thiazides become more effective in subjects accommodated to loop diuretics likely because of functional and structural hypertrophy of the early distal tubule. Thus, this segment becomes of great importance for sodium reabsorption and thiazide drugs acting at this site therefore have increased natriuretic efficacy [56]. However, any increase in

sodium chloride (NaCl) delivery to the collecting duct can increase distal sodium retention via the epithelia sodium channel (ENaC) which enhances the luminal electronegative potential and therefore enhances potassium (K^+) secretion. This can be countered by use of a distal, potassium-sparing diuretic or a mineralocorticosteroid antagonist.

Metolazone and thiazide diuretics retain some effectiveness at GFR levels below 30 mL/min/1.73 m^2. Metolazone is used primarily for resistant edema in patients receiving loop diuretics.

If blood pressure control worsens, or if volume expansion occurs as CKD progresses during treatment with a thiazide diuretic, a loop diuretic should be substituted [57]. Furosemide or bumetanide should be given twice daily, as they have short durations of actions of 3 to 6 hours, although these are increased in patients with renal impairment [58]. Torsemide is longer acting and is eliminated by hepatic metabolism. Therefore, it does not accumulate in renal insufficiency. It may be preferable with patients with CKD. The natriuretic effects of loop diuretics are offset by post-diuretic sodium retention [59]. Patients with advanced CKD (GFR <30 mL/min) who are unresponsive to thiazide alone have a marked natriuresis when a loop diuretic is added, [60] probably by blockade of enhanced distal tubular Na^+ reabsorption. However, such combination therapy should be initiated under close surveillance because of a high incidence of hypokalemia, excessive ECV depletion, and azotemia [61].

There are two principal classes of potassium-sparing diuretics, those that inhibit epithelial sodium channels (triamterene and amiloride) and those that inhibit mineralocorticoid receptors (aldosterone and eplerenone). For both types, the site of action is in the collecting tubule.

The role of spironolactone in resistant hypertension [62] was discussed earlier. Addition of spironolactone to therapy with other diuretics should always be considered in patients with drug-resistant hypertension providing that there is no hyperkalemia. Serum potassium must be monitored regularly during drug therapy. If adverse effects such as gynecomastia or breast tenderness develop, eplerenone should be substituted as it lacks progesterogenic and antiandrogenic effects. A combination of HCTZ/Triamterene or HCTZ/Amiloride is very effective [63], produces less hypokalemia than HCTZ alone and should be considered in patients with a GFR of >30 mL/min/1.73 m^2. Hood et al. [64], crossed over 51 patients with primary hyperaldosteronism between normal and high-dose therapy with bendroflumethazide, amiloride or spironolactone. Remarkably, when used at high-dose, the drugs were equally effective in reducing the blood pressure.

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