Hypertension in Renal Diseases

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Renal disease is closely associated with hypertension. Hypertension belongs to the clinical picture of chronic kidney disease (CKD). Hypertension associated with renal diseases occurs as a complication of various glomerular and interstitial diseases and may accelerate the decline of renal function if inadequately controlled. The pathophysiology through which the kidney raises blood pressure have been considerably clarified in recent years and it could be shown that "hypertension goes with the kidney" in experimental and clinical studies. The combined interactions of multiple independent mechanisms are thought to be involved in the development of hypertension. Impaired renal sodium handling leads to volume expansion. There is inappropriate activation of the renin-angiotensin system. As only recently documented in detail, renal injury raises the sympathetic tone, even when whole kidney glomerular filtration rate (GFR) is unchanged. This results from stimulating afferent signals coming from the kidney. There also is an evidence of impaired endothelial cell dependent vasodilatation even in very early stages of renal dysfunction. And other factors including uric acid, parathyoid hormone (PTH), and calcium may play a role in concert with other factors in the development of hypertension of renal diseases. Understanding these pathophysiologies is important for appropriate antihypertensive treatment.

Key Words : Hypertension, Renal disease, Renin-angiotensin system, Sympathetic nerve system, Chronic renal failure

In the maintenance of peripheral vascular resistance through the action of angiotensin II, which is the final product of renin-angiotensin system and the volume control of cardiac output by the regulation of urinary salt and water excretion, the kidney plays an important role. Because blood pressure is determined by cardiac output and total peripheral resistance, the kidney is indispensable to regulation of blood pressure. Blood pressure regulation in the kidney involves the interplay of renal blood flow, sympathetic nervous system, and pressure-natriuresis control. Therefore, when the kidney is injured by any cause, it leads to a physiological changes that are responsible for progressive hypertensive renal diseases[1]. It is well established that "blood pressure goes with the kidney." in human studies in which genetically hypertension-prone donor's kidney was transplanted to the recipient[2, 3] as well as in animal experiments[4, 5].

Considering the role of kidney in the pathogenesis of hypertension, it is not surprising that hypertension is so often present in various renal diseases. Hypertension is common in patients with overt renal insufficiency (stage 3-5 chronic kidney disease). Generally the prevalence of hypertension in stage 3 to 5 chronic kidney disease is approximately 50 to 75%. But the prevalence is considerably different according to various forms of renal diseases. In chronic glomerulonephritis, 15-85% of patients are hypertensive[6]. Most polycystic kidney disease patients are hypertensive by the time of dialysis[7] and tubulointerstitial disease is also commonly associated with hypertension[8]. Generally renal causes are blamed for the majority of secondary hypertension[9]. As renal function declines, hypertension prevalence and severity increases and hypertension is very common and

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difficult to treat in end stage renal disease. On the other hand, hypertension occurs as a complication of a wide variety of glomerular and interstitial renal diseases and may accelerate the decline in renal function if inadequately controlled or it can be one of the major causes of renal diseases. Therefore, hypertension is both a cause and a consequence of renal disease, and in some cases it may be difficult to distinguish clinically between these two situations. In this paper the pathogenesis of hypertension in renal diseases, especially chronic kidney disease will be briefly discussed.

Pathophysiology/Pathogenesis

Despite much interests and investigations, the precise pathophysiology that are involved in the development of hypertension in kidney diseases remain to be elucidated in many aspects. Hypertension in renal diseases most probably represents the combined interactions of multiple independent mechanisms. Potential factors include impaired sodium handling leading to volume expansion, perturbations of the renin-angiotensin system (RAS), increased sympathetic activity, alterations in endogenous vasodepressor compounds, and possibly increased activity of vasoactive substances as shown in Table 1[10].

Table 1. Hypothesized Pathogenetic Mechanism of High Blood Pressure in CKD

Pre-existing essential hypertension
Extracellular fluid volume overload
Renin-angiotensin aldosterone system stimulation
Increased sympathetic activity
Endogenous digitalis-like factors
Prostaglandins/bradykinins
Alteration in endothelium-derived factors (nitric oxide/endothelin)
Increased body weight
Erythropoietin administration
Parathyroid hormone (PTH) secretion/increased intracellular calcium/hypercalcemia
Calcified arterial tree
Renal vascular disease and renal arterial stenosis
Chronic allograft dysfunction
Cadaver allografts, especially from a donor with a family history of hypertension
Cyclosporine, tacrolimus, other immunosuppressive and corticosteroid therapy

1. Sodium handling and volume overload

In glomerulonephritis blood pressure can range from normal to extremely high levels. Hypertension is frequent and its negative effects in renal function have been described in acute postinfectious glomerulonephritis, IgA nephropathy, lupus nephritis, membranous nephropathy and minimal change disease. The hallmark of hypertension associated with glomerulonephritis appears to be increased salt retention regardless of GFR[11, 12]. The proximal tubule and thick ascending loop of Henle don't appear to be the sites of increased sodium reabsorption observed during experimental glomerulonephritis[13] and evidences point to the cortical collecting duct where activity of Na^+-K^+ ATPase is increased as the principal locus of sodium retention[14]. Several factors including RAS, sympathetic nervous system, resistance to atrial natriuretic peptide (ANP) are thought to be involved in altering the function of ENaC or Na^+-K^+ ATPase[15].

In the chronic kidney disease where GFR is depressed, the situation is somewhat more complex. In early chronic renal failure (CRF), plasma and extracellular fluid volume tend to be normal[16]. As GFR is declined the remaining nephrons are excreting the same amount of salt by increased response to natriuretic factors[17], thus, it is unlikely that hypertension of early renal disease has much to do with salt retention. The effectiveness of diuretics in lowering blood pressure may be related not to salt and water excretion, but to other effects on vessels. In more advanced renal disease, salt and water retention ensues with more accumulation in the hypertensive patients[18]. Plasma volume was found to be elevated and correlated with blood pressure in renal disease, but not in essential hypertension[19]. Extracellular volume expansion is the most consistent finding in hypertensive end stage renal disease (ESRD) patients, but the effect of fluid removal on the blood pressure

is contradictory in various studies[20]. For example some studies showed that volume status affects interdialytic BP, whereas others have failed to show such a relationship.

There is a correlation between loss of weight during hemodialysis and lowering of systolic BP[21]. A reduction in postdialysis mean arterial pressure of >5%, controlled by ultrafiltration, was found more in normotensive hemodialysis patients[22]. Plasma aldosterone and fluid volume removed by ultrafiltration are significantly correlated[23]. Volume sensitivity is higher in hypertensive as compared with normotensive patients[24]. A correlation between blood pressure and interdialytic weight gain does not exist for normotensive patients[25], probably because of an adequate vasodilatory response in these patients that may be less effective or absent in hypertensive hemodialysis patients. Rahman's study also showed also that blood pressure correlated with interdialytic weight gain in the hypertensive patients but not in the normotensive patients, suggesting that the difference between two groups may be in response to volume excess with the hypertensive patients unable to vasodilate in response to volume overload[26]. It seems that in the late stages of renal disease, hypertension is related with an increased peripheral resistance whether or not excess salt and water retention is present. Clinical observations also indicate a disparity between volume status and level of blood pressure. Dialysis patients with little or no residual renal function may have excessive fluid load in the absence of hypertension and some dialysis patients respond to fluid removal by elevation of their blood pressure.

2. Renin-angiotensin aldosterone system

Because of the physiology of the RAS (Fig. 1), its role in the pathogenesis of hypertension in the renal diseases has been the subjects of investigation for over four decades. And the evidences that links this system to the hypertension in renal diseases are compelling although some studies show controversial results.

Although glomerulonephritis usually evolves with signs of fluid retention and suppression of RAS[11] and decreased gene expression of AT1 receptors in the kidneys[27], the angiotensin II levels still are still inappropriately high for the degree of sodium expansion. In the nephritis-associated in the nephritis associated vasculitis, hypertension can result from ischemia-induced activation of the RAS[28].

Several factors support the role for the RAS in the pathogenesis of hypertension in patients with CRF. First, these patients have excessive renin secretion in relation to their extracellular volume status[29]. Second,

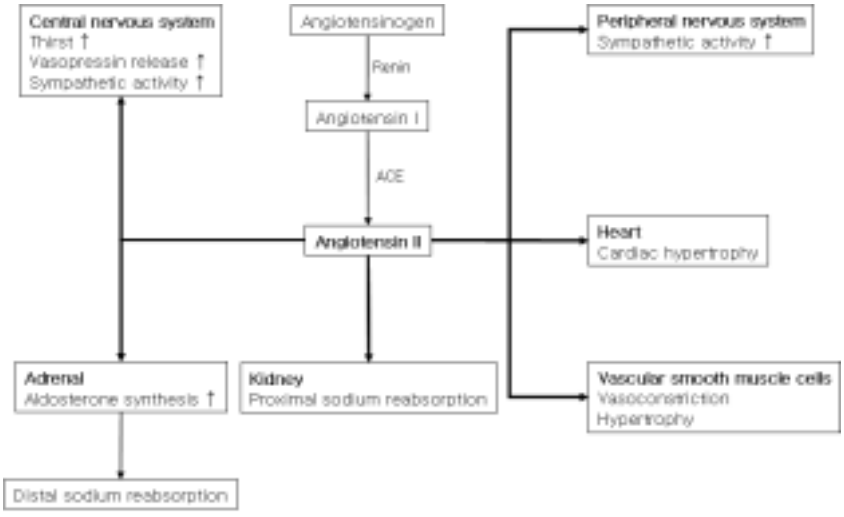

Fig. 1. Renin-angiotensin system.

a direct relationship between plasma renin activity and blood pressure has been found in dialysis patients[30]. Third, aldosterone was shown to contribute to hypertension and renal injury in the remnant kidney model[31]. Fourth, bilateral nephrectomy was used in prior decades for the treatment of severe hypertension in patients with renal transplantation or end stage renal failure (ESRD), although it could act through mechanism other than RAS suppression, including interruption of afferent renal chemoflex fibers that may activate the central sympathetic nervous system. Finally, paradoxical or dialysis-refractory hypertension often responds to ACE inhibitors or angiotensin antagonists. The possibility remains that intrarenal renin system is also active and contributing to the decreased renal flow and salt retention in some of the patients in whom PRA is not elevated[32]. It has been shown that all components of the RAS reside in the kidney. Apart from hemodynamic actions and effects on GFR and renal tubular function, the intrarenal RAS probably play an important role as a regulator of renal sympathetic activity, modifies mesangial cell function, acts as a renal growth promoter, maintains endothelial cell function, and may be an important inflammatory mediator in the kidney. From all the earlier studies, one is inclined to believe that the RAS is a factor in the hypertension of renal disease, but the explanation and evidences for it is not fully sufficient yet.

3. Sympathetic nervous system

It is now widely appreciated that the extensive sympathetic innervation of the kidney is important in the physiological regulation of all aspects of renal functions[33]. Increased renal sympathetic nerve activity results in renal vasoconstriction, with decreased GFR and renal blood flow, and increased renal vascular resistance; increased renal tubular reabsorption of sodium and water throughout the nephron; and increased renal release of renin and norepinephrine. Thus, the renal sympathetic nerves probably serve as the critical link between the sympathetic nervous system and the kidney in hypertension (Fig. 2).

Clinical and experimental data provide strong evidence that hypertension of ESRD is, at least in part, caused by the sympathetic overactivity that is triggered by afferent signals from the diseased kidneys. Dialysis patients with intact native kidneys, on

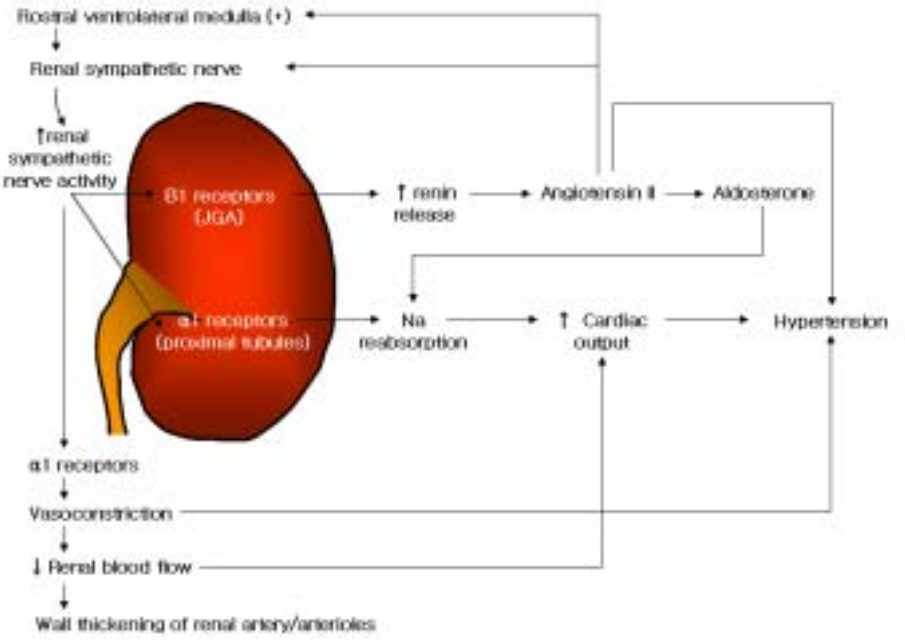

Fig. 2. Roles of renal sympathetic nerve in the initiation of hypertension.

peroneal nerve stimulation, exhibited a 2- to 3-fold increase in sympathetic nerve activity compared to either normal volunteers or anephric ESRD patients and the rate of sympathetic nerve discharge was not correlated with either plasma noradrenaline concentration or plasma renin activity[34, 35]. Despite small number of patients, Converse's findings strongly support the role of the kidney in mediating hypertension in the dialysis patient through increased sympathetic discharge. There now exists some indirect evidence that ACE-inhibition may decrease sympathetic activation in hypertensive patients with CRF[36].

There is evidence that increased peripheral sympathetic nerve activity is not just a feature of advanced or ESRD. In hypertensive patients with mild renal insufficiency muscle sympathetic nerve activity was increased as compared with hypertensive patients with normal renal function[37]. In addition, the ability of phenylephrine-induced increases in arterial pressure to inhibit muscle sympathetic nerve activity reflexively was impaired in hypertensive patients with mild renal insufficiency when compared with hypertensive patients with normal renal function. Thus, early during the course of renal disease, signals that originate from the diseased kidney lead to progressive increases in peripheral sympathetic nerve activity, which can contribute to the development of hypertension.

4. Endothelial factors

A recently appreciated concepts regarding the pathogenesis of hypertension in CRF is abnormal endothelial release of hemodynamically active compounds.

NO, synthesized from L-arginine, contributes to the regulation of blood pressure. Lack of NO production or presence of circulating inhibitors of NO (asymmetric dimethylarginine; ADMA) has been postulated to contribute to the pathogenesis of hypertension[38]. Xiao et al incubated uremic plasma from dialysis patients with cultured vascular endothelial cells[39]. NO synthase (NOS) activity and NO production were was lower in cells incubated with uremic plasma. These findings suggest that low endothelial NOS activity may contribute to hypertension in ESRD patients. Plasma ADMA levels are 6- to 10-fold higher in hemodialysis patients than in healthy subjects. Plasma ADMA levels can be reduced during the dialysis procedure by 65%[38]. Therefore, high plasma ADMA levels may, at least in part, be responsible for impaired endothelium-dependent vasodilation observed in uremia. However no significant correlation was observed between ADMA concentration and blood pressure in dialysis patients[40].

Endothelin-I level is elevated in uremic patients[41] and the plasma level increases further on volume removal by ultrafiltration, which suggests the role for endothelin-I in the maintenance of hypertension in hypertensive hemodialysis patients[42]. But these data does not prove a cause and effect relationship.

5. Calcium and PTH

Secondary hyperparathyroidism tends to start early in the course of renal failure and is commonly seen in CRF. In rats with CRF, hypercalcemia induced blood pressure increase is greater than in normal rats[43]. This vascular hyperesponsiveness is reversed by parathyroidectomy, suggesting that the presence of PTH plays an important role in the hypertensive action of hypercalcemia. Hypertension results from secondary hyperparathyroidism, at least in some patients with ESRD. Raine et al studied 36 hemodialysis patients to investigate possible relationships between hyperparathyroidism, alterations in intracellular free calcium concentration, and hypertension. Intracellular calcium level was increased in patients with elevated PTH, compared with those in whom PTH was normal and a linear relationship was present between serum PTH and mean blood pressure, which suggests that intracellular calcium may be increased early in renal failure, and that this increase occurs in association with both hyperparathyroidism

and hypertension[44].

Cytosolic calcium concentration is the final common pathway for vasoconstriction, cardiac contraction, and sympathetic neuronal activity. A linear relationship between platelet intracellular calcium concentration and blood pressure has been demonstrated in patients with ESRD[45]. It has been shown that increased intracellular calcium may render the blood vessels of renal patients more responsive to vasoconstrictors[46]. Hypertension secondary to early stage kidney disease may be related to an impairment of sodium excretion, leading to an expansion of blood volume and exchangeable body sodium. This may result in increased secretion of endogenous factors, leading to alterations of cytosolic calcium homeostasis of vascular smooth muscle cells followed by elevated peripheral resistance and thus blood pressure. Several mechanisms affecting intracellular calcium concentrations including Na^+-K^+ ATPase inhibitor in the uremic plasma[47] are proposed, but currently no specific defects in those mechanisms have been demonstrated in hypertension or uremia.

6. Other factors

Obesity has been blamed for both hypertension and renal disease[48]. Excess renal sodium reabsorption, probably in the loop of Henle, and a hypertensive shift of pressure and natriuresis may play a role in initiating increased blood pressure associated with weight gain. The mechanisms for it include activation of RAS and sympathetic nervous system and physical compression of the kidneys caused by accumulation of intrarenal fat and extracellular matrix. However, this remains to be a theory with limited data to support it.

Brenner and Mackenzie suggested that the number of functioning nephron units at birth determines an individual's predisposition to the subsequent development of hypertension and renal damage[49].

Increased oxygen free radical activity is also suggested, in part, as a cause of CRF associated hypertension[50].

Hyperuricemia may predict the development of hypertension and is present in 25-40% of hypertensive individuals[51]. Uric acid is increased in subjects with renal diseases as a results of decreased GFR and renal urate excretion. It has been demonstrated that mild hyperuricemia causes hypertension and primary renal microvascular disease in rat[52]. Mild hyperuricemia in rats acutely increases blood pressure by a renin-dependent mechanism that manifests itself under low salt dietary conditions. Chronic hyperuricemia also causes salt sensitivity, in part by inducing preglomerular vascular disease[53]. Although role of uric acid in the development of hypertension of renal diseases has not been elucidated yet, its possibility is still open to the evaluation.

Conclusion

It is evident that numerous and diverse causes and an incompletely defined pathophysiology are involved in the pathogenesis of hypertension in renal diseases. These include sodium retention, increased cardiac output, renin, aldosterone, expanded plasma volume, peripheral vasoconstriction, and etc (Fig. 3). These factors are more or less active in the different stages of hypertension and chronic kidney disease. As renal function deteriorates, excess volume plays a more important role. However, only hypervolemia is not an

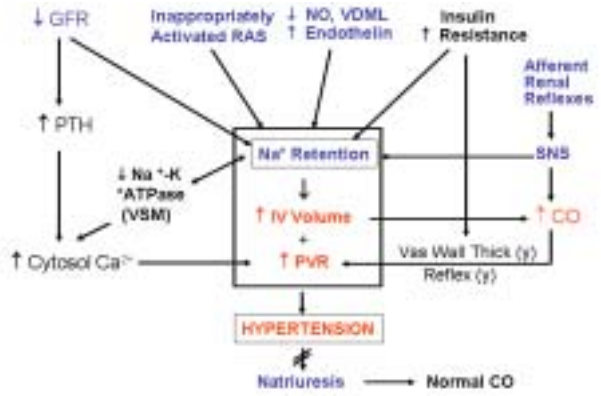

Fig. 3. Proposed mechanisms of hypertension in renal diseases.

adequate explanation. Systemic vasoconstriction, probably related to an active RAS and impaired endothelial function, is the major cause of hypertension in these patients. Additional insight into this complicated problem must await further delineation of pathophysiology of hypertension in renal diseases.

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