Hypertension in renal parenchymal disease: Why is it so resistant to treatment?

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The association between hypertension and chronic renal disease is well known. The pathogenesis of hypertension in patients with chronic kidney disease (CKD) is complex and multifactorial, which may explain why it is resistant to treatment. The traditional paradigm is that hypertension in CKD is due either to an excess of intravascular volume (volume dependent) or to excessive activation of the renin–angiotensin system in relation to the state of sodium/volume balance (renin-dependent hypertension). This review focuses on the importance of less established mechanisms, such as increased activity of the sympathetic nervous system, increased endothelin production, decreased availability of endothelium-derived vasodilators and structural changes of the arteries, renal ischemia, and sleep apnea.

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The association between hypertension and chronic renal disease is well known and renal diseases are by far the most common cause of secondary hypertension. The pathogenesis of hypertension in patients with chronic kidney disease (CKD) is complex and multifactorial, which may explain why it is resistant to treatment. The traditional paradigm is that hypertension in CKD is due either to an excess of intravascular volume (volume dependent) or to excessive activation of the renin–angiotensin system in relation to the state of sodium/volume balance (renin-dependent hypertension) (Table 1). In recent years, this concept has been challenged owing to the recognition that interventions aimed at reducing blood volume and inhibiting the renin–angiotensin system often do not normalize blood pressure (BP), and the unraveling of alternative pathogenic mechanisms (Table 1). Among these are increased activity of the sympathetic nervous system (SNS), increased endothelin (ET) production, decreased availability of endothelium-derived vasodilators/endothelial dysfunction, structural changes of the arteries, renal ischemia, and sleep apnea. In addition, pharmacological interventions aimed at treating the primary renal disease or some of its consequences, such as the use of cyclosporine, steroids, calcium with vitamin D, sympathomimetic agents, erythropoietin, and non-steroidal anti-inflammatory agents, may contribute to sustaining or aggravating hypertension in CKD patients.

This review will not address well-established mechanisms, such as sodium retention and activation of the renin–angiotensin system, both of which have been extensively reviewed.[1] The review will also not address the role of obesity and the metabolic syndrome in hypertension and renal disease, which would require a separate extensive discussion. We will instead emphasize the importance of less established mechanisms, with the belief that therapeutic interventions aimed at those alternative mechanisms may represent the key for adequate BP control in many CKD patients.

ROLE OF INCREASED SNS ACTIVITY

Increased SNS activity has been demonstrated in diverse experimental models,[2,3] as well as in patients with renal disease.[4] Animal studies have shown that the kidney is not only an elaborate filtering device but also a sensory organ, richly innervated with sensory and afferent nerves. Thus, in addition to being the target of the SNS activity, the kidney

Table 1 | Factors implicated in the pathogenesis of hypertension in kidney disease

Traditional factors
Sodium retention and volume excess
Activation of the renin–angiotensin system
Less recognized factors
Activation of the sympathetic nervous system
Renal ischemia
Sleep apnea
Deficit of endothelium-derived vasodepressor substances
Increased endothelin production
Reduced central dopaminergic tone
Reduced baroreceptor sensitivity/abnormal vagal function
Aldosterone
Oxidative stress
Structural changes of the arteries
Obesity/metabolic syndrome
Leptin
Increased plasma [*beta*]-endorphin
Increased [*beta*]-lipotropin
Serotonin
Iatrogenic factors
Erythropoietin
Cyclosporine
Steroids
Divalent ions and vitamin D
Sympathomimetic agents
NSAIDS

NSAID=non-steroidal anti-inflammatory agents.

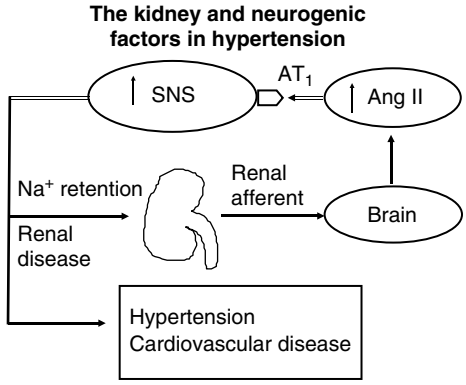

Figure 1 | This schema summarizes current concepts linking renal damage with increased sympathetic nervous system (SNS) activity. Renal damage/ischemia stimulates afferent pathways, which integrate with key brain structures involved in the noradrenergic control of blood pressure. The central mediator of this pathway appears to be angiotensin II, which stimulates SNS activity through specific angiotensin-1 (AT_1) receptors. Specific blockers of these receptors abrogate central SNS activation mediated by renal injury. Efferent SNS pathways may cause hypertension and contribute to cardiovascular and renal damage.

can also be the origin and modulator of this activity. There are two main functional types of renal sensory afferent nerve fibers: (a) hard and sensitive fibers, which increase their firing in response to changes in renal perfusion and intrarenal pressure and (b) chemosensitive fibers, which are stimulated by ischemic metabolites or uremic toxins.[5] The activation of these fibers may establish connections with integrative nuclei of the SNS in the central nervous system.[6,7] In experimental animals, stimulation of these afferent nerves by either ischemic metabolites such as adenosine, or by uremic toxins such as urea, evokes reflex increases in SNS activity and BP.[5] Chronic stimulation of these afferent nerves may lead to SNS overactivity and hypertension. This suggests that ischemic injury to the kidneys, owing to macro- or microvascular disease, may cause hypertension through the activation of these chemosensitive fibers.

Our studies on 5/6 nephrectomized (NPX) rats have provided the most convincing evidence for a role of the SNS in the pathogenesis of hypertension associated with kidney disease. The turnover rate[8] and the secretion of norepinephrine (NE)[9] from the posterior hypothalamic nuclei were greater in NPX than in control rats. Bilateral dorsal rhizotomy at the level T-10 to L-3 prevented the increase in BP and NE turnover in the posterior hypothalamic nuclei. These studies led us to postulate that increased renal sensory impulses generating in the affected kidney and then transmitted to the central nervous system activate brain regions involved in the noradrenergic control of BP resulting in hypertension. This concept is supported by studies in human subjects with end-stage renal disease (ESRD). Converse *et al.*[4] observed increased muscle sympathetic nerve activity (MSNA) and peripheral vascular resistance in hypertensive patients with ESRD. Bilateral NPX patients, on the other hand, manifested lower MSNA, BP, and peripheral vascular resistance compared to patients with native kidneys. In all, these findings support the notion that increased afferent nervous input from the kidney to the central nervous system may play an important role in the pathogenesis of hypertension in CKD and ESRD patients.

In our laboratory, we have developed a model of neurogenic hypertension caused by renal injury without measurable alterations in kidney function. In this model, the injection of 50 μl of phenol in the lower pole of one kidney causes an immediate and persistent elevation of BP and SNS activity in the rat; renal denervation prevents these effects.[9] The studies in the 5/6 NPX rat model, ESRD patients and the 'phenol–renal injury model' have clearly demonstrated that renal injury may activate renal afferent pathways and result in SNS activation and hypertension (Figure 1). Locally released angiotensin II appears to mediate central activation of SNS activity, as specific angiotensin II AT-1 receptor antagonists abrogate SNS activation caused by renal injury in the rat.[10]

One important primary event leading to increased SNS activity is probably renal ischemia. In patients with renovascular hypertension, Miyajima *et al.*[11] demonstrated increased levels of MSNA compared to patients with essential hypertension. Restoration of renal perfusion with renal angioplasty reduced MSNA and BP in these patients. Ligtenberg *et al.*[12] observed an increase in MSNA in patients with CKD and renin-dependent hypertension, when compared with controls, and Klein *et al.*[13] observed increased MSNA in hypertensive but not in normotensive patients with

polycystic kidney disease regardless of kidney function. One potential mechanism for cyclosporine-induced hypertension is through activation of renal afferent pathways, which result in the activation of efferent sympathetic nerves and decreases fractional excretion of sodium.[14]

Other mechanisms potentially responsible for the increase in SNS activity in uremic patients include reduced central dopaminergic tone,[15] reduced baroreceptors sensitivity,[16] abnormal vagal function,[17] increased plasma β-endorphin and β-lipotropin,[18] and increased serum leptin levels.[19]

The increased activity of the SNS does not only contribute to hypertension but it may also contribute to the progression of kidney disease and cardiovascular mortality in ESRD patients. Amann *et al.*[20] observed that proteinuria and the development of glomerulosclerosis were significantly attenuated by sympatholytic drug in subtotally NPX rats. Zoccali *et al.*[21] have shown a correlation between blood levels of NE and cardiovascular mortality in ESRD patients.

For the reasons exposed above, antiadrenergic drugs should be an important component of hypertension management in CKD patients. Of note, angiotensin-converting enzyme inhibitors and angiotensin receptor blockades partially reduce SNS activity, by interfering with effects of angiotensin II on SNS transmission both at peripheral and central sites.

SLEEP APNEA AND CIRCADIAN VARIABILITY OF BLOOD PRESSURE IN CKD

Sleep apnea is common among CKD patients and it may contribute to abnormal circadian BP variability, hypertension and cardiovascular disease.[22] Normally, BP tends to be the highest during the morning, gradually decreases during the course of the day and reaches the lowest levels at night. Approximately 10–25% of patients with essential hypertension does not display the normal nocturnal dipping of BP and are called 'non-dippers', as opposed to those with a normal circadian rhythm who are called 'dippers'. Among CKD patients,[23] and those on maintenance hemodialysis,[24] the prevalence of non-dippers is 74–82%. Sometimes, in these patients, BP during the night can be greater than that measured during the day (nocturnal hypertension). The phenomena of non-dipping and nocturnal hypertension have been associated with greater risk of cardiac concentric hypertrophy, and cardiovascular events in ESRD patients.[25]

Several mechanisms may be responsible for the phenomena of non-dipping in patients with CKD including extracellular volume expansion, uremic neuropathy, and restless leg syndrome. However, sleep disordered breathing also seems to play an important role. Oxygen desaturation, triggered by sleep apnea, occurs in 21–47% of ESRD patients, and it may contribute to raising BP through the activation of chemoreceptors connected with the SNS. Removal of excessive volume with dialysis[26] or treatment with nasal continuous positive pressure may improve nocturnal oxygen desaturation, and reduce SNS activity and BP in these patients.[27]

ROLE OF THE VASCULAR ENDOTHELIUM

The role of the endothelium in vascular and renal physiology and pathology is well recognized. A number of investigators have speculated that an altered balance between endothelium-derived relaxing factors and endothelium-derived constricting factors may play a role in hypertension associated with kidney disease.[28]

ENDOTHELIUM-DERIVED VASOCONSTRICTOR FACTORS

The role of ET in CKD-related hypertension has been the focus of active research and controversy. Two distinct complementary DNAs of ET receptors have been identified. The ET-A receptor is predominately expressed on vascular smooth muscle cells, where its action mediates vasoconstriction. The ET-B receptor is predominately found on endothelial cells, where its action promotes vasodilation via the release of nitric oxide (NO) and prostacyclin.[29] ET-1's affinity for the ET-A receptor is the greatest (ET-1 > ET-2 > ET-3), likely related to its almost irreversible binding to the receptor lasting greater than 2 h. ET-B receptors have equal affinity for all three isoforms.

ETs have a variety of actions, some of which are related to the maintenance of vascular tone. The role of ET in the regulation of vascular tone has been studied in animal and human models through the use of selective receptor antagonists.[30] ET-A blockade results in vasodilatation, probably as a result of an increase in NO generation. By contrast, blockade of ET-B receptors results in vasoconstriction, indicating that there is a balance between the two receptor actions.[31] In addition to its contractile actions on vascular smooth muscle, ET can also modulate SNS activity.[32]

Some controversy exists whether ET secretion exerts a primary role in hypertension or whether it is the result of vascular injury caused by the shear stress or by vasoconstrictors. Cytokines, thrombin, vasoactive hormones such as epinephrine, vasopressin and angiotensin II, and oxidative stress stimulate ET release from endothelial cells, suggesting a secondary role. Interestingly, angiotensin II's stimulation of ET-1 release has been shown to be mediated by oxidative stress. Ortiz *et al.*[33] infused angiotensin II chronically causing hypertension in rats, all of which were blocked by both an antioxidant and ET receptor blockade.

ET may also exert effects on renal tubular sodium handling. The predominant receptor in the kidney is the ET-B receptor,[34] and its activation results in natriuresis. ET-B receptor antagonists exacerbate hypertension in high salt diet-fed rats, although ET-A blockade reverses the hypertension to normal.[35] It has also been shown that ET-B receptor-deficient rats develop salt-sensitive hypertension.[36]

Increased plasma ET-1 levels have been shown in patients with essential hypertension by some investigators[37] but not by others.[38] The systemic levels may not be as important given that ET is released on the basolateral surface and exerts its effect in a paracrine and autocrine manner on nearby endothelial and smooth muscle cells. Hypertensive patients

with CKD[39] and ESRD[40] display higher plasma levels of ET-1 and ET-3 than normotensive subjects. It is unclear whether this is the result of the uremic state or the exposure of blood to an extracorporeal circuit during hemodialysis. ET receptor antagonists have been shown to significantly reduce BP in patients with essential hypertension[41] and to reduce blood pressure and proteinuria in CKD patients.[42] The place of ET-1 antagonists in the management of hypertension in CKD and ESRD patients remains to be further explored.

ENDOTHELIUM-DERIVED VASODILATOR FACTORS

Endothelial cells cause vasodilatation in response to increases in flow, shear stress and agonists through the release of several mediators, which include prostaglandin I_2, endothelium-derived hyperpolarizing factor and NO. The formation of NO by NO synthase (NOS) in the vascular endothelium from the amino-acid L-arginine has opened up a new area of biological research. Several forms of NOS have been identified; endothelial NOS regulates endothelial function and vascular tone, whereas the neuronal isoform of NOS (nNOS) modulates SNS activity.

Impaired endothelium-dependent vasodilation has been observed in CKD and ESRD patients.[43,44] In 5/6 NPX rats, Vaziri *et al.*[45] observed downregulation of endothelial and inducible NOS, and suggested that this may contribute to the BP elevation. Chronic inhibition of NO synthesis by N^G-nitro–L-arginine methyl ester (L-NAME) has been used as a model of arterial hypertension in animals. Administration of nitro-L-arginine to rats causes systemic hypertension, marked renal vasoconstriction and hypoperfusion, as well as a fall in glomerular filtration rate.[46] Sakuma *et al.*[47] have also shown that the increase in renal SNS activity and in BP after administration of N^G-methyl-L-arginine (NOS inhibitor) to male Wistar rats could be reduced by spinal C1–C2 transection, implying that NO may play a role in the central regulation of SNS tone. nNOS is present in a specific area of the brain involved in the modulation of the noradrenergic control of BP[48,49] and is an important component of transduction pathways that tonically inhibit SNS activity.[3] A decrease in central nNOS may result in greater SNS activity and BP. However, in Sprague–Dawley 5/6 NPX rats, we observed that nNOS mRNA gene expression and NO_2/NO_3 content were increased in several brain nuclei involved in the noradrenergic control of BP. L-NAME increased BP and NE turnover rate in those brain nuclei. These studies suggest that the increase in central SNS activity in chronic renal failure rats may be partially mitigated by increased expression of nNOS mRNA in the brain.[3] Some evidence also indicates that NO may modulate peripheral sympathetic neurotransmission.[50]

Vallance *et al.*[49] have shown both *in vitro* and *in vivo* that NO synthesis can be inhibited by an endogenous compound, *NGNG*-dimethylarginine (asymmetrical dimethylarginine). ESRD patients on chronic hemodialysis display significantly higher plasma levels of asymmetrical dimethylarginine and significantly lower plasma arginine-to-dimethylarginine ratio, suggesting asymmetrical dimethylarginine may contribute to hypertension in these patients.[48] In CKD patients, asymmetrical dimethylarginine levels correlated with severity of atherosclerosis,[51] cardiovascular events and mortality.[52]

ROLE OF ARTERIAL STRUCTURAL CHANGES

The importance of large artery function has also been recognized as a factor contributing to hypertension and cardiovascular disease. The distensibility of large vessels serves as a protective mechanism. The heart generates a large forward pressure wave distending the aorta, creating a reflection wave that increases diastolic coronary perfusion and dampens the pressure on the distal microcirculation, preventing mechanical damage.[53] Distensibility is measured by aortic pulse wave velocity, which is simple, non-invasive, and reproducible. Increased aortic stiffness is seen with advancing age, smoking, diabetes mellitus, and CKD, and it is recognized as an independent predictor of cardiovascular risk in hypertensive[54] and CKD patients.[55] Increased aortic stiffness coincides with elevation in systolic BP, and an elevated pulse pressure, which is a strong predictor of cardiovascular mortality in ESRD patients.[56] The two factors that determine distensibility are pressure and the vessel wall structure. The layer of smooth muscle in the vessel wall is substantial, and is regulated by multiple factors including but not limited to sympathetic tone, catecholamines, and endothelial-derived vasoactive substances including NO and ET-1. Uremic patients and laboratory animals with CKD manifest both functional and morphologic changes of resistance arteries, which affect distensibility.[57] Morphological changes include hyperplasia of smooth muscle cells, calcification of media and increased intima-media thickness owing to raised extracellular matrix content. Disturbed calcium–phosphorus balance and secondary hyperparathyroidism contribute to the morphological and functional changes of arteries.[58] These structural changes may supervene during the course of CKD and contribute to sustaining BP, increasing its severity and reducing the response to pharmacological interventions.

Therapeutic modalities aimed at decreasing structural changes in the vessel wall will eventually become an essential component of management. To date, we know that inhibitors of the renin–angiotensin system decrease aortic collagen production in animal models;[59] statins may also decrease arterial stiffness.[60] Studies are now underway looking at drugs that interfere with the advanced glycation end products of collagen and hormone replacement therapy.

RENAL ISCHEMIA

The connection between atherosclerotic renal artery disease and hypertension is well recognized. Also well established is the pathogenic role of the renin–angiotensin system. It is also clear that correction of a renal artery stenosis does not always result in improvement or normalization of BP. Renal artery stenosis, particularly if unilateral, is often an incidental finding or plays a marginal role in hypertension associated

with CKD. Less appreciated is the link between ischemic nephropathy caused by microvascular renal disease and hypertension. Ischemic nephropathy is usually defined as a progressive decrease in glomerular filtration rate owing to atherosclerosis of the main renal arteries. This concept is too restrictive and it does not take into account that atherosclerosis of the renal microcirculation may also lead to renal ischemia, progressive renal failure and contribute to hypertension. Upregulation of the renin–angiotensin system, hypercholesterolemia, upregulation of growth-promoting factors (transforming growth factor-β, leptin, etc.), oxidative stress, and inflammation may all contribute to microvascular disease and hypertension. Microvascular renal disease may also ensue as a result of tubulo-interstitial inflammation and sclerosis, increased interstitial hydrostatic pressure or accumulation of adipose tissue in the interstitium. The role of this type of ischemia and the mechanisms leading to hypertension are less known. The kidney receives a huge supply of oxygenated blood, less than 10% of which it needs for its own metabolic survival. Potentially, intrarenal chemoreceptors could be stimulated by ischemic metabolites, such as adenosine, evoking reflex increases in SNS activity and blood pressure. Adenosine exerts an important role in the pathogenesis of one-clip one-kidney model of hypertension in rats.[61]

OXIDATIVE STRESS AND HYPERTENSION

Considerable attention has been given to the effects of short-lived reactive oxygen species (ROS) and reactive nitrogen species on blood pressure and cardiovascular toxicity. Oxygen radicals and endogenous scavenging systems, such as superoxide dismutase, modulate vascular tone and function. ROS production is increased in several experimental models of hypertension[62,63] and in human hypertension.[64] Vaziri *et al.*[65] have shown that ROS are increased in uremic rats and they react with NO-producing cytotoxic reactive nitrogen species capable of nitrating proteins and damaging other molecules. Antioxidant therapy ameliorated the CKD-induced hypertension, improved vascular tissue NO production and lowered tissue nitrotyrosine. Depletion of glutathione, an endogenous scavenger of ROS, by means of the GSH synthase inhibitor, butathionine sulfoximine (BSO), caused a marked elevation of nitrotyrosine, the footprint of peroxynitrite, and marked elevation of BP in rats.[66]

Whether ROS in hypertension are increased as a result of vasoconstriction or are causative remains to be determined. A causative role is supported by evidence that scavengers of ROS ameliorate hypertension in animal models. Agents such as dimercaptosuccinic acid, lazaroids, cicletanine, tempol (a superoxide dismutase mimetic), and vitamins C and E have been utilized to successfully reduce BP in animal models of hypertension.[67,68] The exact mechanism through which oxidative stress may raise BP has not been fully elucidated. ROS may stimulate vascular contraction directly or through quenching of the vasodilator NO and production of peroxinitrite.[69] One possibility is that ROS may play a role in the regulatory processes of noradrenergic transmission in the brain.

We have shown that tempol (4-hydroxy-2,2,6,6-tetramethyl piperidinoxyl), a superoxide dismutase mimetic, when injected in the lateral ventricle of rats, increases the abundance of IL-1β and nNOS in the posterior hypothalamic and paraventricular nuclei, and this is associated with reduced NE secretion from the posterior hypothalamic and lower BP.[70] In the phenol–renal injury model of hypertension in rat, we have shown that tempol prevents the activation of SNS and the rise in blood pressure caused by renal injury. These data support the hypothesis that oxygen radicals may modulate central SNS activation through regulation of local NO production and contribute to hypertension in renal injury models.

The role of antioxidants in the management of hypertension in CKD remains speculative.

ROLE OF IATROGENIC FACTORS

Several iatrogenic factors may contribute to hypertension in patients with CKD (Table 1). Among these, the rising use of recombinant human erythropoietin is of concern. Recombinant human erythropoietin has substantially improved the management of anemia and reduced the risk of heart failure in ESRD and CKD patients and perhaps retard the progression of kidney disease and heart disease. However, increasing the hematocrit with recombinant human erythropoietin can worsen BP control.[71] Hypertension induced by recombinant human erythropoietin has been attributed to increased blood viscosity, enhanced pressor responsiveness to NE and angiotensin-II, direct vasoconstrictor action, increased cytosolic calcium, increased blood serotonin or ET-1 levels.[72]

REFERENCES

1. Campese VM, Tanacescu A. Hypertension in dialysis patients. In: Henrich WL (ed). *Principles and Practice of Dialysis*. Lippincott Williams & Wilkins: Philadelphia, 2004, pp 227–256.
2. Campese VM, Kogosov E, Koss M. Renal afferent denervation prevents the progression of renal disease in the renal ablation model of chronic renal failure in the rat. *Am J Kidney Dis* 1995; **26**: 861–865.
3. Ye S, Nosrati S, Campese VM. Nitric oxide (NO) modulates the neurogenic control of blood pressure in rats with chronic renal failure (CRF). *J Clin Invest* 1997; **99**: 540–548.
4. Converse Jr RL, Jacobsen TN, Toto RD *et al.* Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327**: 1912–1918.
5. Katholi RE. Renal nerves and hypertension: an update. *Fed Proc* 1985; **44**: 2846–2850.
6. Faber JE, Brody MJ. Afferent renal nerve-dependent hypertension following acute renal artery stenosis in the conscious rat. *Circ Res* 1985; **57**: 676–688.
7. Calaresu FR, Ciriello J. Renal afferent nerves affect discharge rate of medullary and hypothalamic single units in the cat. *J Auton Nerv Syst* 1981; **3**: 311–320.
8. Bigazzi R, Kogosov E, Campese VM. Altered norepinephrine turnover in the brain of rats with chronic renal failure. *J Am Soc Nephrol* 1994; **4**: 1901–1907.
9. Ye S, Ozgur B, Campese VM. Renal afferent impulses, the posterior hypothalamus, and hypertension in rats with chronic renal failure. *Kidney Int* 1997; **51**: 722–727.
10. Ye S, Zhong H, Duong VN, Campese VM. Losartan reduces central and peripheral sympathetic nerve activity in a rat model of neurogenic hypertension. *Hypertension* 2002; **39**: 1101–1106.

11. Miyajima E, Yamada Y, Yoshida Y *et al.* Muscle sympathetic nerve activity in renovascular hypertension and primary aldosteronism. *Hypertension* 1991; **17**: 1057–1062.
12. Ligtenberg G, Blankestijn PJ, Oey PL *et al.* Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure. *N Engl J Med* 1999; **340**: 1321–1328.
13. Klein IH, Ligtenberg G, Oey PL *et al.* Sympathetic activity is increased in polycystic kidney disease and is associated with hypertension. *J Am Soc Nephrol* 2001; **12**: 2427–2433.
14. Zhang W, Li JL, Hosaka M *et al.* Cyclosporine A-induced hypertension involves synapsin in renal sensory nerve endings. *Proc Natl Acad Sci USA* 2000; **97**: 9765–9770.
15. Kuchel OG, Shigetomi S. Dopaminergic abnormalities in hypertension associated with moderate renal insufficiency. *Hypertension* 1994; **23**: I240–245.
16. Pickering TG, Gribbin B, Oliver DO. Baroreflex sensitivity in patients on long-term haemodialysis. *Clin Sci* 1972; **42**: 10P.
17. Zucchelli P, Catizone L, Esposti ED *et al.* Influence of ultrafiltration on plasma renin activity and adrenergic system. *Nephron* 1978; **21**: 317–324.
18. Elias AN, Vaziri ND. Plasma catecholamines in chronic renal disease. *Int J Artif Organs* 1985; **8**: 243–244.
19. Wolf G, Chen S, Han DC, Ziyadeh FN. Leptin and renal disease. *Am J Kidney Dis* 2002; **39**: 1–11.
20. Amann K, Rump LC, Simonaviciene A *et al.* Effects of low dose sympathetic inhibition on glomerulosclerosis and albuminuria in subtotally nephrectomized rats. *J Am Soc Nephrol* 2000; **11**: 1469–1478.
21. Zoccali C, Mallamaci F, Parlongo S *et al.* Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 2002; **105**: 1354–1359.
22. Zoccali C, Benedetto FA, Tripepi G *et al.* Nocturnal hypoxemia, night-day arterial pressure changes and left ventricular geometry in dialysis patients. *Kidney Int* 1998; **53**: 1078–1084.
23. Farmer CK, Goldsmith DJ, Cox J *et al.* An investigation of the effect of advancing uraemia, renal replacement therapy and renal transplantation on blood pressure diurnal variability. *Nephrol Dial Transplant* 1997; **12**: 2301–2307.
24. Peixoto AJ, White WB. Ambulatory blood pressure monitoring in chronic renal disease: technical aspects and clinical relevance. *Curr Opin Nephrol Hypertens* 2002; **11**: 507–516.
25. Amar J, Vernier I, Rossignol E *et al.* Nocturnal blood pressure and 24-hour pulse pressure are potent indicators of mortality in hemodialysis patients. *Kidney Int* 2000; **57**: 2485–2491.
26. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med* 2001; **344**: 102–107.
27. Pressman MR, Benz RL, Schleifer CR, Peterson DD. Sleep disordered breathing in ESRD: acute beneficial effects of treatment with nasal continuous positive airway pressure. *Kidney Int* 1993; **43**: 1134–1139.
28. Shultz PJ. An emerging role for endothelin in renal disease. *J Lab Clin Med* 1992; **119**: 448–449.
29. Gray GA, Webb DJ. The endothelin system and its potential as a therapeutic target in cardiovascular disease. *Pharmacol Ther* 1996; **72**: 109–148.
30. Haynes WG, Ferro CJ, O'Kane KP *et al.* Systemic endothelin receptor blockade decreases peripheral vascular resistance and blood pressure in humans. *Circulation* 1996; **93**: 1860–1870.
31. Verhaar MC, Strachan FE, Newby DE *et al.* Endothelin-A receptor antagonist-mediated vasodilatation is attenuated by inhibition of nitric oxide synthesis and by endothelin-B receptor blockade. *Circulation* 1998; **97**: 752–756.
32. Hoang D, Macarthur H, Gardner A, Westfall TC. Endothelin-induced modulation of neuropeptide Y and norepinephrine release from the rat mesenteric bed. *Am J Physiol Heart Circ Physiol* 2002; **283**: H1523–1530.
33. Ortiz MC, Manriquez MC, Romero JC, Juncos LA. Antioxidants block angiotensin II-induced increases in blood pressure and endothelin. *Hypertension* 2001; **38**: 655–659.
34. Davenport AP, Morton AJ, Brown MJ. Localization of endothelin-1 (ET-1), ET-2, and ET-3, mouse VIC, and sarafotoxin S6b binding sites in mammalian heart and kidney. *J Cardiovasc Pharmacol* 1991; **17**(Suppl 7): S152–S155.
35. Pollock DM, Pollock JS. Evidence for endothelin involvement in the response to high salt. *Am J Physiol Renal Physiol* 2001; **281**: F144–F150.
36. Gariepy CE, Ohuchi T, Williams SC *et al.* Salt-sensitive hypertension in endothelin-B receptor-deficient rats. *J Clin Invest* 2000; **105**: 925–933.
37. Saito Y, Nakao K, Mukoyama M, Imura H. Increased plasma endothelin level in patients with essential hypertension. *N Engl J Med* 1990; **322**: 205.
38. Schiffrin EL, Thibault G. Plasma endothelin in human essential hypertension. *Am J Hypertens* 1991; **4**: 303–308.
39. Koyama H, Tabata T, Nishzawa Y *et al.* Plasma endothelin levels in patients with uraemia. *Lancet* 1989; **1**: 991–992.
40. Suzuki N, Matsumoto H, Miyauchi T *et al.* Endothelin-3 concentrations in human plasma: the increased concentrations in patients undergoing haemodialysis. *Biochem Biophys Res Commun* 1990; **169**: 809–815.
41. Krum H, Viskoper RJ, Lacourciere Y *et al.* The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. Bosentan Hypertension Investigators. *N Engl J Med* 1998; **338**: 784–790.
42. Goddard J, Eckhart C, Johnston NR *et al.* Endothelin A receptor antagonism and angiotensin-converting enzyme inhibition are synergistic via an endothelin B receptor-mediated and nitric oxide-dependent mechanism. *J Am Soc Nephrol* 2004; **15**: 2601–2610.
43. Thambyrajah J, Landray MJ, McGlynn FJ *et al.* Abnormalities of endothelial function in patients with predialysis renal failure. *Heart* 2000; **83**: 205–209.
44. Passauer J, Bussemaker E, Range U *et al.* Evidence *in vivo* showing increase of baseline nitric oxide generation and impairment of endothelium-dependent vasodilation in normotensive patients on chronic hemodialysis. *J Am Soc Nephrol* 2000; **11**: 1726–1734.
45. Vaziri ND, Ni Z, Wang XQ *et al.* Downregulation of nitric oxide synthase in chronic renal insufficiency: role of excess PTH. *Am J Physiol* 1998; **274**: F642–F649.
46. Chen PY, Sanders PW. -arginine abrogates salt-sensitive hypertension in Dahl/Rapp rats. *J Clin Invest* 1991; **88**: 1559–1567.
47. Sakuma I, Togashi H, Yoshioka M *et al. NG*-methyl-L-arginine, an inhibitor of L-arginine-derived nitric oxide synthesis, stimulates renal sympathetic nerve activity *in vivo*. A role for nitric oxide in the central regulation of sympathetic tone? *Circ Res* 1992; **70**: 607–611.
48. Anderstam B, Katzarski K, Bergstrom J. Serum levels of *NG NG*-dimethyl-L-arginine, a potential endogenous nitric oxide inhibitor in dialysis patients. *J Am Soc Nephrol* 1997; **8**: 1437–1442.
49. Vallance P, Leone A, Calver A *et al.* Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. *Lancet* 1992; **339**: 572–575.
50. Kolo LL, Westfall TC, Macarthur H. Nitric oxide decreases the biological activity of norepinephrine resulting in altered vascular tone in the rat mesenteric arterial bed. *Am J Physiol Heart Circ Physiol* 2004; **286**: H296–H303.
51. Kielstein JT, Boger RH, Bode-Boger SM *et al.* Asymmetric dimethylarginine plasma concentrations differ in patients with end-stage renal disease: relationship to treatment method and atherosclerotic disease. *J Am Soc Nephrol* 1999; **10**: 594–600.
52. Zoccali C, Bode-Boger S, Mallamaci F *et al.* Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study. *Lancet* 2001; **358**: 2113–2117.
53. Mitchell GF, Parise H, Benjamin EJ *et al.* Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 2004; **43**: 1239–1245.
54. Blacher J, Asmar R, Djane S *et al.* Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999; **33**: 1111–1117.
55. Blacher J, Guerin AP, Pannier B *et al.* Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; **99**: 2434–2439.
56. Klassen PS, Lowrie EG, Reddan DN *et al.* Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. *JAMA* 2002; **287**: 1548–1555.
57. Morris ST, McMurray JJ, Spiers A, Jardine AG. Impaired endothelial function in isolated human uremic resistance arteries. *Kidney Int* 2001; **60**: 1077–1082.
58. Rostand SG, Drueke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int* 1999; **56**: 383–392.
59. Albaladejo P, Bouaziz H, Duriez M *et al.* Angiotensin converting enzyme inhibition prevents the increase in aortic collagen in rats. *Hypertension* 1994; **23**: 74–82.
60. Ferrier KE, Muhlmann MH, Baguet JP *et al.* Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. *J Am Coll Cardiol* 2002; **39**: 1020–1025.
61. Katholi RE, Whitlow PL, Hageman GR, Woods WT. Intrarenal adenosine produces hypertension by activating the sympathetic nervous system via the renal nerves in the dog. *J Hypertens* 1984; **2**: 349–359.

62. Kerr S, Brosnan MJ, McIntyre M *et al.* Superoxide anion production is increased in a model of genetic hypertension: role of the endothelium. *Hypertension* 1999; **33**: 1353–1358.
63. Vaziri ND, Liang K, Ding Y. Increased nitric oxide inactivation by reactive oxygen species in lead-induced hypertension. *Kidney Int* 1999; **56**: 1492–1498.
64. Touyz RM, Schiffrin EL. Increased generation of superoxide by angiotensin II in smooth muscle cells from resistance arteries of hypertensive patients: role of phospholipase D-dependent NAD(P)H oxidase-sensitive pathways. *J Hypertens* 2001; **19**: 1245–1254.
65. Vaziri ND, Ni Z, Oveisi F, Liang K, Pandian R. Enhanced nitric oxide inactivation and protein nitration by reactive oxygen species in renal insufficiency. *Hypertension* 2002; **39**: 135–141.
66. Vaziri ND, Wang XQ, Oveisi F, Rad B. Induction of oxidative stress by glutathione depletion causes severe hypertension in normal rats. *Hypertension* 2000; **36**: 142–146.
67. Gonick HC, Cohen AH, Ren Q *et al.* Effect of 2,3-dimercaptosuccinic acid on nephrosclerosis in the Dahl rat. I. Role of reactive oxygen species. *Kidney Int* 1996; **50**: 1572–1581.
68. Vaziri ND, Ding Y, Ni Z, Gonick HC. Altered nitric oxide metabolism and increased oxygen free radical activity in lead-induced hypertension: effect of lazaroid therapy. *Kidney Int* 1997; **52**: 1042–1046.
69. Hu Q, Corda S, Zweier JL *et al.* Hydrogen peroxide induces intracellular calcium oscillations in human aortic endothelial cells. *Circulation* 1998; **97**: 268–275.
70. Campese VM, Ye S, Zhong H *et al.* Reactive oxygen species stimulate central and peripheral sympathetic nervous system activity. *Am J Physiol Heart Circ Physiol* 2004; **287**: H695–703.
71. Eschbach JW, Kelly MR, Haley NR *et al.* Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. *N Engl J Med* 1989; **321**: 158–163.
72. Vaziri ND. Mechanism of erythropoietin-induced hypertension. *Am J Kidney Dis* 1999; **33**: 821–828.