

Hypertension in Chronic Kidney Disease and Dialysis: Pathophysiology and Management

Rajiv Agarwal, MD^{a,b,*}

^aDivision of Nephrology, Department of Medicine, Emerson Hall Room 520,
Indiana University School of Medicine, 1481 West 10th Street, Indianapolis, IN 46202, USA

^bRoudebush VA Medical Center, 1481 West 10th Street 111 N, Indianapolis, IN 46202, USA

Hypertension affects 24% of the adult United States population [1]. In the United States, 3% of the adult population has an elevated serum creatinine level, and 70% of these patients have hypertension [2]. The prevalence of hypertension in chronic kidney disease (CKD) depends on the patient's age and the severity of renal failure, proteinuria, and underlying renal disease [3]. As patients with CKD progress to end-stage renal disease (ESRD), 86% are diagnosed with hypertension [4]. It has long been recognized that kidney function affects and is affected by hypertension. This article discusses the pathophysiology and management of hypertension in patients with CKD.

Pathophysiology of hypertension

Sodium and water

It has been recognized for at least 50 years that increasing sodium intake leads to a variable but consistent increase in blood pressure in animals. Dahl et al [5] thought this heterogeneity in response resulted from the interaction between genetic and environmental factors and that by ingenious inbreeding experiments in Sprague-Dawley rats fed a high-sodium diet, within three generations they could create colonies that were hypertensive. The

predisposed animals did not develop increased blood pressure when fed a sodium-poor diet, but a sodium-rich diet caused an elevation in blood pressure in the sodium-sensitive animals. This finding confirmed the importance of the interaction between sodium intake and genetic predisposition in causing hypertension.

The most definitive experiments investigating the significance of sodium in hypertension in primates were performed over a span of 2.5 years in chimpanzees fed a high-sodium diet [6]. Chimpanzees, who typically consume a vegetarian, potassium-rich, sodium-poor diet, were fed a diet that was gradually supplemented with dietary sodium to a level of 15 g/d that was sustained over 16 months. At the end of supplementation period, blood pressure had increased by 10/33 mm Hg together with suppression of plasma renin activity. Within 20 weeks after sodium supplementation was stopped, blood pressure returned to baseline.

Human data support the findings in animals. In primitive societies, such as the New Guinea Highlanders, Yanomamo Indians in Amazon rain forest [7], Bushmen in the Kalahari, or Kenyan tribal farmers, sodium content in the diet is extremely low (1–10 mEq/d). Hypertension and age-related increase in blood pressure is not seen in these populations. In contrast, the mean dietary intake of sodium in Akita, Japan, is 450 mEq/d (26 g/d), and a high incidence of hypertension and strokes is seen. Furthermore, the increase in dietary sodium intake that occurs when members of primitive societies move to an urban area is associated with rapid increase in blood pressure.

Guyton et al [8] studied the hemodynamic basis of the development of hypertension in

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* Division of Nephrology, Department of Medicine, Emerson Hall Room 520, Indiana University School of Medicine, 545 Barnhill Drive, Indianapolis, IN 46202.

E-mail address: ragarwal@iupui.edu

response to volume overload. Guyton's group studied the time course of change in cardiac output and vascular resistance in dogs after removing 40% of one kidney and infusing isotonic saline for 13 days. During the first 3 days of saline administration, blood pressures increased together with a rise in cardiac output, but peripheral vascular resistance fell. Subsequently, cardiac output dropped, but peripheral vascular resistance increased and resulted in hypertension. These results were explained by an increase in blood volume, an increase in mean circulatory filling pressure, and a higher cardiac output at the initial stages of volume expansion. These effects were followed by autoregulatory vasoconstriction that resulted in increased peripheral vascular resistance. Perfusion of kidneys at higher pressures caused pressure natriuresis and restoration of cardiac output. Because of persistently elevated peripheral vascular resistance, hypertension was sustained even after the reduction in cardiac output [8,9].

It is increasingly being recognized that sodium has an important influence on vascular endothelial and adventitial function. For example, cultured vascular smooth muscle cells undergo hypertrophy when exposed to high concentrations of sodium chloride [10]. In Dahl salt-resistant rats, a high-sodium diet induced hypertrophy of the arterial wall and increased mortality compared with a normal-sodium diet, independent of hypertension [11]. Increased sodium intake impairs nitric oxide (NO) bioavailability and induces oxidative stress. Furthermore, increased sodium intake accelerates vascular production of angiotensin II despite reduction in plasma renin activity, suggesting that angiotensin II production in blood vessels is independent of plasma renin activity [12]. Finally, increased dietary sodium can increase the release of sodium-pump ligands that inhibit the sodium pump on cell membranes (eg, digoxin) and increase smooth muscle tone. Reducing dietary sodium to less than 60 mmol/d increases arterial compliance and reduces arterial stiffness within 1 to 2 weeks, with a concomitant reduction of 6 mm Hg in systolic ambulatory blood pressure [13]. It is clear that sodium has an effect on blood pressure and cardiac responses above and beyond its effect on plasma volume and hemodynamic responses.

The renin-angiotensin system

In addition to the hemodynamic actions of angiotensin II that include vasoconstriction,

sympathetic activation, and sodium retention, other nonhemodynamic effects are well recognized. These effects include endothelial, mesangial, and renal tubular activation and oxidative stress. Inflammation and fibrosis can occur with elevated levels of this angiotensin II in a variety of kidney diseases. For example, the activity of angiotensin-converting enzyme (ACE) can be higher in areas of renal injury than in noninjured areas [14]. The resultant overexpression of angiotensin II can lead to progressive renal damage and hypertension [15].

Oxidative stress

Reactive oxygen species, such as superoxide and hydrogen peroxide, are important signaling molecules. They participate in vascular smooth muscle cell growth and migration; modulation of endothelial function, including endothelium-dependent relaxation and expression of adhesion molecules, chemoattractant compounds, and cytokines rendering a proinflammatory phenotype; and modification of the extracellular matrix.

Haugen et al [16] examined three models to assess the direct effect of angiotensin II on the structure and function of the kidney by oxidative stress. In the first model, angiotensin II was administered using mini-osmotic pumps to rats maintained on standard diets. Oxidative stress and hypertension were observed. In the second model, rats were made hypertensive with deoxycorticosterone acetate and salt, but they were not given angiotensin II. In this model, suppression of the renin-angiotensin system would be expected, and hypertension without oxidative stress was noted. In the third model, rats maintained on antioxidant-deficient diets were studied while infused with angiotensin II. Proteinuria and decreased creatinine clearance were noted in addition to oxidative stress and hypertension. Others have demonstrated that rats with renin-mediated hypertension have AT1 receptor-mediated endothelial dysfunction associated with increased oxidative stress and increased vascular xanthine oxidase activity [17]. In contrast, knockout mice that are genetically deficient in gp91(phox), a nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunit protein, show lower baseline blood pressures and demonstrate less oxidative stress-mediated vascular injury in response to angiotensin II [18]. Nishiyama et al [19] have demonstrated that the effect of angiotensin II in elevating blood pressure is partly

caused by inactivation of NO through the generation of oxygen-derived free radicals. In humans with CKD, the author and colleagues have found that blockade of the renin-angiotensin system can reduce oxidative stress [20] and profibrotic cytokines [21] independent of the reduction in proteinuria or blood pressure [22].

Taken together, these experiments offer direct evidence that angiotensin II induces oxidative stress *in vivo*, which contributes to renal injury. This injury seems to be predominantly localized to the renal proximal tubules. The NADPH oxidase-derived superoxide anion seems to be important for the regulation of basal blood pressure as well as in the pathogenesis of hypertension. Furthermore, these studies reveal a pressure-independent vascular hypertrophic response to angiotensin II and suggest that oxidative stress is causally important in the genesis of renal parenchymal hypertension.

Nitric oxide and circulating inhibitors of nitric oxide

Endothelial derived NO plays a critical role in the maintenance and regulation of vascular tone and modulates key processes mediating vascular disease including leukocyte adhesion, platelet aggregation, and vascular smooth muscle proliferation [23]. Endothelial NO synthase enzymatically produces NO from the substrate L-arginine. NO vasodilates the vasculature through activation of guanylate cyclase, which subsequently produces cyclic guanosine monophosphate (c-GMP) [24]. c-GMP activates a protein kinase enzyme that phosphorylates and activates a calcium-dependent potassium channel, leading to potassium efflux and vasodilation [25]. In hypertensive patients, this mechanism has been found to be defective [26–28]. Also, L-arginine supplementation can partially reverse renal failure-associated endothelial dysfunction [29]. Reactive oxygen species can impair the activity of NO. Superoxide quenches NO to produce peroxynitrite, which is devoid of vasodilating activity [30].

A circulating inhibitor of NO synthase, asymmetrical dimethyl arginine (ADMA), competes with L-arginine for NO synthase. In humans with salt-sensitive hypertension, a high-salt diet increases plasma ADMA and blood pressure [31]. Circulating ADMA is increased in persons with CKD [32] and ESRD [33] and may contribute to endothelial dysfunction and increased blood pressure. In patients with ESRD, ADMA is correlated

with increased left ventricular thickness and reduced ejection fraction, consistent with its ability to increase systemic vascular resistance [34].

Of the 300 $\mu\text{mol/d}$ ADMA normally generated, the kidneys in healthy volunteers excrete only 50 $\mu\text{mol/d}$. The remaining amount is degraded enzymatically by dimethylarginine dimethylaminohydrolase (DDAH) [35]. Pharmacologic inhibition of DDAH causes accumulation of ADMA and generalized vasoconstriction. In contrast, overexpression of DDAH reduces ADMA, improves NO bioavailability, and reduces systolic blood pressure. Oxidative stress that impairs DDAH activity by oxidizing a sulfhydryl moiety critical for its enzymatic activity leads to accumulation of ADMA and promotes endothelial dysfunction. The inflammation, increased homocysteine levels, reduced antioxidant defenses, and increased free radicals in ESRD therefore may explain the relationship between oxidative stress, endothelial dysfunction, and the generation of hypertension [33].

The sympathetic nervous system

Strong evidence has emerged that implicates enhanced sympathetic activity as a cause of hypertension in patients with CKD and ESRD [36]. Microvascular and tubulointerstitial damage induced by repeated injections of phenylephrine in animals leads to the development of sodium-sensitive hypertension [37]. On the other hand, there is also ample evidence that the sympathetic nervous system is activated in CKD. Diminished vascular response to norepinephrine in animal models of chronic renal failure provided initial indirect evidence of increased sympathetic nerve activity that decreased the expression of adrenergic receptors [38]. Later studies provided more direct evidence of elevated sympathetic tone in patients with ESRD [36] by direct measurement of efferent sympathetic nerve activity [39]. Using microneurography, investigators have demonstrated that the sympathetic activity is increased in patients receiving chronic hemodialysis who still have their native kidneys. In contrast, patients with bilateral nephrectomy have reduced sympathetic activity, lower vascular resistance in the calf, and lower mean arterial pressure [36]. Thus, the kidney, even when devoid of excretory function, serves as an afferent organ to signal the midbrain region to increase sympathetic activity. The central mechanisms of increased sympathetic activity may involve dopaminergic neuronal transmission. Experiments in hypertensive hemodialysis patients

show that administration of the dopamine-releasing drug bromocriptine decreased plasma norepinephrine and lowered mean arterial pressure [40]. In animals with chronic renal failure, norepinephrine turnover rate is increased in the posterior hypothalamic nuclei, and endogenous NO may be an important regulator of sympathetic activity [41]. NO inactivation in the central nervous system by an arginine analogue resulted in higher blood pressures and increased renal sympathetic nerve activity in rabbits [42]. Baroreceptor desensitization has also long been recognized in hypertensive patients with ESRD and may contribute to elevated blood pressure [43].

Drugs and toxins

Erythropoietin

Erythropoietin (EPO) can cause hypertension in approximately 20% of patients. Originally, EPO-induced hypertension was attributed to the rise in hematocrit and blood viscosity that occurred with treatment [44,45]. In both animal and human studies, however, results have consistently shown that the rise in blood pressure with EPO administration is independent of hematocrit [46–49]. For example, Vaziri et al [50] have shown that if EPO is administered to anemic animals with chronic renal failure, but hemoglobin is kept stable by feeding these animals an iron-deficient diet, hypertension still occurs. In blood vessels harvested from these animals, vasodilatory responses to NO donors were impaired, but response to several vasoconstrictors was normal.

Vascular smooth muscle cells use intracellular calcium to initiate vasoconstriction [51]. Platelet cytosolic calcium concentrations have been shown to correlate with vascular smooth muscle cytosolic calcium concentrations and blood pressure [52]. Thus, platelet cytosolic calcium serves as a surrogate for smooth muscle calcium concentration. In this context, EPO increases platelet cytosolic calcium in animals [50] as well as in hypertensive patients [53]. EPO can activate calcium channels through tyrosine kinase [54]. Felodipine, a calcium-channel blocker, lowered platelet cytosolic calcium concentrations and blood pressures in rats treated with EPO [55].

Lead

Low-level lead exposure is associated with impaired renal function [56] and hypertension [57–60]. Oxidative stress and impaired endothelial vasodilation seem to be important in the

mechanism of lead-induced hypertension. Lead-exposed rats had hypertension and biomarkers of oxidative stress that improved with the administration of an antioxidant [61]. Similarly, tempol, an antioxidant that reduces superoxide levels, lowered blood pressures in lead-exposed rats while having no effect in the control rats [62]. Finally, lead-exposed rats, in addition to having hypertension, have reduced endothelial guanylate cyclase expression, suggesting endothelial dysfunction [63].

Cocaine

Cocaine, blocks the uptake of catecholamines in presynaptic sympathetic nerves [64], leading to peripheral vasoconstriction and elevated blood pressure. Cocaine infusions in laboratory rats raised blood pressure in a biphasic manner: after a rapid initial increase in blood pressure, a more sustained response ensued. The blood pressure-raising effect of cocaine is caused, at least in part, by its ability to impair endothelial function [65].

Cyclosporine

Cyclosporine, a calcineurin immunosuppressive agent, causes afferent arteriolar vasoconstriction and tubulointerstitial fibrosis [66] that can lead to hypertension and a reduced glomerular filtration rate. Reduced NO bioavailability may play a primary role in the pathogenesis of cyclosporine's toxicity. In vitro, cyclosporine increases the production of reactive oxygen species, primarily superoxide and hydrogen peroxide, that can be reduced by free radical scavengers [67]. Administration of cyclosporine to laboratory rats increased angiotensin II superoxide levels and blood pressure [68]. Nephrotoxicity of cyclosporine can be abrogated in laboratory rats by antioxidant therapy [69].

Nonsteroidal anti-inflammatory drugs

Prostaglandins promote vasodilation and enhance natriuresis [70]. Nonsteroidal anti-inflammatory drugs (NSAIDs) block the synthesis of prostaglandins and lead to an elevation in blood pressure of about 5 mm Hg [70,71]. Elderly persons, hypertensive persons, and those with CKD carry an increased risk of developing hypertension when taking NSAIDs. Aspirin and sulindac seem to have the least effect on increasing blood pressure [71]. Increased vascular resistance and expanded extracellular volume have both been associated with the genesis of NSAID-induced hypertension. Like NSAIDs, the coxibs

can also increase blood pressure and cause renal injury [72,73].

The pathophysiology of hypertension and CKD can be summarized as follows. Renal injury occurs from a variety of reasons that include hypertension, diabetes mellitus, immunologic diseases, and drugs and toxins. The underlying abnormalities in a variety of kidney diseases include activation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system. Some of these factors (eg, the renin-angiotensin system, sympathetic system, and cocaine use) can by themselves aggravate hypertension. Many of these processes are accompanied by tubulointerstitial disease. Tubulointerstitial inflammation results in the release of oxidants by the invading inflammatory cells, the inactivation of local NO, and the heterogeneous activation of the intrarenal renin-angiotensin system. Tubular and vascular barotrauma, characterized by afferent arteriopathy, leads to a right-shifted pressure-natriuresis curve. This response relieves the renal ischemia but does so at the expense of higher blood pressure, leading to the development of hypertension that causes further renal injury. Dietary sodium excess, by inactivating DDAH, can reduce NO activity, cause vascular smooth muscle hypertrophy, and further accelerate tubular and microcirculatory damage. Extracellular volume expansion by sodium overload can, by itself, aggravate hypertension. Renal inflammation and hypertension eventually lead to renal fibrosis, progressive CKD, and target-organ damage, including ESRD.

Management of hypertension in chronic kidney disease

Ascertaining the blood pressure level is the essential first step in treating hypertension but can be particularly problematic in patients receiving hemodialysis, who have large swings in blood pressure related to the dialysis treatment [74]. In such patients, home [75] and ambulatory blood pressure monitoring [76,77] can be of particular value.

Life-style modifications can improve blood pressure levels per se and can enhance the efficacy of antihypertensive therapies. Reducing sodium intake, increasing physical activity, losing weight, limiting alcohol intake, and smoking cessation are recommended strategies [78].

A meta-analysis of trials of sodium restriction in normotensive and hypertensive individuals concluded that a 50 mEq/d reduction in dietary sodium (which can be achieved simply by taking

away table salt), would lead to a decrease in systolic blood pressure of 5 mm Hg on average and 7 mm Hg in those who are more hypertensive [79]. At least 5 weeks of sodium restriction would be required to see such an effect.

Systolic hypertension, not diastolic blood pressure, is the key treatment target [80]. Systolic hypertension is more prevalent than diastolic hypertension [81], and reduction of systolic blood pressure is associated with improved cardiovascular outcomes [82,83]. The recommended target blood pressure is less than 130/80 mm Hg in patients with CKD and less than 125/75 mm Hg in those with proteinuria in excess of 1 g/d [78]. To achieve these goals, multiple agents are required—on average, three to four per day [84]. It is obvious that more medications are required if blood pressure goals are more aggressive [85]. The guidelines set forth in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommend combination therapy if blood pressure is more than 20/10 mm Hg above goal [78]. Drug interactions should be monitored, especially with polypharmacy. NSAIDs, cyclooxygenase inhibitors, nasal decongestants, and amphetaminelike drugs can markedly worsen blood pressure control and should be avoided in patients with kidney disease [71]. Over time, the number of agents required to achieve the goal is likely to increase, so continual monitoring and titration are needed.

Hypertension in dialysis patients

Once a patient reaches end-stage renal disease and requires hemodialysis, a procedure that is typically performed three times per week, the sodium and water removed during the treatment must at least match the interdialysis gain of sodium and water. Furthermore, the absolute content of total body water and sodium must be at a level that does not cause signs and symptoms of volume overload, including hypertension, or signs and symptoms of sodium and water depletion, such as dizziness and hypotension. The assessment of total body water and sodium that is associated neither with volume overload nor with volume depletion is imperfect. The optimal level is called the dry weight.

Observational studies in dialysis patients show an association between large interdialysis weight gain and total mortality in patients with diabetes mellitus and poor nutritional status [86]. Foley

et al [87] reported results from a historically prospective study of 11,142 patients receiving dialysis on December 31, 1993 randomly selected from the US Renal Data System Dialysis Morbidity and Mortality Study Waves 3 and 4. After accounting for multiple comorbid factors, they reported an interdialysis weight gain greater than 4.8% was associated with increased mortality. Dietary salt restriction, a strategy to limit interdialysis weight gain that is as old as dialysis itself, would, if practiced diligently, facilitate the achievement of dry weight. Like many other lifestyle modifications, however, it is not practiced widely [88]. Nevertheless, centers that have encouraged dietary salt restriction have been rewarded with less use of antihypertensives and better blood pressure control [89,90].

Another strategy to limit interdialysis weight gain and thirst is to lower the dialysate sodium concentration. Whereas increased dialysate sodium concentration increases interdialysis weight gain [91,92], the data supporting the reverse phenomenon are not as strong. Nevertheless, in one preliminary study, dialysate sodium was reduced at a rate of 1 mEq/L over 3 or 4 weeks, from 140 mEq/L to 135 mEq/L, in combination with a prescription sodium diet of less than 6 g/d [93]. Predialysis blood pressure improved from 147/88 mm Hg to 136/80 mm Hg (mean decrease in arterial pressure from 108 to 98 mm Hg; $P = 0.02$) without change in dry weight. Furthermore, four of the eight patients were able to stop using blood pressure medications completely. Others, in a study involving six hemodialysis patients, have not observed such an improvement [94]. In another study, sodium intakes of 15 dialysis patients were restricted so that their estimated dietary sodium intakes were reduced from 10 g/d to 7 g/d [95]. Dialysis parameters and dry body weight were kept constant. Predialysis blood pressure decreased with dietary salt restriction, from 139/79 to 132/75 mm Hg ($P < 0.01$ systolic; $P < 0.05$ diastolic), and mean arterial pressure was reduced from 99 to 94 mm Hg ($P < 0.01$). Interdialysis weight gain decreased with salt restriction from 2.3 ± 0.73 kg to 1.8 ± 0.52 kg ($P < 0.001$), whereas postdialysis weight did not change, (66.1 ± 11.9 kg to 66.1 ± 11.8 kg; not statistically significant). Clearly, these data need to be confirmed in adequately powered larger trials, but it seems that dietary sodium restriction may provide blood pressure lowering.

In another study, lowering the sodium concentration of the dialysate by individualizing dialysate prescriptions reduced thirst and interdialysis

weight gain, improved hemodynamic stability, and reduced intradialysis symptoms [96]. In persons who were initially hypertensive, this strategy improved blood pressure control. In individuals with limited cardiovascular reserve relative to the ultrafiltration rates, a high sodium dialysate confers hemodynamic stability [91]. Lowering dialysate sodium may, at least theoretically, cause intradialysis hypotension; if the hypotension results in a limited ability to ultrafilter, lowering dialysate sodium may, paradoxically, increase blood pressure. Drug therapies for hypertension in hemodialysis patients are discussed elsewhere [97].

Choice of agent

In a meta-analysis of 15 studies to assess the impact of race on antihypertensive response, Sehgal et al [98] reported that for drug-associated changes in diastolic blood pressure, the mean difference between whites and blacks ranged from 0.6 to 3.0 mm Hg, whereas the SD within each race ranged from 5.0 to 10.1 mm Hg. On average, beta blockers and ACE inhibitors produced a greater reduction in blood pressure in white patients than in black patients (mean reduction in systolic blood pressure, 6 versus 4.6 mm Hg). In contrast, diuretics and calcium-channel blockers achieved greater mean reductions in black patients than in white patients (3.5 versus 2.4 mm Hg). In all the studies analyzed, however, the difference the size of the blood pressure reduction between white patients and black patients was smaller than the SD in each group. For example, the difference in systolic blood pressure between black and white patients after treatment with ACE inhibitors was 4.6 mm Hg, whereas the SD within each group was approximately 12 to 14 mm Hg. Thus, the small difference between whites and blacks in response to certain antihypertensives is dwarfed by the variation within each race. Furthermore, combination therapies such as diuretics plus ACE inhibitors or calcium-channel blockers plus ACE inhibitors nullify the effect of race. Thus, the choice of antihypertensive therapy should be an ACE inhibitor or angiotensin-receptor blocker in patients with kidney disease, regardless of race [85]. Water-soluble ACE inhibitors such as lisinopril and enalapril can be dosed less frequently because of their reduced renal clearance. In hemodialysis patients, postdialysis administration of lisinopril controls hypertension effectively [99].

In patients with a glomerular filtration rate below 30 mL/min, loop diuretics are effective in reducing blood pressure and have a synergistic response when used in combination with an ACE inhibitor, angiotensin-receptor blocker, or beta blocker. Torsemide and furosemide are equally effective in effecting natriuresis and reducing blood pressure, but torsemide has the advantage of once-daily administration [100]. Three to 4 weeks are required before maximal blood pressure reduction is achieved [101].

Water-soluble beta blockers such as atenolol should be reduced in dose and titrated to heart rate. They can accumulate with progressive renal failure, but atenolol given after hemodialysis three times per week effectively controls hypertension [102]. Some studies suggest that nondihydropyridine calcium-channel blockers can have incremental reduction in proteinuria compared with dihydropyridine calcium-channel blockers [103,104]. Direct vasodilators [105] and centrally acting agents [106] are commonly used and are effective in reducing blood pressure. Short-acting vasodilators should be avoided to prevent large swings in blood pressure and sympathetic activation.

In proteinuric patients, combination therapy with ACE inhibitors and angiotensin-receptor

blockers can have incremental reduction in proteinuria [107], oxidative stress [20], and urinary excretion of fibrogenic cytokines [21], but definitive studies to support their use in preventing progression of renal disease have not yet been performed. Hyperkalemia and renal failure are potential complications of such combination therapies [108]. Antihypertensive medications are frequently titrated to achieve reduction in proteinuria. Although post hoc analyses of randomized, controlled trials find an association between reduction in proteinuria and reduction in cardio-renal end points [109], a cause-and-effect relationship remains to be firmly established. Other cardioprotective therapies such as aspirin and statins should be considered for cardio-renal protection in this high-risk population [110].

Reverse epidemiology of hypertension in hemodialysis?

High blood pressure has a continuous, graded, and etiologically significant relationship with cardiovascular outcomes in the general population [78], but studies in hemodialysis patients have found an inverse relationship between high blood

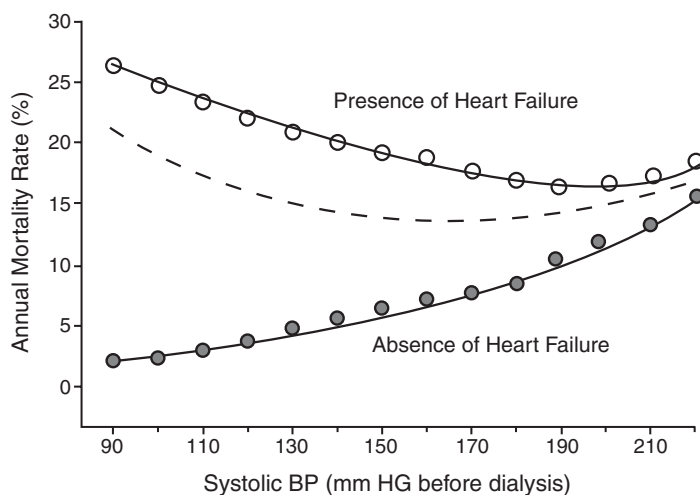


Fig 1. Impact of confounding variables influencing the relationship between hypertension and mortality: consideration of confounding variables, such as heart failure, can help explain the U-shaped relationship between blood pressure and total mortality (dotted line) seen in some studies. Well-controlled blood pressure in the presence of poor cardiac function is likely to be associated with high cardiovascular mortality (open circles, upper line). In contrast, poorly controlled blood pressure with intact cardiac function is expected to be associated with increased mortality (solid circles, lower line). If patients with impaired cardiac function constitute a large part of an observational cohort, a U-shaped relationship between blood pressure and total mortality is seen (dotted line). (From Agarwal R. Exploring the paradoxical relationship of hypertension with mortality in chronic hemodialysis. *Hemodialysis Int* 2004;8:208.)

pressure and outcomes [111,112]. Thus, patients with high blood pressures have a lower mortality than those with low blood pressures. It is intellectually troublesome to find such an association, because high blood pressure, which was such an important risk factor for cardiovascular disease before onset of dialysis, suddenly becomes a protective factor. Clinicians strive to lower blood pressure more aggressively in patients with chronic kidney disease who are not yet receiving hemodialysis than in patients with uncomplicated essential hypertension. If the observation of reverse epidemiology is etiologically significant, is treating high blood pressure in hemodialysis patients a wise practice?

Analyzing a prognostic value of blood pressure in observational cohort studies requires consideration of various other factors. One factor that is often ignored in considering hypertension as a prognostic variable in dialysis patients is reverse causation. Reverse causation means that the dependent process has a direct or indirect effect on the independent predictor. Fig. 1 shows the hypothesized relationship between hypertension and mortality when a confounding variable is considered [113]. Long-standing, poorly controlled hypertension may lead to heart failure, which may lower blood pressure, an example of reverse causation. If the confounding variable of heart failure is not considered, the conclusion that lower blood pressure is damaging would be inappropriate.

Thus, the author believes that, in hemodialysis patients, hypertension should be considered in the context of cardiovascular function and other parameters that modify blood pressure. In those who are otherwise healthy, complacency about high blood pressure would be inappropriate.

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