

Hypertension Secondary to Parenchymal Renal Diseases

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Introduction

The association between hypertension and chronic renal disease is well recognized. Hypertension occurs in approximately 80% of patients with end-stage renal disease (ESRD), and renal disease is by far the most common cause of secondary hypertension. Hypertension is an important presenting feature of renal disease and contributes to its progression. A history of long-standing arterial hypertension is associated with an increase in cardiovascular mortality, the leading cause of death in patients receiving maintenance hemodialysis. Although no controlled studies are available on the beneficial effect of antihypertensive therapy in patients on hemodialysis, maintenance of good blood pressure control is of great importance for the long-term survival of these patients. Hypertension is the single most important predictor of coronary artery disease in uremic patients, even more predictive than cigarette smoking or hypertriglyceridemia.

A large number of hypertensive hemodialyzed patients manifest no diurnal variation of blood pressure and absent or reduced nocturnal dipping of blood pressure. This is of particular clinical relevance, as a relationship

seems to exist between the absence of nocturnal fall in arterial blood pressure and severity of cardiovascular target organ damage.

Pathogenesis

The pathogenesis of hypertension in renal parenchymal diseases is multifactorial (Table 1). However, the most important factors

Table 1. Factors Implicated in the Pathogenesis of Hypertension in End-stage Renal Disease (ESRD)

1. Sodium and volume excess
2. The renin-angiotensin system
3. The adrenergic system and baroreceptor activity
4. Endothelium-derived vasodepressor substances
5. Endothelium-derived vasoconstrictor substances
6. Erythropoietin use
7. Divalent ions and parathyroid hormone
8. Atrial natriuretic peptide
9. Structural changes in the arteries
10. Preexistent essential hypertension
11. Miscellaneous:
 - Anemia
 - A-V fistula
 - Vasopressin
 - Serotonin
 - Thyroid function
 - Calcitonin gene-related peptide.

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appear to be sodium retention, activation of the renin-angiotensin system, and increased activity of the sympathetic nervous system.

The Role of Sodium and Volume Status

Sodium retention and volume expansion occur in a large number of patients with renal functional impairment and play a major role in the genesis and maintenance of hypertension in these patients. Restriction of dietary sodium intake and removal of excessive fluids with dialysis may result in improvement or normalization of blood pressure in approximately 50 – 60% of patients.

The mechanisms by which sodium excess may lead to arterial hypertension in patients with renal parenchymal diseases are complex. According to Guyton's hypothesis [1], initially sodium excess leads to volume expansion and to increased cardiac output. Eventually, this is followed by an increase in total peripheral vascular resistance and by normalization of cardiac output. In patients with renal failure and normal blood pressure, the increase in cardiac output is fully compensated by a decrease in peripheral vascular resistance. This compensatory adaptation does not occur in patients who develop hypertension. The increase in peripheral vascular resistance may be due to inappropriately elevated levels of angiotensin II in relation to the body fluids and volume status. Alternatively, sodium overload may increase the secretion of digitalis-like inhibitors of the Na-K-ATPase in vascular smooth muscle cells, resulting in hypertension. Boero et al. [2] found lower erythrocyte Na-K-ATPase activity in hypertensive than in normotensive uremic patients. In the hypertensive group, an inverse correlation was present between Na-K-ATPase activity

and peripheral vascular resistance. Inhibition of the Na-K-ATPase pump leads to increased cytosolic sodium and calcium concentrations, enhanced vascular tone, and enhanced vascular responsiveness to vasoconstrictors. The increase in intracellular sodium may also cause swelling of arteriolar walls and narrowing of the lumen of arterioles, which may contribute to the increased peripheral vascular resistance. The inhibition of the Na-K-ATPase pump could also result in activation of the sympathetic nervous system.

The Role of the Renin-angiotensin System

The role of the renin-angiotensin system in the pathogenesis of hypertension in patients with chronic renal failure has long been well recognized. This is supported by several observations. First, in these patients an abnormal relationship frequently exists between exchangeable sodium or blood volume and plasma renin-activity (PRA), and between PRA and blood pressure. Second, in most of these patients blood pressure can be effectively reduced by the administration of inhibitors of the renin-angiotensin system, such as angiotensin (Ang) converting enzyme (ACE) inhibitors or angiotensin II antagonists. Finally, bilateral nephrectomy almost always normalizes even the most severe forms of hypertension in patients with renal failure.

The Role of the Sympathetic Nervous System

The kidney is a sensory organ richly innervated with sensory and afferent nerves of two types:

- renal baroreceptors which increase their firing in response to changes in renal perfusion and intrarenal pressure;
- renal chemoreceptors, which are stimulated by ischemic metabolites or uremic toxins [3, 4].

The activation of these chemosensitive receptors and renal afferent nerves may establish connections with integrative nuclei of the sympathetic nervous system in the brain [5]. Stimulation of these afferent nerves by ischemic metabolites, such as adenosine, or by urea, evokes a reflex increase in sympathetic nerve activity and blood pressure [6].

In patients with chronic renal failure, plasma norepinephrine (NE) levels are frequently high. Direct microelectrode recordings of postganglionic sympathetic action potentials in peroneal nerves have shown greater sympathetic nerve discharge in dialysis patients with their native kidneys than in patients with bilateral nephrectomy or control subjects. These findings support the notion that increased afferent nervous inputs from the kidney to the central nervous system may play a role in the pathogenesis of hypertension in uremic patients.

The strongest evidence yet supporting a role of the sympathetic nervous system in the pathogenesis of hypertension in chronic renal failure (CRF) derives from animal experiments. The turnover rate of NE was greater in the posterior hypothalamic (PH) nuclei and in the locus coeruleus of rats with chronic renal failure than in control rats. Chemical destruction of the PH by micro-injection of a neurotoxin, 6-OH-dopamine, reduced blood pressure almost to normal in CRF animals [7]. Bilateral dorsal rhizotomy (T10 to L2) prevented the development of hypertension and the increase in NE turnover rate in the PH and in the locus coeruleus of CRF rats [8]. This suggests that renal afferent impulses from a

diseased kidney activate areas of the brain involved in the neuroadrenergic regulation of blood pressure and contribute to the development of hypertension in CRF rats.

The Role of Endothelial-derived Vasodilator Factors

The endothelial cells serve as the interface between the circulating blood and vascular smooth muscle cells and play a crucial role in regulating regional blood flow and vascular resistance. The endothelium is the major source of prostacyclin, which increases cyclic adenosine monophosphate (cAMP) in the vascular smooth muscle cells, leading to vasodilatation. The acetylcholine-induced arterial relaxation is endothelial dependent and is caused by the generation of a diffusible and transferable substance that relaxes smooth muscle cells. This substance is nitric oxide (NO). Prostacyclin and NO potentiate each other's vascular and platelet anti-aggregating effects even at subthreshold concentrations.

NO is formed in the vascular endothelium by NO synthase from the amino acid L-arginine. Several forms of NO synthase have been identified. The first is a constitutive, cytosolic Ca^{2+} /calmodulin-dependent form that releases NO for short periods in response to receptor or physical stimulation. The second is an inducible form that is Ca^{2+} -independent and can be activated by tetrahydrobiopterin and cytokines. Among other NO synthases is the neuronal form, which exerts a modulatory action on the activity of the sympathetic nervous system. Chronic inhibition of NO synthesis by L-Nitro-Arginine-Methyl-Ester (L-NAME) causes a sustained elevation of blood pressure and marked renal vasoconstriction, a fall in glomerular filtration rate and a rise in filtration fraction, plasma

renin levels, and SNS activity [9, 10]. Widespread arteriolar narrowing, focal arteriolar obliteration, and segmental fibrinoid necrosis of the glomeruli may also occur [11]. Vallance et al. [12] have shown that NO synthesis can be inhibited both in vitro and in vivo by an endogenous compound, N^GN^G-dimethylarginine (asymmetrical dimethylarginine, ADMA). They found higher plasma levels of ADMA in uremic patients on chronic hemodialysis and suggested that hypertension in the uremic patient may be due to NO synthesis inhibition caused by accumulation of this endogenous inhibitor.

We have evaluated the effects of L-arginine and L-NAME on blood pressure and SNS activity in Sprague Dawley 5/6 nephrectomized (CRF) or sham operated rats. NE turnover rate was increased in the posterior hypothalamic nuclei, locus coeruleus, paraventricular nuclei, and rostral ventral medulla of CRF compared to control rats. NO synthase (NOS) messenger RNA (mRNA) gene expression and NO₂/NO₃ content were also increased in the same brain nuclei. L-NAME increased blood pressure and NE turnover rate in the brain of control and CRF rats. In CRF rats, a significant relationship was present between the percent increment in NO synthase mRNA gene expression related to the renal failure, and the percent increase in norepinephrine turnover rate caused by L-NAME. This suggests that endogenous NO partially inhibits the activity of the SNS in brain nuclei involved in the neurogenic regulation of blood pressure, and this inhibition is enhanced in CRF rats [13].

The Role of Endothelium-derived Vasoconstrictor Factors

The endothelium releases very potent vasoconstrictors, such as endothelin (ET) [14],

Prostaglandin H₂, and epidermal growth factor. These vasoactive peptides may play a role in disease states such as hypertension.

Compelling evidence that ET may play a role in the pathophysiology of hypertension derives from two cases of hemangioendothelioma with plasma levels of ET 10–15-fold greater than in normal subjects. Surgical removal of the tumor led to resolution of hypertension in both cases. In one patient, the tumor recurred along with a rise in plasma ET level and hypertension [15]. Increased plasma ET-1 levels have been shown in patients with essential hypertension by some, but not all investigators.

The role of ET in dialysis-related hypertension has been the focus of active research and controversies. Hypertensive patients with CRF have higher plasma ET-1 levels than normotensive subjects. Elevated plasma ET-1 and ET-3 levels have also been shown in hemodialysis patients, and they have been attributed to either the uremic state or exposure of the cells to an extracorporeal circuit during hemodialysis. Higher ET-1 concentration and mean blood pressure have been observed more frequently in hemodialysis patients than in continuous ambulatory peritoneal dialysis (PD) patients.

The Role of Erythropoietin

The availability of recombinant human erythropoietin (rHu-EPO) has improved the management of anemia and the quality of life in patients with chronic renal failure. However, treatment with rHu-EPO frequently results in increased blood pressure, greater requirement for antihypertensive drugs, and potentially increased cardiovascular morbidity. Multicenter trials with rHu-EPO in dialysis patients have shown an increase in diastolic

pressure of >10 mm Hg and the need for increased antihypertensive medications in 88 of 251 (35%) of previously hypertensive patients; a similar increase in BP was noted in 31 of 71 (44%) normotensive patients [16]. The rise in blood pressure usually occurs within 2 – 16 weeks after the initiation of therapy with rHu-EPO. Patients at greater risk for developing hypertension are those with severe anemia, those whose anemia is corrected too rapidly, those with preexisting hypertension, and perhaps those with their native kidneys. The rise in blood pressure has not been observed in patients with normal renal function, suggesting that renal disease may confer a particular susceptibility to the hypertensive action of rHu-EPO.

The level of the hematocrit is important in the regulation of both systemic and renal hemodynamics. Anemia causes a hyperdynamic state characterized by an increase in cardiac output and a decrease in total peripheral vascular resistance (PVR). These changes are necessary to maintain an adequate oxygen supply to peripheral tissues. Left ventricular mass and end diastolic diameter increase in response to this hyperdynamic state. Correction of the anemia with rHu-EPO leads to a decrease in cardiac output and a rise in PVR. Patients who become hypertensive or experience an exacerbation of their blood pressure during rHu-EPO therapy either have an exaggerated rise of PVR in response to the increase in hematocrit, or do not decrease their cardiac output because of reduced compliance, or impaired baroreflex function. The increase in blood viscosity during rHu-EPO therapy correlates with the increase in PVR, but not blood pressure changes. Thus, the rise in blood pressure caused by rHu-EPO cannot be exclusively attributed to changes in blood viscosity. Studies in rats have shown that renal insufficiency is a prerequisite for the development of hypertension during rHu-EPO therapy. This

suggests the contribution of other factors, such as enhanced pressor responsiveness to norepinephrine and to Ang II.

In some studies, no vasoconstriction was evident in the isolated rat kidney or isolated human resistance arterioles after infusion of rHu-EPO. In other studies, vasoconstriction was observed in isolated renal and mesenteric resistance vessels of rats. This action was endothelial-independent and not affected by verapamil or phentolamine.

Some studies suggest that rHu-EPO may affect intracellular calcium homeostasis. Others found no correlation between absolute blood pressure levels and platelet intracellular calcium in hemodialyzed patients treated with rHu-EPO.

The administration of rHu-EPO to normal and uremic rats causes a rise in blood and platelet serotonin and an increase in blood pressure. These effects were abolished by ketanserin, an antagonist of 5-hydroxytryptophan (5-HT₂) receptors. The study suggests that serotonin may play a role in the development of hypertension caused by rHu-EPO.

Others have shown that hemodialysis patients on rHu-EPO therapy manifest increased ET-1 levels.

There is no evidence that decreased NO is responsible for rHu-EPO-associated hypertension, because rHu-EPO stimulates NO production.

The Role of Divalent Ions and Parathyroid Hormone (PTH)

A relationship between platelet or lymphocyte intracellular Ca²⁺ concentration ([Ca²⁺]_i) concentration and blood pressure has been demonstrated in patients with essential hypertension, as well as in patients with ESRD. The mechanisms leading to the increase in [Ca²⁺]_i

are not clear. This could be the result of increased circulating pressor hormones, such as NE or Ang II, or increased secretion of an ouabain-like factor in response to volume expansion. Finally, the increase in $[Ca^{2+}]_i$ in vascular smooth muscle cells could be caused by secondary hyperparathyroidism. CRF is frequently associated with secondary hyperparathyroidism, which leads to increased $[Ca^{2+}]_i$.

Recently, Raine et al. [17] studied 36 patients with chronic renal failure, 10 with normal serum PTH levels, 17 with elevated serum PTH, and 9 with elevated PTH but treated with nifedipine. Platelet $[Ca^{2+}]_i$ was significantly greater in the 17 patients with increased serum PTH than in patients with normal serum PTH. In addition, a significant relationship was present between serum PTH and platelet $[Ca^{2+}]_i$ or between platelet $[Ca^{2+}]_i$ and mean blood pressure and between PTH and mean blood pressure. In patients with high serum PTH receiving nifedipine, platelet $[Ca^{2+}]_i$ was not increased. Nine patients with hyperparathyroidism were restudied during treatment with alfacalcidol, a vitamin D metabolite. In these patients, serum PTH, platelet $[Ca^{2+}]_i$ and mean blood pressure all decreased significantly. The changes in blood pressure during treatment with alfacalcidol were linearly related with the changes in serum PTH and in $[Ca^{2+}]_i$. These studies suggest that increased serum levels of PTH may be responsible for both the rise in $[Ca^{2+}]_i$ and the increase in blood pressure in these patients. Treatment of secondary hyperparathyroidism with oral calcium may reduce blood pressure in hemodialysis patients.

Dialysis patients may occasionally develop hypercalcemia as a result of exogenous administration of vitamin D analogs, oral calcium supplementation, granulomatous diseases, multiple myeloma, or severe secondary hyperparathyroidism. In these patients, hy-

percalcemia may either aggravate or cause hypertension. Hypercalcemia is more likely to raise blood pressure in the presence of increased serum levels of PTH, and it does so primarily by increasing systemic vascular resistance, whereas cardiac output usually remains unchanged.

In rats with CRF, acute hypercalcemia raised blood pressure more than in normal rats [18]. This appeared to be secondary to the state of secondary hyperparathyroidism, because parathyroidectomy reduced the pressor response to acute hypercalcemia. These studies suggest that the presence of the parathyroid hormone plays an important role for the hypertensive action of hypercalcemia in uremic rats.

The Role of Cyclosporin A

Cyclosporin A is a potent orally active immunosuppressive agent used in the management of patients with a variety of renal diseases and with organ transplantation. It is known to be nephrotoxic and to raise blood pressure. The mechanisms of cyclosporin-induced hypertension are complex. It increases possibly because of direct action on vascular smooth muscle cells or activation of the sympathetic nervous system. Cyclosporin increases the activity of efferent sympathetic nerves and decreases the fractional excretion of sodium. Renal denervation and alpha-blocking agents prevent the decrease in renal blood flow (RBF) caused by cyclosporin.

The role of the sympathetic nervous system in cyclosporin-induced hypertension is less clear. Plasma and urinary catecholamines do not change during administration of this drug, but these levels are a poor marker of regional sympathetic nervous system activity. The role of the renin-angiotensin system is also uncer-

tain. Acute administration of cyclosporin increases PRA, but chronic treatment does not.

Cyclosporin increases the production of thromboxane A₂ and inhibits the production of prostaglandin E₂. Administration of inhibitors of thromboxane lessens cyclosporin's renal hemodynamic effects. Cyclosporin also increases the concentration of serotonin in the blood and platelets. It can cause magnesium deficiency, which may also cause increased PVR.

Pathophysiology of Hypertension in Specific Renal Parenchymal Diseases

Glomerulonephritis

In acute glomerulonephritis with endocapillary proliferation, e.g. poststreptococcal glomerulonephritis, the urine output and sodium excretion are reduced leading to volume expansion, increased cardiac output and hypertension. PRA is usually normal or reduced. Interestingly, in acute forms of glomerulonephritis characterized by extracapillary proliferation (e.g. Goodpasture, crescentic glomerulonephritis, and microscopic vasculitis), hypertension is mild or absent, despite the frequent coexistence of oliguria or anuria. Thus, sodium retention and volume expansion are not the only factors responsible for the rise in blood pressure in these conditions.

In chronic forms of glomerulonephritis, hypertension is very common, and the prevalence is highly conditioned by the type of histologic lesion and the presence or absence of renal insufficiency.

In minimal change disease, the prevalence of hypertension is very low. It increases with the age of the patient and probably is not greater than in the general population matched for age and ethnic background.

In patients with membranous glomerulonephritis, the prevalence of hypertension is approximately 10%, but this value rises with worsening renal function.

In patients with focal and segmental glomerulosclerosis, the prevalence of hypertension is very high at the time of discovery of the disease (42% at onset), due in part to the impaired renal function. Blood pressure increases as renal function deteriorates.

Hypertension is also common among patients with *IgA nephropathy*. In a retrospective analysis of 374 patients, 36% of subjects had hypertension at the time of renal biopsy, while only 24% had renal insufficiency. After an average follow-up of 5 years, 63% of patients were hypertensive and 46% had impaired renal function [19]. This prevalence of hypertension in IgA glomerulonephritis is higher than in the healthy population, and has been confirmed [20].

D'Amico et al. have shown that the prevalence of hypertension in patients with IgA nephropathy varies with the type of renal histological lesion. Glomerular sclerosis, interstitial fibrosis and arteriolar hyalinosis were more likely to be associated with hypertension [21]. The presence of hypertension in patients with IgA nephropathy is associated with an adverse renal outcome. The 3 year renal survival is 70% after the onset of hypertension, and treatment of hypertension, particularly with an ACE inhibitor, may prolong the renal survival.

The pathophysiology of hypertension in IgA glomerulonephritis is uncertain. Zucchelli et al. [20] found normal levels of exchangeable sodium, whereas Valvo et al. [22] found expanded blood volume in both nor-

normotensive and hypertensive patients with IgA nephropathy. Valvo et al. described increased PVR in hypertensive patients and suggested that this might be related to increased sympathetic nervous system activity, but Zucchelli et al. found normal plasma NE levels in these patients.

Among patients with membranoproliferative glomerulonephritis (MPGN), hypertension is present in about 30% of patients at the onset of the disease, and the prevalence increases with worsening renal function.

Diabetes Mellitus (DM)

Diabetes mellitus and hypertension are commonly associated, and their frequency is increasing as our patient population ages. Diabetic patients show a higher prevalence of hypertension, particularly when diabetic nephropathy ensues. Hypertension in diabetic patients greatly increases the risk of cardiovascular disease, nephropathy, and retinopathy. Treatment of hypertension appears to delay the onset of these complications.

The pathophysiology of hypertension in diabetic patients is poorly understood. However, genetic factors, insulin resistance, abnormalities of sodium and calcium metabolism, increased activity of the sympathetic nervous system, and endothelial dysfunction appear to play a role.

In patients with insulin Type I DM, hypertension often develops in connection with the appearance of nephropathy. Patients without nephropathy usually remain normotensive. This has led some investigators to suggest that the susceptibility to renal disease in Type I DM patients is associated with a genetic predisposition to hypertension.

In patients with Type II DM, hypertension may follow but often precedes the development of diabetes. Several studies have shown

increased serum insulin concentrations in a substantial number of patients with essential hypertension and in normotensive offspring of hypertensive parents. Elevated insulin levels in patients with essential hypertension are a compensatory response to a defect in insulin-stimulated glucose uptake. This has led many investigators to postulate a causal relationship between hyperinsulinemia and hypertension, although this notion is not universally shared. Hyperinsulinemia is not present in some ethnic groups with high prevalence of essential hypertension, and hypertension is rare in ethnic groups, such as the Pima Indians, with a high prevalence of insulin resistance and hyperinsulinemia. Moreover, in some studies the relationship between hyperinsulinemia and hypertension could entirely be accounted for by obesity and age. In other studies, the relationship was found in individuals with normal body mass index, and in one study a negative correlation between hypertension and hyperinsulinemia was found.

Repetitive hyperinsulinemia occurring during food ingestion rather than baseline secretion could provide the stimulus for hypertensive mechanisms, such as sodium retention [23], stimulation of the sympathetic nervous system [24], and alteration of cation transport.

The causal relationship between hyperinsulinemia and hypertension remains controversial, mostly because administration of insulin leads to vasodilatation rather than vasoconstriction. It appears more likely that insulin resistance, rather than hyperinsulinemia, may be linked to hypertension. Resistance to the vasodilator action of insulin could lead to a rise in PVR and hypertension.

Some evidence suggests that alterations of calcium metabolism may contribute to insulin resistance and may cause increased PVR, exaggerated pressor response to vasoactive substances and hypertension in Type II DM patients.

Autosomal Dominant Polycystic Kidney Diseases (ADPKD)

Hypertension is very common in patients with ADPKD. In the series of Zeier et al. [25] the prevalence of hypertension, defined as casual blood pressure $\geq 140/90$ mm Hg, was as high as 82% in adults with ADPKD and normal renal function, and in virtually all ADPKD patients with impaired renal function. The rise in blood pressure may occur at a young age, even before any demonstrable manifestation of renal involvement. In a study of children and adolescents with ADPKD, circadian blood pressure profile, particularly nocturnal blood pressure, was significantly higher in patients with the disease than in matched controls, although most values were still $<140/90$ mm Hg. Left ventricular mass index was also significantly higher in children and adolescents with ADPKD than in matched controls.

The pathophysiology of hypertension in ADPKD is probably multifactorial [26]. Some studies have shown that patients with ADPKD, even with a normal GFR, have a reduced ability to excrete an acute sodium load and have an expanded extracellular volume and reduced PRA levels [27]. Certainly, hypertension in patients with ADPKD is sodium-sensitive, and dietary sodium restriction consistently decreases blood pressure in these patients. This is also substantiated by the presence of higher levels of atrial natriuretic peptide (ANP) in hypertensive patients with ADPKD than in controls [25].

Hypertensive ADPKD patients with normal or near normal renal function have a significantly higher intracellular sodium concentration and fractional sodium excretion, and a lower rate for ouabain-sensitive sodium efflux from erythrocytes. Studies suggest that abnormal cell sodium handling may play a role in the pathophysiology of hypertension in these patients.

Other studies have shown higher PRA levels in patients with ADPKD than in age- and blood pressure-matched controls. By immunostaining for renin, Graham et al. found hyperplasia of the juxtaglomerular apparatus in ADPKD kidneys [28]. The activation of the renin-angiotensin system seems to be a function of cyst size and rate of growth [29]. Renin concentration was increased in ADPKD cyst fluid compared with the concentration in fluid from simple renal cysts, and renin mRNA was expressed in the tubulocystic epithelium of patients with ADPKD, suggesting that the tubulocystic epithelium has the potential to synthesize renin. ACE inhibitors reduce blood pressure and renal vascular resistance without altering glomerular filtration rate (GFR) or urinary excretion of kallikrein and PGI₂ in these patients. These studies suggest that the decrease in renal blood flow in patients with ADPKD is due to activation of the renin-angiotensin system and that ACE inhibitors may be of particular value in the treatment of these patients. Harrap et al. [30] showed that reduced renal blood flow, higher PRA, and increased body sodium levels precede hypertension, because these changes occur in normotensive individuals with ADPKD.

There is also increased release of ET into the stretched and narrow arterioles and increased afferent nerve activity from the kidneys that may lead to an increase in sympathetic nervous system activity. Iversen et al. [31] found that muscle sympathetic nervous system activity was higher in patients with hypertension and ADPKD than in normal controls. However, in a different study, plasma NE levels were not different between hypertensive and normotensive patients with ADPKD [32].

Hydronephrosis

Hypertension is very common among patients with hydronephrosis. The exact mechanisms of hypertension in these patients are unknown, but an imbalance between vasoconstrictors, such as Ang II, and vasodilators, such as kallikrein, may play a role. In dogs with unilateral midureter occlusion, Vaughan et al. [33] observed a transient rise in blood pressure and in the activity of the renin-angiotensin system. After 6 months of ureteral occlusion, PRA was normal, but NE levels were elevated in the kidney with ureteral occlusion.

Among eight patients with unilateral hydronephrosis and hypertension, peripheral PRA was normal in 7 and borderline high in 1 [34]. Four patients had hydronephrotic/contralateral kidney renin ratio > 1.5 , suggesting excessive renin release from the diseased kidney. Nephrectomy normalized blood pressure in each of these patients. This study suggests that hypertension associated with unilateral hydronephrosis is partly renin dependent.

In patients with bilateral ureteral obstruction and decreased GFR, sodium retention and volume expansion also occur and participate in the genesis of hypertension. In these patients, relief of the obstruction result in postobstructive diuresis with a rapid normalization of the excessive volume and blood pressure.

The role of renal afferent nerves in the pathogenesis of hypertension associated with hydronephrosis has not been explored.

Chronic Pyelonephritis

There is an increased prevalence of hypertension in patients with pyelonephritis: 10% in children, 33% in adults, and 46% after a

mean follow-up of 69 months [35]. The pathogenesis of hypertension in this condition is uncertain. However, the presence of increased PRA in renal venous plasma from the diseased kidney in unilateral pyelonephritis lends support to the role of renin in the hypertension of chronic pyelonephritis.

Acute Renal Failure

The prevalence of hypertension is extremely high in patients with ARF due to glomerular or vascular diseases (approaching 90% in the more severe forms), but it is lower (10–15%) in patients with tubular-interstitial diseases. The pathophysiology of hypertension in ARF has not been well defined. Improvement of renal function in these patients results in resolution of hypertension in the majority of cases.

Hypertension is a frequent but not universal finding in patients with renal atheroembolic disease. When it occurs, it is often episodic, difficult to control, and probably related to activation of the renin-angiotensin system. The sporadic hypertension in this disorder may be related to repeated showers of atheromatous material to the kidney resulting in renal ischemia, activation of the renin-angiotensin system, and hypertension.

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