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Pathologic Basis and Treatment Considerations in Chronic Kidney Disease–Related Hypertension

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Chronic kidney disease (CKD) is both a cause and an effect of hypertension and is multifactorial in its origin. Beyond volume expansion, CKD-related hypertension is without defining characteristics of any consistency. Consequently, the order in which antihypertensive medications are given to the CKD patient with hypertension is arbitrary, although prescription practice is for the most part mindful of the need for multiple drug classes with at least one of them being a diuretic. It is not without reason that blood pressure goals in the hypertensive CKD patient are set at lower levels than those for patients with essential hypertension, but it remains to be determined how much the blood pressure should be decreased in the CKD patient.
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At the turn of the millennium, the United States Renal Data System reported a prevalence of more than 370,000 people in the United States with end-stage renal disease (ESRD), with nearly 100,000 new patients requiring dialysis in the year 2000 alone. It has been projected that by the year 2010, in excess of 660,000 people will develop ESRD.[1] The number of patients with ESRD is a straightforward statistic. Obtaining an estimate for numbers of patients with chronic kidney disease (CKD) is more challenging. By using data from the Third National Health and Nutrition Examination Survey (NHANES III), it was projected that approximately 11% of the US adult population has CKD; moreover, this number is increasing geometrically in the United States, with a 104% increase in chronic kidney failure between 1990 to 2001.[2]

Hypertension is extremely common among those with CKD. Based on a NHANES III data set of 15,600 patients, approximately 40% of those with a glomerular filtration rate (GFR) of 60 to 90 mL/min/1.73 month[2] had a blood pressure (BP) that exceeded 140/90 mm Hg. As the GFR decreases, the prevalence of hypertension increases significantly; in fact, among the NHANES III participants with a GFR of less than 30 mL/min/1.73 month,[2] approximately 75% were found to be hypertensive (Fig 1).[3]

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Many theories have been advanced to explain the increasing prevalence of hypertension with a decreasing GFR including volume expansion, activation of the sympathetic and/or renin-angiotensin-aldosterone systems (RAAS), hyperparathyroidism, vessel compliance changes with or without calcification, large- or small-vessel renovascular disease, and adverse changes in other endogenous substances such as uric acid, homocysteine, prostaglandins, and/or endothelin.[4,5] In this article, potential causes and select treatment aspects of CKD-related hypertension are discussed. Patients on renal-replacement therapy, by the nature of the process, have additional contributing factors to their hypertension. These are discussed if relevant.

Pathogenesis

Nonhormonal Factors

In most CKD patients there typically are multiple factors contributing to the pathogenesis of their hypertension; despite this, a sensible approach to sorting out the pathogenesis of hypertension in a CKD patient can be arrived at by its classification into volume-dependent and volume-independent categories based on the response to diuresis or ultrafiltration (in the case of ESRD). Volume-dependent hypertension is by far the more common of these 2 categories in patients with CKD and as a rule is characterized by normal to low plasma renin activity, with a decrease in BP in response to either dietary sodium (Na^+) restriction or gradual net volume removal during consecutive dialysis sessions.[6,7] Volume-independent forms of hypertension in patients with CKD are accompanied by a relative, if not an absolute, increase in the

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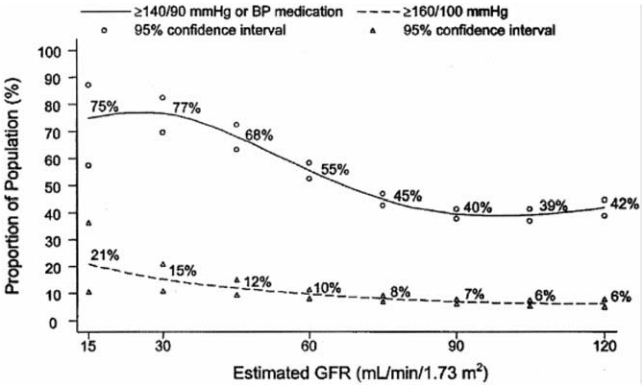

Figure 1 Prevalence of high blood pressure by level of GFR (estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation) from NHANES III. Hypertension was defined as Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) stage 1 (systolic BP 140 mm Hg or diastolic BP 90 mm Hg, or taking medications for hypertension) or JNC stage 2 (systolic BP 160 or diastolic BP 100 mm Hg). Values are adjusted to age 60 years using a polynomial regression. The 95% confidence intervals are shown at selected levels of estimated GFR. Reprinted with permission from the National Kidney Foundation.[3]

activity of the RAAS and a limited BP reduction in response to volume removal and/or dietary Na^+ restriction.

Although it is of some use to divide CKD-related hypertension into these broad categories, there are additional factors that undoubtedly contribute to its pathogenesis. When present, such additional factors always should be thought out in the framework of a patient's prevailing volume status/hemodynamic profile. Because mean arterial pressure is a product of both cardiac output and systemic vascular resistance both factors play a defining role in the pathogenesis of CKD-related hypertension. Early phases of hypertension in CKD generally are marked by an increase in cardiac output and low to normal peripheral resistance values. Progressive renal disease regularly is accompanied by the onset of anemia and/or the creation of an arteriovenous fistula, circumstances that reinforce the high cardiac output state. Changes in cardiac output can be attenuated with correction of anemia,[8] in which case the continued presence of hypertension becomes a function of increased systemic vascular resistance, which has a positive correlation with the increase in exchangeable Na^+ that underscores the progression to ESRD.[9] Finally, the BP response to changes in Na^+/volume status may be influenced by alterations in the activity of and/or response to a variety of neurohumoral pathways.[10]

Hormonal Factors

Although activation of the RAAS (as it relates to an increase in angiotensin II levels) is a frequently cited factor in the pathogenesis of CKD-related hypertension, it is the predominant factor in only a handful of patients; the significance of this system being activated lies more so in its being suppressed improperly in the volume-expanded environment, which distinguishes most CKD patients.[11] Tissue-based production of angiotensin II and endothelin-1 also may be implicated in the hypertension and cardiovascular (CVR) disease patterns of the CKD patient; however, both neurohormones have been studied sparingly in this context.[12,13]

Aldosterone (as both an autocrine and paracrine substance) also is viewed increasingly as a contributor to the pathobiology of CVR and renal disease; however, its exact pathogenic role in the CKD patient with hypertension remains to be determined.[14,15] Of note, aldosterone receptor antagonist (ARA) therapy reduces protein excretion in excess of what might be expected solely with BP reduction. This effect occurs when ARAs are given either as monotherapy or when administered with angiotensin-converting enzyme (ACE) inhibitors.[16,17]

Increased activity of the sympathetic nervous system (SNS) may be involved either directly or indirectly in CKD-related hypertension.[18,19] However, uncomplicated techniques for the measurement of SNS activity are not available; thus, much has been inferred incorrectly from relatively nonspecific indicators of SNS activity, such as the physical findings of BP and pulse rate and/or plasma norepinephrine concentrations. The latter proves particularly difficult to interpret in CKD because normal plasma catecholamine concentrations approximately are doubled in advanced CKD.[20] More accurate measures of SNS activation exist in the ascertainment of sympathetic nerve traffic. In 1 such study, Converse et al[21] found that peroneal nerve sympathetic discharge was 2.5-times higher in hemodialysis patients than in normal patients and could be normalized by bilateral nephrectomy.

These findings suggest that reduced sympathetic nerve discharge may be one mechanism by which bilateral nephrectomy reduces BP in CKD-related hypertension. Moreover, neuropeptide Y, a 36-amino acid vasoactive peptide, is released during sympathetic stimulation as occurs with volume overload,[22] and in ESRD is associated independently with left ventricular hypertrophy and systolic dysfunction.[23] An increase in neuropeptide Y is but one of several pathways by which SNS activation indirectly influences cardiovascular structure and function.

Miscellaneous Factors

A host of other factors have been suggested to be of importance in the pathogenesis of hypertension in this population including nitric oxide deficiency, circulating inhibitors of Na^+-K^+-adenosine triphosphatase, abnormalities in the calcium-phosphate axis, and hyperuricemia.

Nitric oxide deficiency occurs in CKD and has been proposed as one of several factors contributing to hypertension in this population.[24,25] Nitric oxide production by the vascular endothelium is inhibited by asymmetric dimethylarginine (Fig 2). Levels of asymmetric dimethylarginine are 6- to 10-fold higher in hemodialysis patients than in healthy patients. Although levels are reduced by as much as 65% during a standard 5-hour hemodialysis session, any reduction in plasma level is short-lived.[26] In patients whose plasma asymmetric dimethylarginine levels decrease with dialysis, a decrease in the mean 24-hour ambulatory blood pressure has

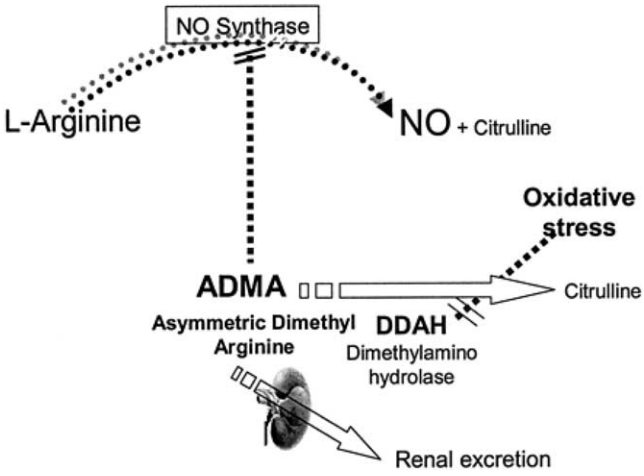

Figure 2 Basic biochemical steps regulating nitric oxide synthesis. Reprinted with permission from Modlinger et al.[24]

been observed.[27] Of note, the exhaled nitric oxide concentration is increased in hemodialysis patients prone to low BP.[28]

Circulating natriuretic substances (including digoxin-like immunoreactive substances) appear to accumulate in patients with CKD and in so doing could bring about a generalized inhibition of Na^+-K^+-adenosine triphosphatase. The ensuing increase in intracellular Na^+ concentration in vascular smooth muscle cells then could diminish the Na^+/Ca^{2+} exchange and thereby increase the intracellular Ca^{2+} concentration with an end result of a persistent state of vasoconstriction.[29] Consistent with these data, both false-positive digoxin levels (relating to digoxin-like immunoreactive substances)[30] and circulating Na^+-K^+-adenosine triphosphatase inhibitors have been identified in hemodialysis patients and are correlated with interdialytic weight gain in ESRD patients.[31] Defects in Ca^{2+} metabolism are ubiquitous in dialysis patients and typically are manifest by secondary hyperparathyroidism, which may increase BP via Ca^{2+} entry into vessel-wall smooth muscle cells.[32] Allosteric activators of the Ca^{2+}-sensing receptor, which reduces parathyroid hormone levels in the setting of secondary hyperparathyroidism, have been associated with a reduction in BP.[33]

Although hyperuricemia long has been associated with renal disease, uric acid has not been considered causal but rather an effect of an altered economy for uric acid (as occurs in progressive CKD).[34,35] The observation that hyperuricemia commonly is associated with other risk factors of CVR and renal disease, especially hypertension, has made it difficult to establish a unique effect for uric acid itself. To this end, plausible biologic hypotheses now exist for how hyperuricemia might cause (or contribute to) hypertension. First, uric acid causes renal vasoconstriction, a process mediated by endothelial dysfunction with reduced nitric oxide levels and activation of the RAAS.[36,37] This form of hypertension is salt-resistant and responds to maneuvers that reduce uric acid values.[36] In addition, hyperuricemia brings about progressive renal microvascular disease (a lesion resembling arteriolosclerosis), and with sufficient arteriolar luminal narrowing a component of the hypertension becomes salt-driven and independent of uric acid levels.[38]

Strategies aimed at modifying uric acid levels in some sort of systematic fashion offer an intriguing possibility for intervening in progressive CKD/hypertension that possibly may be independent of more traditional treatment strategies. In general, the effect of antihypertensive therapy on serum uric acid level either is to maintain values at baseline or, at the worst, to increase concentrations. Losartan, an inherently uricosuric compound, is the exception to this.[39]

Sleep Apnea and Renovascular Hypertension

Sleep disturbances are extremely common in both CKD and dialysis patients. Subjective sleep complaints are reported in up to 80% of those surveyed and sleep apnea, restless legs syndrome, and periodic limb movement disorder are much more prevalent than in the general population.[40] The high frequency of sleep apnea (SA) in CKD is explained in part by the fact that the most common comorbid conditions of ESRD, namely atherosclerosis and diabetes, also are associated independently with this syndrome.

Although SA in the general population is mostly of the obstructive type, the obstructive and the central SA types are equally frequent in patients with ESRD. Uremic patients with pre-existent heart failure are likely to present a predominantly central SA pattern. Despite the confounding effect of pre-existent CVR disease, there is little doubt that uremia per se is associated with SA and that this disturbance plays a major role in disrupting sleep in CKD patients.[41]

Long-term sequelae of SA may be caused by direct sympathetic activation secondary to chemoreceptor stimulation by episodic hypoxemia and hypercapnia and stress from chronic disruption of sleep. Intermittent hypoxia causes sympathetic activation that outlasts the triggering stimulus.[42] These factors both indirectly and directly relate to the presence of hypertension in the CKD patient. SA should be considered in the CKD patient with resistant hypertension and no other obvious causes, particularly when there is a readily apparent deposition of fat in the neck (with narrowing of the pharyngeal airway).

Identification and reversing the loss of kidney function beyond occlusive disease of the renal arteries poses a major clinical challenge. Recent studies indicate that atherosclerotic renal artery stenosis develops as a function of increasing age and oftentimes is coupled with other forms of microvascular disease. The risks for renal artery stenosis are related both to decreasing renal function and to accelerated CVR disease, with increased morbidity and mortality. Drugs, including agents that block the RAAS, have improved the level of BP control for renovascular hypertension. Progressive renovascular disease during medical therapy (without RAAS interruption) can produce refractory hypertension, heart failure, and CKD with tubulointerstitial fibrosis. Recent studies have indicated a unique interaction of oxidative stress, endothelial dysfunction, and fibrogenic cytokine activation in the setting

of renal hypoperfusion produced by experimental atherosclerosis.[43]

In clinical settings, antihypertensive therapy is directed at decreasing mean arterial pressures to garner those cardiovascular benefits known to occur with BP reduction. The price of these benefits for patients with renovascular disease may be underperfusion of the poststenotic kidney(s). This can develop during therapy with any antihypertensive agent and can produce a loss of GFR when perfusion pressures decrease to less than the autoregulatory range.[44] The widespread use of ACE inhibitors/angiotensin II receptor blockers and other effective antihypertensive agents partly may be responsible for the increasing ages of patients who are sent for revascularization because detection of their disease may have been delayed by effective RAAS blockade.

Special Considerations for Drug Therapy in the Hypertensive Patient With CKD

Renal clearance is an important contributor to the total body clearance of a number of compounds, which in CVR therapeutics include ACE inhibitors, certain β-blockers, and most diuretics.[45-47] Renally cleared compounds accumulate at GFR values less than 60 mL/min, a process of particular relevance when the GFR decreases to less than 30 mL/min.[45]

Drug accumulation is relevant in a number of ways for antihypertensive compounds. First, if the compound administered has a narrow therapeutic window its accumulation quickly can exceed the boundaries of the desired pharmacologic effect with undesirable consequences. For instance, the accumulation of an antihypertensive compound can result in an exaggerated decrease in BP. If GFR decreases as the result of such a decrease in BP, the renal clearance of a compound can be reduced further, the drug further accumulates, and the BP decreases even more.[48] Second, if an administered compound has well-established concentration-related side effects they will occur more often and with possibly greater severity with drug accumulation. This is the case with renally cleared β-blockers, such as atenolol and nadolol, and the side effect of lethargy and/or sedation. Finally, drug accumulation increases the risk for drug-drug interactions and thereby manufactures a risk from concurrent therapy that otherwise would not be present.

Medication dose adjustment in patients with CKD may entail one of several approaches. To maintain a therapeutic level and, at the same time, avoid drug accumulation and toxicity in a patient with reduced renal function, the clinician must consider either reducing the size of the maintenance dose or extending the interval between doses. In many instances, a combination of both approaches is used. In practice, these changes should match the degree of decrease in renal clearance for a particular compound. Of note, drugs such as ACE inhibitors (mainly renally cleared compounds) are dosed to effect, and although prescribing information suggests dosing adjustments for these drugs in the patient with advancing CKD, it is unusual for such changes to be implemented.

Table 1 Unresolved Issues With Anihypertensive Medications and CKD

Appropriate BP targets (<130 mm Hg) for optimal vascular (coronary artery disease and stroke) outcomes in patients with proteinuric and nonproteinuric kidney disease[54]
Are ACE inhibitors and ARBs needed in progressive renal disease or does BP reduction alone suffice.[55,56]
The role of nocturnal BP control in forestalling the development/progression of proteinuric renal disease[57]
Best doses of ACE inhibitors or ARBs in protrinuric kidney disease and heart failure, and how to assess (independent of BP reduction) that an optimal dose is beign provided
Benefits of combining ACE inhibitors and ARBs in proteinuric kidney disease and heart failure

Abbreviation: ARB, angiotensin II receptor blocker.

Basis for Use of Antihypertensive Medications in CKD

Antihypertensive medications are used in the CKD patient for several reasons. First, BP reduction will slow the rate of progression of CKD. This occurs irrespective of the medication (or medications) classes being used.[3,49,50] Second, certain antihypertensive compounds, such as ACE inhibitors and angiotensin II receptor blockers, significantly reduce protein excretion and in so doing further slow the progression rate of CKD (beyond what is seen with BP reduction).[51,52] Third, antihypertensive compounds, such as ACE inhibitors and angiotensin II receptor blockers, also exhibit strong CVR protective effects, which is an important feature of drug therapy in CKD because these patients typically exhibit a high CVR event rate spanning the entire spectrum of CKD.[3,49,53]

However, despite the strength of the evidence supporting BP and proteinuria reduction in the CKD patient, there remain several unanswered questions (Table 1).

Diuretics in Renal Disease

There is an important interface between the treatment of CKD-related hypertension and the level of extracellular fluid volume (ECV) expansion. It is well known that ECV is expanded in the CKD patient. In these patients, the process of ECV expansion parallels the degree of GFR impairment and corresponds to approximately 5% to 10% of body weight, even in the absence of peripheral edema.[7] Of note, Na^+ retention not only has a major role in the pathogenesis of secondary hypertension in patients with CKD, but it also precludes optimal control of BP during pharmacologic treatment with nondiuretic antihypertensive agents, especially vasodilators. In the presence of persistently poor adherence to salt restriction (urinary sodium excretion $>$ 100 mmol/d) and/or

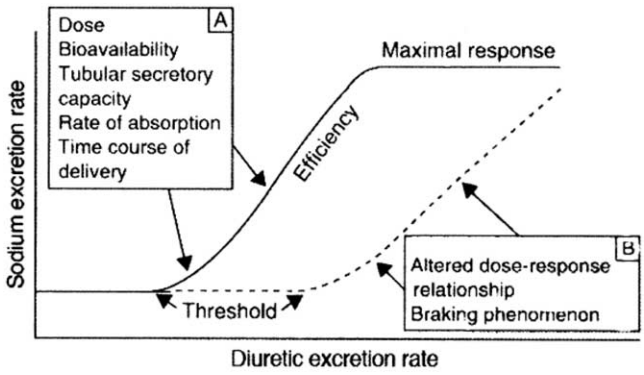

Figure 3 Determinants of diuretic response. Sodium excretion rate as a function of tubular delivery of diuretic. "A" represents pharmacokinetic determinants of the diuretic response for an orally administered diuretic. The solid sigmoidal-shaped dose-response curve has 3 components: threshold (diuretic delivery rate sufficient to first produce a diuresis), efficiency (rate of delivery that produces an optimal response for any amount of diuretic entering the urine), and maximal response (urinary delivery of diuretic above which no additional diuretic response can occur). "B" represents altered pharmacodynamic determinants in diuretic resistance, in which the normal sigmoidal-shaped curve is shifted downward and to the right. The diuretic delivery necessary to achieve a threshold response can vary substantially in diuretic resistance.

marked ECV expansion, natriuretic agents become the cornerstone in the treatment of CKD-related hypertension.[6] Moreover, efficient control of ECV expansion significantly improves the antiproteinuric effects of agents that interrupt the RAAS.[58]

Although thiazide diuretics can be considered for use in stages I to III CKD, a loop diuretic is typically the diuretic of choice in stages IV and V CKD.[59] A thiazide-type diuretic that still is considered for use in stages IV and V CKD is metolazone. In the instance of metolazone it often is given together with a loop diuretic, particularly in diuretic-resistant states. In the process, multiple nephron segments responsible for Na^+ resorption can be blocked and an effective diuresis develops. Metolazone is absorbed very poorly and this should be taken into account when both a dose and frequency of dosing are being determined.[60]

Although a large dose of a thiazide diuretic will initiate a diuresis in patients with mild renal insufficiency, the response in patients with a creatinine clearance (CL_{creat}) of less than about 50 mL/min is more limited. In the setting of CKD, patients are not resistant to a thiazide diuretic per se; rather, the basis for failure of a thiazide diuretic is an insufficient potency to meet the needs of such patients (Fig 3). Patients receiving fixed-dose combination antihypertensive therapy containing a thiazide diuretic should be considered for conversion to a loop diuretic (together with the other component of the fixed-dose combination) when CL_{creat} values decrease to less than 50 mL/min if BP control is inadequate and/or edema is present.[5] Fixed-dose combination antihypertensive therapies with a thiazide diuretic component do not require change in the nonedematous CKD patient with good BP control.

Potassium-sparing diuretics generally are used cautiously in patients with CKD because of the risk for hyperkalemia. The potassium-sparing diuretics spironolactone and eplerenone differ mechanistically from amiloride and triamterene in that they are ARAs. This blockade of aldosterone effect is the basis for their expanding use in hypertension, renal disease, and heart failure.[61] Dosage adjustment for ARAs is not based exclusively on the level of renal function; rather, it is governed in part by the possibility of clinically relevant hyperkalemia.[62] Spironolactone and/or its metabolites have a prolonged potassium-sparing effect, which should be accounted for when it is prescribed. Although not formally studied in CKD, the shorter duration of action of eplerenone may result in less significant changes in serum potassium levels.

Conclusions

There are a multitude of factors potentially at play in the development of hypertension in the CKD patient. Of these factors, volume expansion and SNS activation appear to be observed most consistently in experimental and clinical circumstances. Hypertension in CKD should not be viewed as a process suddenly developing during the progression of CKD; rather, it is an entity that commonly precedes progressive CKD and one whose character changes with progression of CKD. A number of new causative factors can be recruited pathobiologically relative to the hypertensive pattern in the CKD patient with progressive disease, but these are difficult to sort out on a clinical basis. The approach to therapy in the CKD patient with hypertension is one of multiple drugs from several drug classes with control of a patient's volume state being of some considerable importance to effecting BP control.

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