© 2011 International Society of Nephrology

Major pathways of the reno–cardiovascular link: the sympathetic and renin–angiotensin systems

Peter J. Blankestijn[1], Gerard London[2], Danilo Fliser[3], Kitty J. Jager[4], Bengt Lindholm[5], David Goldsmith[6], Andrzej Wiecek[7], Gultekin Suleymanlar[8], Rajiv Agarwal[9], Alberto Ortiz[10], Ziad Massy[11,12], Alberto Martinez-Castelao[13], Adrian Covic[14], Friedo W. Dekker[15] and Carmine Zoccali[16], EUropean REnal and CArdiovascular Medicine working group of the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA)

[1]Department of Nephrology, University Medical Center, Utrecht, The Netherlands; [2]INSERM U970, Hôpital Européen Georges Pompidou, Paris, France; [3]Department of Internal Medicine IV, Saarland University Medical Centre, Homburg/Saar, Germany; [4]ERA–EDTA Registry, Department of Medical Informatics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [5]Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; [6]Renal Unit, Guy's and St Thomas' NHS Foundation Hospital, King's Health Partners, London, UK; [7]Division of Internal Medicine and Nephrology, Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia, Katowice, Poland; [8]Nephrology Division, Department of Medicine, Akdeniz University Medical School, Antalya, Turkey; [9]Indiana University and VAMC, Indianapolis, Indiana, USA; [10]Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Fundación Renal Iñigo Alvarez de Toledo, Madrid, Spain; [11]INSERM ERI-12 (EA 4292), Amiens and Amiens University France, Amiens, France; [12]Amiens University Hospital and the Jules Verne University of Picardie, Amiens, France; [13]Hospital Universitario de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain; [14]Clinic of Nephrology, C.I. Parhon University Hospital, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania; [15]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands and [16]Nephrology, Dialysis and Transplantation Unit and CNR-IBIM Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension, Reggio Calabria, Italy

Chronic kidney disease is often characterized by enhanced activity of the renin–angiotensin system (RAS) and the sympathetic nervous system. Independent of their effect on blood pressure, these systems also contribute to the pathogenesis of both structural and functional cardiovascular abnormalities and contribute importantly to clinical outcome. There is much evidence that the diseased kidneys are of central importance in the pathogenesis of both abnormalities. Inhibitors of the RAS also reduce sympathetic overactivity. Future research should be aimed at addressing the pathophysiological mechanisms causing the enhanced activities. Given the fact that even a small kidney lesion can cause enhanced activity of the RAS and the sympathetic nervous system, it is likely that these pathophysiological mechanisms are operational in more disease conditions, including essential hypertension, heart failure, and obesity/metabolic syndrome.

Kidney International Supplements (2011) **1,** 13–16; doi:10.1038/kisup.2011.3

KEYWORDS: chronic kidney disease; hypertension; renin angiotensin; sympathetic activity

TO CITE THIS ARTICLE:
Blankestijn PJ, London G, Fliser D *et al.* Major pathways of the reno–cardiovascular link: the sympathetic and renin–angiotensin systems. *Kidney Int Sup* 2011; **1**: 13–16.

Correspondence: *Peter J. Blankestijn, Department of Nephrology, University Medical Center, Room F03.220, PO Box 85500, 3508 GA, Utrecht, The Netherlands. E-mail: P.J.Blankestijn@umcutrecht.nl*

Both the renin–angiotensin system (RAS) and the sympathetic nervous system are often activated in chronic kidney disease (CKD). Independent of their effect on blood pressure, these systems also contribute to the pathophysiology of both structural and functional cardiovascular (CV) abnormalities and contribute significantly to clinical outcome. There is conclusive evidence that these systems do not operate independently, but interact throughout the CV system.

In multiple species, including humans, kidney ischemia leads to renin secretion. Inappropriate renin secretion in relation to the state of sodium-volume balance has long been recognized. Kidney ischemia is the central mechanism of stimulation of the RAS and leads to high sympathetic nerve activity (review by Siddiqi *et al.*[1]). In humans, intravenous infusion of angiotensin II (AngII) stimulates muscle sympathetic nerve activity (MSNA), which is the centrally originated sympathetic outflow toward resistance vasculature. Even a small locus of injury in one kidney, caused by intrarenal injection of phenol, which does not affect glomerular filtration rate, leads to hypertension in association with increased central sympathetic activity.[2] Renal denervation or unilateral nephrectomy results in a reduction or total prevention of hypertension.[2] Long-term low-dose AngII infusion in rats produces a gradual increase in blood pressure, which was partially prevented by kidney denervation. Using the kidney transplantation model, very convincing evidence is presented that kidney AngII receptors are of crucial importance in the pathogenesis of AngII-mediated hypertension and organ

damage. Experimental studies suggest that AngII can act on different sites, that is, in the kidney, in the central nervous system, and on peripheral sites, enhancing noradrenaline release from sympathetic nerve terminals. Whether the effects of kidney injury on sympathetic nerve activity at the kidney level are direct or mediated by AngII is unclear. Further, increased sympathetic activity enhances the renin system. Therefore, there may be a reciprocal potentiation. Thus, kidney injury, which is generally characterized by an increased activity of the RAS, can lead to high sympathetic nerve activity, hypertension, and organ damage. Renal innervation has a crucial role, because all these abnormalities are largely prevented by destruction of the renal nerves, at least in experimental settings (review by Siddiqi *et al.*[1]).

CLINICAL EVIDENCE OF SYMPATHETIC HYPERACTIVITY IN CKD

In CKD patients, there is the parallel activation of the renin and the sympathetic system.[1] Further, in normal subjects and in CKD patients, both systems show parallel shifts, with changes in fluid status.[3] These findings are very compatible with the idea of a cause and effect relationship or a common origin. Bilateral nephrectomy in CKD patients results in MSNA levels comparable to normal, whereas unilateral nephrectomy in healthy persons for transplantation purposes does not result in change in MSNA.[3] In CKD patients not on dialysis, with a creatinine clearance ranging from 10 to 100 ml/min, and in healthy controls, sympathetic activity increases with age, both in controls and in patients; however, for any age, sympathetic activity in patients is higher than in controls. In hemodialysis patients, MSNA is even higher.[4]

In sum, there seem to be (at least) two types of sympathetic activity: a kind of 'baseline activity', present in healthy controls, which exits also in bilaterally nephrectomized patients when variables of the RAS are undetectable, and an additional type, which is generated in diseased kidneys. This last type closely correlates with the activation of the RAS. The pathophysiological mechanisms are discussed in more detail elsewhere.[5,6]

CLINICAL RELEVANCE

There is vast experimental evidence linking sympathetic activity to CV organ damage. In humans as well, there is direct evidence to suggest that this is the case. For instance, sympathetic activity correlated with blood pressure.[1] Much more importantly, it has been shown that sympathetic activity is associated with CV organ damage and outcome. There are a number of studies showing the relationship between sympathetic activity and left ventricular mass (review by Siddiqi *et al.*[1] and Mancia *et al.*[7]). Such a relationship is also established in CKD patients.[8] More recently, it was reported in CKD patients not on dialysis that left ventricular mass (quantified by magnetic resonance imaging) is greater than in controls.[9] Importantly, sympathetic activity quantified by MSNA correlated closely with left ventricular mass, despite the fact that blood pressure was reasonably well controlled and all patients were on a RAS inhibitor. In fact, MSNA appears to be a predictor for left ventricular mass independently of blood pressure and other relevant factors. In hemodialysis patients, the relationship between plasma noradrenaline and all-cause mortality and CV morbidity and mortality was established a few years ago.[10] Recently, this relationship was also reported in predialysis patients.[11] Several data sets suggest that sympathetic activity is also involved in kidney failure progression (review by Joles and Koomans[6]). Thus, to summarize, there is substantial evidence that sympathetic activity contributes at several levels to the development of CV organ damage.

TREATMENT

With these pathophysiological mechanisms in mind, it seems logical to hypothesize that angiotensin-converting enzyme inhibition reduces this sympathetic hyperactivity. Indeed, more than a decade ago it was shown that enalapril reduced MSNA in CKD patients.[12] Importantly, use of amlodipine, although an effective antihypertensive, resulted in an increase in MSNA.[12] The study showed that, by inhibiting RAS, sympathetic activity was reduced. Over the past few years, in a set of studies in CKD patients, the effect of different agents was evaluated, including enalapril, losartan, eprosartan, and aliskiren. The effects of the tested agents in the dosage used in these studies did not differ much. During these treatments, MSNA is reduced but not fully normalized.[4,9,12–14] These results indicate that additional treatment might be beneficial. Moxonidine, which is a centrally acting sympatholytic agent, added to the chronic treatment with eprosartan, resulted in a further decrease in blood pressure and MNSA.[13] This was confirmed in dialysis patients in a recent study.[15]

The fact that additional sympathetic blockade indeed improves prognosis was shown a few years ago. In dialysis patients with impaired cardiac function treated with usual medication including RAS inhibitor, addition of carvedilol improved clinical outcome.[16] Therefore, these data suggest that we have a strong rationale to block sympathetic activity and that addition of a sympatholytic agent to RAS inhibitor treatment might be beneficial in selected patient groups.

More frequent dialysis is associated with better blood pressure control. A switch from 3 times weekly hemodialysis to 6 times weekly hemodialysis is associated with a decrease in sympathetic activity, no change in cardiac output, and therefore a decrease in peripheral vascular resistance.[17] It is tempting to speculate about the mechanisms of these effects; apparently, the balance between sympatho-inhibiting and stimulating factors changed substantially.

FUTURE PERSPECTIVES

An almost unexplored idea is that there is not only an enhanced sympathetic activity but also an insufficient activity of the 'counter balance' system, that is, the parasympathetic system. Unfortunately, this concept is difficult to study in humans.

If we accept the basic idea on the pathogenesis, that is, that the diseased kidneys are the primary source of stimulation of

the central nervous system to increase sympathetic outflow, treatment can be delivered at several levels, that is, within the kidneys, within the central nervous system, and at a peripheral level.

Recently, catheter-based renal denervation was presented as a treatment option. Renal nerves are located around the arteries. These are both the afferent and efferent nerves. The catheter is advanced from the femoral artery, a procedure very similar to an ordinary arteriogram. By applications of energy on various spots that in totality cover the circumference, renal nerves can be destroyed. Initial results in a group of $\sim$50 patients with uncontrolled hypertension despite three antihypertensive agents suggest a considerable and prolonged effect. A substantial drop in MSNA was reported in one patient.[18] More recently, this antihypertensive effect was confirmed in a randomized trial.[19] These data give strong support for the idea that, in humans as well, the kidneys are important in the pathogenesis of hypertension, at least in this category of patients. Interestingly, the effect after 12 months seems even larger than that after 3 months. This treatment is definitely worth studying in more detail and in a wider range of patients for several reasons. First, it offers a new treatment option with a prolonged effect of a single intervention. Second, it will provide more information about pathophysiology. It is particularly interesting to identify those patients in whom this very localized intervention has an effect on systemic variables.[20]

In addition, it seems worth exploring options that address kidney ischemia itself. There are some data to suggest that manipulation of the hypoxia-inducible factor complex would affect sympathetic activity and hypertension. Hypoxia-inducible factor is the central complex trying to protect the tissues and organs from the detrimental effects of hypoxia. It forms the crucial step in the regulation of the expression of a large number of genes, including, for instance, the *EPO* gene. Expression of this complex can be manipulated by various compounds, including the so-called prolyl hydroxylase inhibitors. These compounds are now being tested as a sort of new erythropoietin-like molecules; some of them also appear to lower blood pressure. Of obvious concern is the fact that these compounds may have unwanted effects, such neo-angiogenesis.

At present, much interest is focused on the potential of bone marrow-derived cells to 'repair' tissue injury. The idea that such treatment would reduce kidney failure progression/repair kidney tissue, lower sympathetic outflow and blood pressure is appealing.

Recent insights into the regulation of the RAS and sympathetic activity may offer new avenues for exploring therapeutic approaches, such as modulation of renalase. Renalase is a recently described catecholamine-metabolizing enzyme. Plasma concentrations are markedly reduced in CKD patients.

As mentioned above, there exists some evidence that additional sympatholytic therapy (added to RAS inhibition) might be beneficial. Several experts in the field have already suggested this option, but it still needs to be studied in more detail.

Define patient characteristics that are especially predictive for the presence of an activated renin/sympathetic system.

Study the effect of additional sympatholytic therapy, for instance, beta-blockers added to renin–angiotensin system (RAS) inhibitors, on meaningful clinical end points in chronic kidney disease (CKD) patients over a wide range of CKD stages.

Study the effect on meaningful clinical end points of renal denervation in properly designed clinical trials in a wider range of patients.

Focus on therapies aiming to address the central abnormalities in pathogenesis, namely, kidney injury/ischemia; for instance, stem cell infusion, modulators of hypoxia-inducible factor (HIF), and renalase.

Apply modern radiological techniques that may help to identify/quantify/localize areas of kidney ischemia. Study whether these techniques can be used not only as a diagnostic tool but also to guide/monitor therapy.

Figure 1 | Subjects for future research.

It is likely that the degree of kidney ischemia may differ between patients, between kidney diagnoses, and between stages of CKD. For instance, it is possible that, in dialysis patients, progressive scarring ultimately destroys the kidneys, with disappearance of the areas of ischemia and reduction of the activated renin and sympathetic system. It is important to focus research on these areas. Sympathetic activity is difficult to measure in humans. Measurement of indices of the RAS might be easier to implement, although these measurements need to be taken in a very standardized manner. Modern radiological techniques may be helpful. For instance, the blood oxygen level-dependent magnetic resonance imaging technique may identify areas of ischemia in tissue. It seems worthwhile to apply this technique in CKD.

Finally, it is important to realize that already a small kidney lesion, not affecting kidney function, can activate these pathophysiological mechanisms. It is very likely that they are also operational in other disease conditions, including, for instance, some forms of essential hypertension, heart failure, sleep apnea syndrome, and obesity/metabolic syndrome.

CONCLUSION

It is clear that injured kidneys are at the core of the pathogenesis of the enhanced activity of the RAS and the sympathetic nervous system. This knowledge can help us define research questions in an effort to improve the treatment of our patients (Figure 1).

DISCLOSURE

AC has received consulting fees from Abbott Laboratories and received lecture fees from F. Hoffmann-La Roche, Amgen, and Fresenius Medical Care Holdings. AM-C has received consulting fees from Abbott Laboratories, Roche Spain, and Abbott Spain. AO has received grant support from the Spanish Government. AW has received lecture fees from Amgen, F. Hoffmann-La Roche, and Janssen-Cileg. AW has also received grant support from Astellas Pharma. DF has received funding from the EU. DG has received consulting fees and lecture fees from Shire, Genzyme, Novartis AG, Sandoz, Pfizer, and Fresenius Medical Care Holdings. FWD has

received funding from Amgen and Baxter. GL has received consulting fees from Amgen and Sandoz. GL has also received lecture fees from Amgen, Sandoz, Genzyme, and Shire. PJB has received consulting fees from Medtronic and has received grant support from Ardian and Novartis AG. RA has received consulting fees from Amgen, Abbott Laboratories, Merck, Affymax, Takeda Pharmaceutical Company, Daiichi Sankyo, Celgene, Watson Pharmaceuticals, and Rockwell Medical. RA has also received lecture fees from Abbott Laboratories, Merck, and Medscape. ZM has received lecture fees from Amgen, Shire, Genzyme, FMC, and Merck Sharp & Dohme. ZM has received grant support from Baxter, Amgen, FMC, Shire, and Genzyme. The remaining authors declared no competing interests.

REFERENCES

1. Siddiqi L, Joles JA, Grassi G *et al.* Is kidney ischemia the central mechanism in parallel activation of the renin and sympathetic system? *J Hypertens* 2009; **27**: 1341–1349.
2. Campese VM. Neurogenic factors and hypertension in renal disease. *Kidney Int Suppl* 2000; **75**: S2–S6.
3. Klein IH, Ligtenberg G, Neumann J *et al.* Sympathetic nerve activity is inappropriately increased in chronic renal disease. *J Am Soc Nephrol* 2003; **14**: 3239–3244.
4. Neumann J, Ligtenberg G, Klein IH *et al.* Response to sympathetic hyperactivity in hypertensive chronic kidney disease patients is reduced during standard treatment. *Hypertension* 2007; **49**: 506–510.
5. Neumann J, Ligtenberg G, Klein II *et al.* Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. *Kidney Int* 2004; **65**: 1568–1576.
6. Joles JA, Koomans HA. Causes and consequences of increased sympathetic activity in renal disease. *Hypertension* 2004; **43**: 699–706.
7. Mancia G, Grassi G, Giannattasio C *et al.* Sympathetic activation in the pathogenesis of hypertension and progression of organ damage. *Hypertension* 1999; **34**: 724–728.
8. Zoccali C, Mallamaci F, Tripepi G *et al.* Norepinephrine and concentric hypertrophy in patients with end-stage renal disease. *Hypertension* 2002; **40**: 41–46.
9. Siddiqi L, Prakken NH, Velthuis BK *et al.* Sympathetic activity in chronic kidney disease patients is related to left ventricular mass despite antihypertensive treatment. *Nephrol Dial Transplant* 2010; **25**: 3272–3277.
10. 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.
11. Penne EL, Neumann J, Klein IH *et al.* Sympathetic hyperactivity and clinical outcome in chronic kidney disease patients during standard treatment. *J Nephrol* 2009; **22**: 208–215.
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. Neumann J, Ligtenberg G, Oey L *et al.* Moxonidine normalizes sympathetic hyperactivity in patients with eprosartan-treated chronic renal failure. *J Am Soc Nephrol* 2004; **15**: 2902–2907.
14. Klein IH, Ligtenberg G, Oey PL *et al.* Enalapril and losartan reduce sympathetic hyperactivity in patients with chronic renal failure. *J Am Soc Nephrol* 2003; **14**: 425–430.
15. Hausberg M, Tokmak F, Pavenstadt H *et al.* Effects of moxonidine on sympathetic nerve activity in patients with end-stage renal disease. *J Hypertens* 2010; **28**: 1920–1927.
16. Cice G, Ferrara L, Di BA *et al.* Dilated cardiomyopathy in dialysis patients–beneficial effects of carvedilol: a double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2001; **37**: 407–411.
17. Zilch O, Vos PF, Oey PL *et al.* Sympathetic hyperactivity in haemodialysis patients is reduced by short daily haemodialysis. *J Hypertens* 2007; **25**: 1285–1289.
18. Schlaich MP, Sobotka PA, Krum H *et al.* Renal sympathetic-nerve ablation for uncontrolled hypertension. *N Engl J Med* 2009; **361**: 932–934.
19. Esler MD, Krum H, Sobotka PA *et al.* Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; **376**: 1903–1909.
20. Blankestijn PJ, Ritz E. Renal denervation: potential impact on hypertension in kidney disease? *Nephrol Dial Transplant* 2011 (in press).