# Chapter 3
# Resistant Hypertension in Patients with Chronic Kidney Disease

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## Introduction

The incidence of chronic kidney disease (CKD) is steadily increasing worldwide due to multiple factors including diabetes, hypertension, and other chronic diseases. The management of CKD to prevent end-stage renal disease (ESRD) requires aggressive control of predisposing risk factors. The main principle in the management of CKD is to stabilize the renal function and avoid ESRD. CKD is an important cause of morbidity, disability, and mortality.

Systemic hypertension is a major global public health problem contributing to premature cardiovascular disease (CVD), cerebrovascular disease (CeVD), and CKD. The prevalence of hypertension is rising globally, in part due to the newer lower thresholds to define "hypertension." A majority of patients with CKD, particularly those with a glomerular filtration rate (GFR) < 60 ml/min (CKD stages 3–5) have significant hypertension. Blood pressure (BP) is poorly controlled in patients with CKD; only 10 % achieve the BP level < 130/85 mmHg [1]. Hypertension in patients with CKD/ESRD greatly increases the risk of CVD which accounts for more than half of mortality in patients with CKD. In fact, patients with CKD are a high-risk group for premature and extensive CVD in the community. A majority of patients succumb to CVD. CKD promotes and *accentuates* the full spectrum

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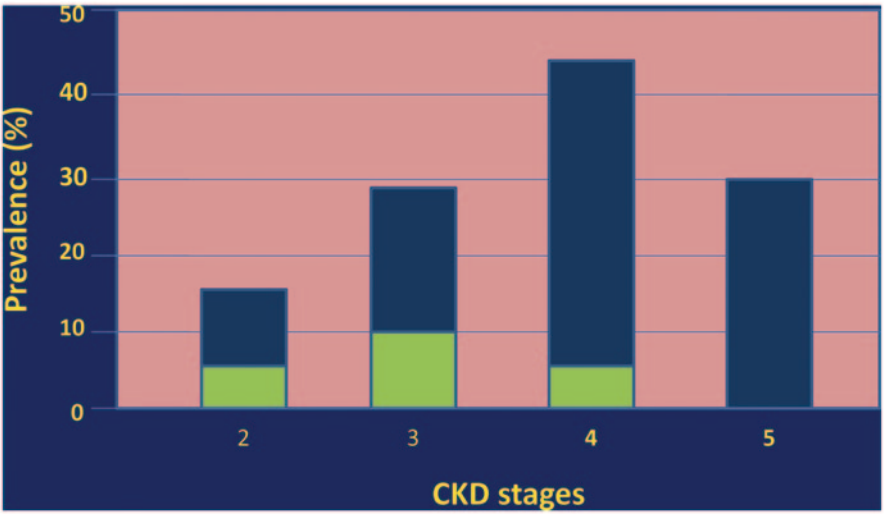


**Fig. 3.1** True resistant hypertension (*blue bar*) and pseudoresistant hypertension (*green bar*) in CKD. (Adapted from Nicola et al. [31]. With permission from Elsevier)

of CVD. Hypertension and diabetes are contributing factors for a vast majority of patients with CKD/ESRD.

Hypertension and CKD are linked to each other via common pathophysiological pathways and similar susceptibilities. An overwhelming majority of patients with CKD/ESRD have chronic and often significant hypertension. Both hypertension and CKD contribute to significant CVD. As stated elsewhere, uncontrolled hypertension leads to CKD and vice versa; thus, as comorbidities, they are inseparable.

Resistant hypertension (RH) is very common and problematic in patients with CKD. RH is defined as office BP level >140/90 mmHg for general population and >130/80 mmHg for those patients with CKD [2, 3] despite the use of three antihypertensive drugs including a diuretic or the requirement of four antihypertensive drugs to achieve the target BP level. One has to assess patient adherence and proper optimal dosing of antihypertensive drugs before to make a distinction between true RH and uncontrolled hypertension or pseudo RH (Fig. 3.1). In the context of RH, CKD is an important etiological factor. The prevalence of CKD worldwide is increasing; 10% of the adult global population has CKD [4].

Observational studies have documented a high prevalence of RH in patients with CKD [5–8]. Despite the use of multiple antihypertensive drugs, hypertension remains above goal in patients with diabetic and nondiabetic CKD [9, 10].

## *Etiological Factors for RH in Patients with CKD*

The pathogenetic mechanisms for RH in patients with CKD and ESRD are complex and multifactorial, with an interdigitating basis. The classical explanation

**Table 3.1** Resistant hypertension: factors

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|---|
| Noncompliance to therapy |
| Excessive salt intake |
| Increasing body weight |
| White coat hypertension |
| Drug–drug interactions |
| Excessive alcohol use |
| Drugs which cause hypertension—steroids, nasaids, erythropoietin, cyclosporine, certain herbal preparations, etc. |

for RH in CKD is an adverse interplay between intravascular volume and the renin–angiotensin–aldosterone system (RAAS). Hence, the traditional therapy for hypertension in CKD patients has been based on reducing the volume and or using RAAS blockade. However, it has become evident that despite volume control and adequate RAAS blockade, BP remains out of control in most patients with CKD. Thus, additional etiopathogenetic factors may be operative in sustaining elevating BP levels in patients with CKD. Among these alternate pathways of persistent RH in CKD are—inappropriate activation of sympathetic nervous system (SNS), enhanced production of endothelin (a potent vasoconstrictor), decreased availability of nitric oxide (NO), blunted endothelial function, obstructive sleep apnea (OSA), and structural changes in the arterial tree. Furthermore, therapies for underlying renal disease—such as steroids, cyclosporine, calcium/vitamin D, erythropoietin, and nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the BP in patients with CKD (Table 3.1).

Obesity and metabolic syndrome may also participate in the pathogenesis of hypertension in CKD.

An important pathophysiological observation in patients with CKD is excess sodium and water retention (due to ↓GFR). The consequent expansion of extracellular volume (ECV) makes the BP control difficult and is the cause of resistance to antihypertensive drugs even at high doses. ECV expansion is inversely related to GFR, thus creating an unfavorable connective loop. Even in the absence of visible edema, ECV expansion is a potent factor in the development of RH. Salt sensitivity and volume retention are twin interactive features of sustained hypertension in patients with CKD [11, 12]. The presence of nocturnal hypertension (nondipping status) is also indicative of ECV expansion in patients with CKD.

It is well known that inappropriate activation of RAAS despite volume excess contributes to sustained hypertension in patients with CKD. From a physiological point, ECV expansion should inhibit the activity of RAAS. However, in patients with CKD such an inverse relationship between volume and RAAS is lost. Any level of RAAS in the face of volume expansion therefore raises the BP level. On this basis, RAAS blockers are widely used as antihypertensive strategy in patients with CKD. BP response to RAAS blockade is indirectly reflective of the role played by RAAS in the pathogenesis of hypertension in patients with CKD.

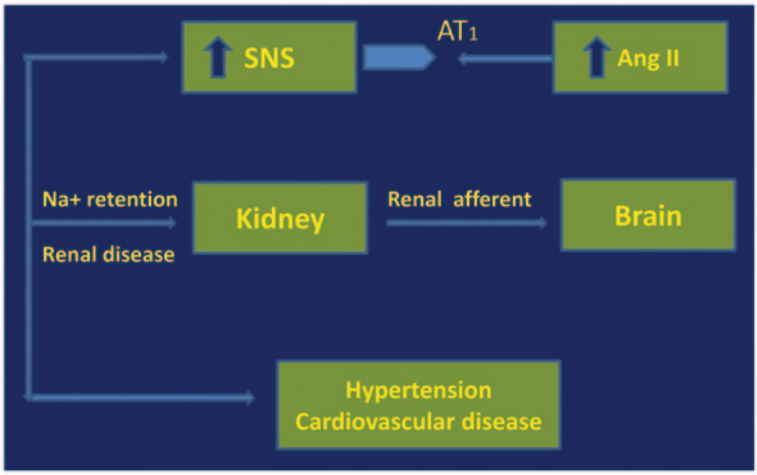


**Fig. 3.2** Neurogenic factors in renal hypertension

## *Increased SNS Activity*

Augmented activity of SNS has been demonstrated in CKD. Kidney is a sensor of systemic circulation and is endowed with intrinsic SNS functional activity—both efferent and afferent nerves. The kidney is not only a target of SNS but also a dynamic reservoir of SNS functions. Activation of chemoreceptors in the kidney (by ischemic or uremic toxins) precipitates nerve traffic to and from the central nervous system. Chronic stimulation of the renal (afferent) nerves leads to SNS activation with resultant hypertension (Fig. 3.2). The synthesis and turnover rate of norepinephrine from the hypothalamic region are enhanced in experimentally induced renal dysfunction [13]. Muscle sympathetic nerve activity (MSNA) is excessive in patients with CKD compared to normal. It is possible that excessive SNS activity in CKD may also be mediated to some extent by the RAAS. Reduced baroreceptor function and increased levels of leptin also contribute to SNS activation in CKD.

## *Endothelin, CKD, and Hypertension*

Endothelin-1(ET-1) a peptide derived from endothelial cells is a powerful vasoconstrictor. ET-1 exerts a number of biological effects including vasomotor tone, cell growth, (renal) sodium, and water retention. Thus, excessive activity of ET-1 impacts systemic vascular resistance (SVR) and the BP level. Studies have demonstrated that the ET system is important in the pathophysiology of CKD-associated hypertension [14–16]. A number of intrarenal mechanisms (cytokines, protein load,

nephron loss, decreased GFR) may stimulate ET-1 production which can cause hypertension and further progression of CKD. ET-1 levels correlate with the level of renal function and proteinuria in diabetic nephropathy [17]. It is possible that the deleterious consequences of ET-1 may also be mediated via SNS and RAAS in the pathogenesis of advancing hypertension associated with CKD.

## *Obstructive Sleep Apnea*

OSA is independently linked to hypertension and related CVD [18–21]. A number of pathways in OSA principally mediated by hypoxia cause vasoconstriction and hypertension. It has been reported that OSA is more prevalent in patients with CKD compared to the controls [22–25]. OSA has been correlated with GFR and proteinuria in patients with CKD but whether OSA is an independent risk factor for CKD is not established.

## *Circadian Variability of BP*

It has been suggested that in patients with CKD, normal circadian variability of BP is lost. Normally, BP levels are highest in the early morning gradually decreasing during the course of the day and reach a low level during sleep ("dippers"). The so-called nondippers do not display such BP variability and their nocturnal BP does not drop. In patients with CKD and ESRD, the prevalence of "nondippers" status is high [26–29]. The occurrence of nondipping and therefore nocturnal hypertension in patients with CKD is a factor in the genesis of RH in patients with worsening renal function. Nocturnal hypertension is associated with significant target organ damage (TOD) and excessive cardiovascular events in patients with CKD.

## *Oxidative Stress*

Oxidative stress, a state of imbalance between production and breakdown of reactive oxygen species (ROS), is a marker of vascular function. A high production of ROS causes vascular dysfunction. Excessive production of ROS causes intense vasoconstriction and hypertension. Thus, ROS can cause severe hypertension directly or by depleting nitric oxide (NO). Oxidative stress has been proposed as a possible link between CKD and severe hypertension [30]. Renal damage is associated with oxidative stress even in the early stages of CKD. The oxidative stress not only causes vigorous vasoconstriction but also accelerates kidney injury. Oxidative stress, a potent factor in the development of CVD also plays a role in the occurrence of vascular disease and pathogenesis of hypertension in patients with CKD.

## *RH in Patients with CKD: Significance and Prognosis*

Hypertension in patients with CKD often requires utilization of multiple antihypertensive drugs in maximum doses. A substantial number of patients, however, remain "resistant" to optimal combination of potent antihypertensive drugs. Typically, RH is defined as BP that remains above therapeutic goals despite the concurrent use of three antihypertensive drugs or requirement of four or more classes of drugs to achieve the goal BP level. The so-called treatment RH is common and severe in patients with CKD. Treatment RH in patients with CKD predisposes to adverse cardiovascular outcomes and premature death.

RH in patients with CKD is associated with lower estimated GFR (eGFR) and proteinuria. In addition to aggressive therapy for hypertension, it is important to identify the factors for the decline of renal function in patients with CKD. Close follow-up is recommended based upon the level of BP, GFR, and serum potassium. RH in CKD is often volume-dependent; hence, effective diuretic treatment is of critical value. Selected causes of RH include:

- Excessive sodium intake
- Fluid retention
- Inadequate diuretic dosage
- Erroneous choice of a diuretic
- Inappropriate combination of antihypertensive drugs
- Drug–drug interactions
- Drugs-induced BP elevation
- Obesity
- Sleep apnea
- Insulin resistance

After excluding aggravating/causative factors, intense BP monitoring and aggressive therapy should be implemented. Volume control is of major benefit in patients with CKD who have RH. With the understanding that RH is a risk factor for rapid decline in renal and cardiovascular functions, BP control is of immense importance. Persistent hypertension in patients with CKD is due to an interplay of etiological factors such as volume overload, increased activity of the RAAS and of SNS. ECV expansion in patients with CKD is directly related to the degree of renal failure; thus, tight control of volume is advocated along with blockade of the RAAS and SNS to improve the BP levels in patients with CKD. Renal denervation (RDN) therapy may be indicated for some patients with CKD who have persistent, severe, complicated, or RH.

RH increases the morbidity and mortality in patients with CKD. Uncontrolled hypertension causes further renal damage, which in turn causes rapid deterioration in BP control. It is a vicious cycle. While the office and clinic BP measurements are routinely used to classify and treat hypertension in patients with CKD, ambulatory BP monitoring (ABPM) is the best method to identify true RH in clinical practice. Various cardiorenal events in patients with RH can be correlated to the BP status as

determined by ABPM [31, 32]. Greater application of ABPM in patients with CKD will likely identify those patients who need most rigorous antihypertensive therapy.

It should be clearly understood that RH in patients with CKD predisposes to serious adverse cardiorenal outcomes [33, 34]. RH is a powerful harbinger of adverse prognosis in patients with CKD [35, 36]. RH increases the risk of renal death. RH in contrast to treatable hypertension predicts CVD in patients with CKD; on the other hand, patients with pseudoresistance have favorable prognosis. One can surmise then that persistence of hypertension despite optimal antihypertensive treatment identifies individuals with severe and advancing vascular disease and "fixed" structural vascular abnormalities. Conditions associated with RH in patients with CKD include—left ventricular hypertrophy, diabetes, proteinuria, and high salt intake. Not surprisingly, these concomitant disorders are also accompanied by increased pulse wave velocity, endothelial dysfunction, and arterial stiffness. While a low GFR is a recognized risk factor for premature mortality in patients with CKD, proteinuria is a better marker of CVD.

## *Principles of Treating RH in Patients with CKD*

The complex pathophysiological mechanisms of RH in patients with CKD dictate application of multiple therapeutic strategies to control hypertension in this high-risk population. In addition to hypertension, there are other factors which contribute to the progression of CKD to ESRD; these include (but are not limited to) hyperlipidemia, obesity, diabetes, tobacco use, and OSA. Hence, all of these predisposing factors should also be addressed in the management of patients with CKD. One of the cornerstones of BP reduction in patients with CKD is restriction of sodium intake to prevent ECV expansion. Patients with CKD are particularly prone to the negative consequences of high salt intake. Excessive salt intake may also trigger other markers of CKD such as oxidative stress, endothelial damage, proteinuria, and vascular inflammation. There is evidence to suggest that salt restriction is beneficial to treat RH in patients with CKD. Unless there are contraindications, salt restriction is recommended as an initial measure to manage RH. Most guidelines recommend an upper limit of 100 mmol of sodium per day (=2300 mg or 6 g sodium chloride). Dietary education and counseling are critical measures to ensure that the CKD patients understand and comply with salt restriction.

The definition of RH includes optimal use of a diuretic. However, in patients with CKD, the selection and dosage of a diuretic are important to control the volume status. The choice of a diuretic and its dosage are dictated by the level of kidney function and stage of CKD. Patients with mild renal dysfunction (GFR > 40 ml/min) may respond to thiazide diuretics. With advancing CKD, loop diuretics with proper dosing and titration are recommended [37]. The dosage of loop diuretics has to be adjusted to correct sodium retention and to obtain desired weight reduction. Adequate use of loop diuretics is strongly recommended to treat RH in CKD patients unless there are contraindications. The uncommon phenomenon of "diuretic

resistance" can be overcome by judicious addition of drugs like metolazone, which permit additional inhibition of sodium reabsorption in the distal tubule. Studies have also shown that aldosterone antagonists such as spironolactone may be a useful addition to treat RH in CKD patients [38]. Despite the efficacy of aldosterone antagonists in RH in CKD patients, these drugs should be used with great caution and under close surveillance due to the risk of hyperkalemia.

## *RAAS Blockers*

RAAS blockers like angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are frequently indicated to treat RH in CKD patients. As a rule, RAAS blockers are used in combination with other classes of antihypertensive drugs to treat hypertension in general, and in CKD patients in particular. Despite their pharmacological benefits and protection against TOD, RAAS blockers have not been shown to reduce all-cause mortality in patients with CKD. ACEIs have been shown to exert significant anti-proteinuric and antihypertensive effects in patients with CKD [39]. ACEIs lower the intraglomerular pressure by dilating the efferent arterioles. The reduction in intraglomerular pressure protects the kidney. ARBs like ACEIs exert beneficial antihypertensive, anti-proteinuric, and renal protective properties. ARBs are well tolerated and effective in managing hypertension in patients with CKD. The combination of ACEIs and ARBs has not been shown to offer any advantages in treating hypertension; the combination may show additive effects on proteinuria reduction but no additional outcome benefits. Dual RAAS blockade is not helpful for BP control or target organ protection. Trials with direct renin inhibitors have not yielded any advantages or favorable outcomes and thus are not recommended routinely. The use of RAAS blockers to treat RH in CKD patients while necessary requires close vigilance of renal function and potassium level. Despite the advocacy of RAAS blockade in controlling hypertension, these drugs should be used with considerable caution in patients with worsening renal function (e.g., serum creatinine > 2.5 mg/dl and K+ level > 5.5 meq/l).

## *Calcium Channel Blockers*

Although calcium channel blockers (CCBs) are not preferred for initial therapy in patients with CKD, they are often required to treat RH. Dihydropyridine (DHP) CCBs are effective antihypertensive drugs and should be utilized as a component of combination therapy to control hypertension. All DHP CCBs are equally effective and can be conveniently added to antihypertensive regimen for CKD patients with RH. While there is some concern that DHP CCBs may have an adverse effect on proteinuria in patients with diabetes, such a consideration is irrelevant to reach the target BP goal in patients with RH. Moreover, this potential adverse effect is less likely when DHP CCBs are given on the background of RAAS blockade. Cilinidip-

ine, a new generation DHP CCB with a dual mode of action, may have special renoprotective properties [40]; this novel CCB may have a place in patients with CKD. In patients with CKD, DHP CCBs are generally prescribed as second- or third-line agents in the titration of antihypertensive drugs to achieve desired BP reduction.

### *α- and β-Blockers and Central Agonists*

While of no specific advantage for patients with CKD, α- and β-blockers can be used as add-on drugs for hypertension control based on the clinical circumstances and patient profile. β-blockers in particular may be indicated for cardiovascular protection in CKD patients. Central agonists like clonidine are considered as add-on drugs for BP control in CKD patients with RH. Adrenergic blockers and central agonists are not contraindicated in CKD. Since there is an aggravation of SNS in patients with CKD, β-blockers can be a rational component of antihypertensive drug regimen in this population. In this context, vasodilating β-blockers (like nebivolol and carvedilol) may be most suitable due to their pharmacological advantages.

### *Direct Vasodilators*

Direct vasodilating drugs like hydralazine and minoxidil are potent antihypertensive drugs of importance to control RH in CKD patients. Both hydralazine and minoxidil are effective drugs and should be dosed properly. Due to reflex tachycardia, SNS activation, and fluid retention, direct vasodilators must only be prescribed in conjunction with a β-blocker and a diuretic. In other words, the usage of direct vasodilators is always in conjunction with sufficient dosage of a diuretic and a β-blocker. Both hydralazine and minoxidil are powerful vasodilators which have an important therapeutic role in the treatment of RH. And, one should not hesitate to apply these drugs (along with a diuretic and a β-blocker) to achieve BP targets in patients with CKD.

## Summary

RH is common in CKD due to multiple factors—low GFR, sodium retention, inappropriate activity of RAAS and SNS. The cardiovascular and hemodynamic milieu in CKD is complex, governed by multiple hormonal and circulatory aberrations. Thus, RH in CKD is a highly complicated phenomenon with serious prognostic implications. Patients with CKD are at a risk of developing various cardiovascular complications. Hence, RH in CKD qualifies as a high-risk signal. Persistent hypertension in CKD causes inexorable progression of vascular disease leading to excessive mortality, morbidity, and permanent disability.

From a public health perspective, it is imperative to control hypertension aggressively in patients with CKD. Uncontrolled hypertension in CKD is a forerunner of dangerous cardiorenal sequelae. RH in CKD should be managed aggressively. To characterize the level of hypertension and to classify hypertension properly in patients with CKD, ABPM and home BP monitoring should be considered. These diagnostic tools define the hypertension load accurately in patients with CKD. Whenever possible, these modalities should be utilized in the evaluation and management of RH in patients with CKD.

While RH has serious implications, it is not clear to what extent cardiorenal complications can be substantially modified by successful BP control. A concerted effort should be made to advocate salt restriction, nonpharmacological therapy, and careful combination and titration of antihypertensive drugs. There is no evidence to recommend any one particular class of drugs over others to treat RH in patients with CKD. However, implementation of a low-salt diet and adequate use of a diuretic should be the foundation of sequential antihypertensive drugs. A wide variety of antihypertensive drugs are available to treat RH in CKD patients. The precise role of RDN therapy as a modality to control hypertension in CKD patients remains to be determined by ongoing clinical trials and global registries. Due to the high prevalence of RH in patients with CKD and the casual contribution of SNS, RDN therapy is of considerable interest and possible benefit [41].

RH, CKD, and CVD are intrinsically connected through a cascade of a pathophysiological interactions; aggressive control of BP is a rational avenue to interrupt this dangerous link. The principal target of antihypertensive therapy in RH is a BP goal of < 135/85 mmHg. If this target is achieved with a reduction in proteinuria, additional benefits may be conferred. Careful monitoring of BP, renal function, proteinuria, and serum potassium level should all be integrated to provide optimal care to patients with RH and CKD. Recent studies have suggested that excessive reduction of BP (diastolic BP (DBP) < 70 mmHg) in patients with CKD may be harmful [42]. Much research is needed to identify genetic and other markers which predispose to progression of hypertension, nephrosclerosis, and diabetic nephropathy in patients with CKD. Further understanding of mechanisms of RH [43] will likely yield effective strategies to halt the progression of CVD in patients with CKD.

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