Pathophysiology of Resistant Hypertension in Chronic Kidney Disease

Vito M. Campese, MD

Summary: Hypertension associated with chronic kidney diseases often is resistant to drug treatment. This review deals with two main aspects of the management of CKD patients with hypertension: the role of sodium/volume and the need for dietary salt restriction, as well as appropriate use of diuretics and what currently is called *sequential nephron blockade*; the second aspect that is addressed extensively in this review is the role of the sympathetic nervous system and the possible clinical use of renal denervation.
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The pathophysiology of hypertension associated with chronic kidney disease (CKD) is complex and multifactorial and often is resistant to drug treatment.

The traditional paradigm is that hypertension in CKD is caused either by an excess of intravascular volume (volume dependent) or by excessive activation of the renin-angiotensin system in relation to the state of sodium/volume balance (renin-dependent hypertension). In recent years, alternative pathogenic mechanisms have unraveled (Table 1). Among these are increased activity of the sympathetic nervous system (SNS), increased endothelin (ET) production, decreased availability of endothelium-derived vasodilators/endothelial dysfunction, structural changes of the arteries, renal ischemia, and sleep apnea. In addition, pharmacologic interventions aimed at treating the primary renal disease or some of its consequences, such as the use of cyclosporine, steroids, sympathomimetic agents, erythropoietin, vascular endothelial growth factor antagonists, and nonsteroidal anti-inflammatory agents, may contribute to sustaining or aggravating hypertension in CKD patients.

ROLE OF SODIUM AND VOLUME

Excessive dietary sodium ingestion and volume expansion contribute importantly to hypertension in CKD and to resistance to antihypertensive treatment. In a randomized cross-over evaluation of low-sodium (50 mmol/24 h × 7 d) and high-sodium diets (250 mmol/24 h × 7 d) separated by a 2-week washout period, Pimenta et al[1] examined the effects of dietary salt restriction on office and 24-hour ambulatory blood pressure in 12 subjects with resistant hypertension on an average of 3.4 ± 0.5 antihypertensive medications and a mean office blood pressure (BP) of 145.8 ± 10.8/83.9 ± 11.2 mm Hg. The mean urinary sodium excretion was 46.1 ± 26.8 versus 252.2 ± 64.6 mmol/24 h during low-salt versus high-salt intake. A low-salt compared with a high-salt diet decreased office systolic and diastolic blood pressure by 22.7 and 9.1 mm Hg, respectively. A substantial reduction in dietary salt intake should be part of the treatment of patients with resistant hypertension, particularly those with CKD. This also explains the need to include a diuretic in the regimen of patients before labeling them as having resistant hypertension. The diuretic commonly used in the management of hypertension is hydrochlorothiazide. Chlorthalidone significantly has reduced stroke and cardiovascular end points in several landmark trials; however, hydrochlorothiazide remains favored in practice with the assumption that these drugs are interchangeable. Ernst et al[2] conducted a randomized, single-blind, 8-week active treatment, cross-over study comparing 12.5 mg/d chlorthalidone (force-titrated to 25 mg/d) and 25 mg/d hydrochlorothiazide (force-titrated to 50 mg/d) in untreated hypertensive patients. The main outcome, 24-hour ambulatory BP monitoring, was assessed at baseline and at week 8, along with standard office BP readings every 2 weeks. Thirty patients completed the first active treatment period, and 24 patients completed both treatment periods. Week 8 ambulatory BPs indicated a greater reduction from baseline in systolic BP with 25 mg/d chlorthalidone compared with 50 mg/d hydrochlorothiazide (24-hour mean, −12.4 ± 1.8 versus −7.4 ± 1.7 mm Hg; $P = .054$; nighttime mean, −13.5 ± 1.9 versus −6.4 ± 1.8 mm Hg; $P = .009$). These differences were not apparent with office BP measurements. This study indicates that within recommended doses, chlorthalidone is more effective in decreasing systolic BP than hydrochlorothiazide and it should be the diuretic of choice in patients with hypertension.

Division of Nephrology, Keck School of Medicine, University of Southern California, Los Angeles, CA.

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Address reprint requests to Vito M. Campese, MD, Physiology and Biophysics, Division of Nephrology and Hypertension Center, Keck School of Medicine at University of Southern California, 2020 Zonal Ave, Los Angeles, CA 90033. E-mail: campese@usc.edu

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Table 1. Factors Implicated in the Pathogenesis of Hypertension in Chronic Kidney Disease

Sodium and volume excess
The renin-angiotensin-aldosterone system
The sympathetic nervous system
Endothelium-derived vasodepressor substances
Endothelium-derived vasoconstrictor substances
Divalent ions and parathyroid hormone
Natriuretic peptides
Structural changes of the arteries
Renovascular disease
Pre-existent essential hypertension
Medications
Cyclosporine, steroids, sympathomimetic agents, erythropoietin, vascular endothelial growth factor antagonists, and nonsteroidal anti-inflammatory agents
Miscellaneous
Anemia/hypoxia, vasopressin, serotonin, thyroid dysfunction, calcitonin gene-related peptide

In patients with an estimated glomerular filtration rate less than 30 mL/min, thiazide diuretics are unlikely to be effective if given alone, but they can potentiate the efficacy of loop diuretics.

In patients with resistant hypertension, diuretic therapy may need to be intensified to achieve its full effectiveness. Bobrie et al[3] introduced the concept of "sequential nephron blockade." They performed a prospective, randomized, open, blinded, end point study in 167 patients with hypertension resistant to treatment with 300 mg/d irbesartan, 12.5 mg/d hydrochlorothiazide, and 5 mg/d amlodipine. These patients were randomized to sequential nephron blockade (consisting of sequential administration of 25 mg/d spironolactone, followed by 20 and then 40 mg/d furosemide, and 5 mg/d amiloride) or sequential renin-angiotensin system blockade (consisting of 5 mg/d ramipril followed by 10 mg/d ramipril, 5 mg/d bisoprolol, and 10 mg/d bisoprolol). At week 12, the mean between-group difference in daytime ambulatory blood pressure was 10/4 mm Hg in favor of sequential nephron blockade. The investigators concluded that in patients with resistant hypertension, sequential nephron blockade induced a large and well-tolerated reduction in blood pressure via a progressive increase in sodium depletion, and was more effective than sequential renin-angiotensin system blockade. In patients with CKD the addition of potassium-sparing diuretics increases the risk of hyperkalemia and should be implemented with extreme caution.

In the past few years the concept of a nonosmotically active Na^+ reservoir has emerged. Nonosmotically active Na^+ accumulates primarily in the skin and cartilage. In cartilage, the negative charges of glycosaminoglycans may increase the local concentration of Na^+ to 450 mmol/L and they can provide an actively regulated interstitial cation exchange mechanism that participates in volume and blood pressure homeostasis.[4] Whether the osmotically inactive Na^+ storage pool is regulated dynamically still is debated.[5–7] Titze et al[8] speculated that the skin is an osmotically inactive Na^+ reservoir that accumulates Na^+ when dietary salt intake is excessive. Titze et al[9] also observed skin retention of Na^+ in deoxycorticosterone acetate (DOCA)–salt-loaded animals compared with controls and speculated that this might contribute to hypertension. The potential contribution of an inactive Na^+ reservoir to increased peripheral vascular resistance and resistant hypertension remains to be shown.

ROLE OF INCREASED SNS ACTIVITY

Substantial experimental and clinical evidence supports a major role of increased SNS activation in the pathophysiology of hypertension associated with chronic kidney disease.

The kidney is not only an elaborate filtering device but also a richly innervated sensory organ. The kidney can be the target of the SNS activity, but also can be the origin and modulator of this activity. There are two main types of renal sensory receptors and afferent nerves: baroreceptors, which increase their firing in response to changes in renal perfusion, and pressure and renal chemoreceptors, which are stimulated by ischemic metabolites or uremic toxins.[10] These receptors, through renal afferent nerves, may establish connections with integrative nuclei of the SNS in the central nervous system.[11,12] In experimental animals, acute stimulation of these afferent nerves by either ischemic metabolites such as adenosine, or by urea, evokes reflex increases in efferent SNS activity and in BP. Chronic stimulation of these afferent nerves by renal ischemia or other factors also may lead to increased SNS activity and to hypertension. This suggests that ischemic injury to the kidneys, as a result of macrovascular or microvascular disease, may cause hypertension through the activation of these chemosensitive receptors.

In 5/6 nephrectomized rats we observed that the turnover rate[13] and the secretion of norepinephrine[14] from the posterior hypothalamic nuclei (two markers of sympathetic nerve trafficking in the brain) were greater in CKD than in control rats. Bilateral dorsal rhizotomy at the T-10 to L-3 level prevented the increase in BP and activation of the SNS. In our laboratory, we have developed a model of neurogenic hypertension caused by renal injury without measurable alterations in kidney function. In this model, the injection of 50 mL phenol in the lower pole of one kidney causes an immediate and permanent increase of SNS activity and BP in the rat; renal denervation prevents these effects.[14]