The effect of ACE inhibitors and atrial natriuretic factor on the cardiorenal axis in man

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Introduction

Primary renal diseases such as glomerulonephritis are normally immunological in origin but renal function is also abnormal in a large variety of general medical conditions and in these latter conditions the abnormality is in renal haemodynamics rather than being of immunological origin. For example, in hypertension, it has long been known that if the kidney is transplanted from a spontaneously hypertensive rat to a normotensive rat, then the hypertension follows the kidney. This suggests that the kidney is of major aetiological importance in the development of essential hypertension. It has also recently been shown that one of the earliest abnormalities to be found in the first degree relatives of hypertensive patients is a decrease in renal blood flow and this is at a stage when they are still normotensive (van Hooft *et al.*, 1991).

The next general medical condition where renal function is abnormal is chronic heart failure where renal sodium and fluid retention is usually the first clinical sign of the disease. Diabetes mellitus is another medical disease where renal dysfunction is prominent. Curiously in diabetes, there is initially an increase in glomerular filtration rate (GFR) which gives way to microalbuminuria and subsequently to a decreased GFR and frank nephropathy. Lastly cyclosporin is a drug in widespread use which causes renal vasoconstriction leading to nephrotoxicity and hypertension.

Before we will be able to unravel the renal abnormalities in each of the above diseases, we have to learn more about how the normal kidney functions. Much of this article is devoted to understanding how the normal kidney functions but I will later on directly discuss both chronic heart failure and cyclosporin.

There are a large number of different regulators of renal function. I will discuss only the three main ones of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS) and atrial natriuretic factor (ANF).

Sympathetic nervous system

The SNS consists of two components: neuronally released noradrenaline and circulating plasma noradrenaline (NA). Most of our information about the role of the SNS on the kidney comes from fairly crude animal experiments where the renal nerves were cut. We decided to examine

the effect of the SNS on renal function in normotensive man and to compare the differential effects of neuronally released NA and circulating NA. We assessed the former by infusing tyramine and the latter by infusing noradrenaline itself.

We found to our surprise that a pressor dose of tyramine increased urinary sodium output whereas an equipotent pressor dose of noradrenaline decreased urinary sodium output (Lang & Struthers, unpublished observations). Changes in urine sodium output matched the changes in renal blood flow (RBF) in that tyramine increased RBF while noradrenaline decreased RBF. Our explanation for this differential effect is that tyramine caused its pressor effect mainly by increasing cardiac output which in turn increased RBF and U_{Na} whereas noradrenaline caused its pressor effects mainly by causing peripheral and renal vasoconstriction which decreased RBF and U_{Na} . These data challenge the whole concept of 'pressure natriuresis' in that noradrenaline and tyramine caused the same increase in pressure and yet had opposite effects on urine sodium. Renal blood flow as well as renal perfusion pressure should be considered in assessing the influence of the renal artery on urinary sodium output.

More importantly it has previously been assumed that SNS activation always caused sodium retention but this no longer seems to be the case. One possible clinical relevance relates to young hypertensive subjects: they are known to have an increased cardiac output, increased urinary catecholamines and to have a decreased total body sodium. It is interesting to note that this triad is exactly akin to what tyramine did in our normal volunteers and re-awakens the possibility that an activated SNS initiates the hypertensive process.

Renin-angiotensin-aldosterone system

We set out to define the renal dose-response curve to infused angiotensin II (AII) in normal man. We found that there was a fairly flat dose-response curve in that 2, 5 and 10 ng kg⁻¹ min⁻¹ of AII produced much the same antinatriuretic effect even although they had very different effects on blood pressure.

In this experiment we also looked specifically at urine magnesium output. This is because magnesium (Mg) is acquiring an increasingly prominent role in cardiovascular

disease especially after acute myocardial infarction when several studies suggest that intravenous magnesium reduces arrhythmias and death (Woods, 1991). In our work, we found that an infusion of AII caused a fall in urine Mg while an infusion of aldosterone caused an increase in urine Mg output. This is a curious finding since AII and aldosterone are adjacent components of the RAAS cascade and yet appear to have completely opposite effects on Mg output. This biphasic effect of the RAAS may explain why we found that lisinopril had no significant effect on urine or erythrocyte Mg in a group of patients with mild heart failure.

The SNS/RAAS interaction

There is a wealth of animal data to suggest that there is a major interaction between the SNS and the RAAS. This interaction appears to involve mainly AII and NA.

We sought evidence for such an interaction in normal man. We found that enalapril pretreatment was able to abolish totally the antinatriuretic effect of noradrenaline. We also did the opposite experiment and found that a low, subpressor dose of prazosin markedly blunted the antinatriuretic effect of infused AII (Lang *et al.*, 1992a). In other words, the renal effects of AII and of NA are interdependent. For NA to cause renal sodium retention, the coincidental presence of AII is required and *vice versa*. The clinical relevance of this is that as a patient goes from early heart failure to late heart failure, one feature is that their kidneys retain more salt and water. If ACE inhibitors are given during early heart failure, this might prevent not only the antinatriuretic effect of angiotensin II but also the antinatriuretic effect of noradrenaline.

Renal AII/prostaglandin interaction

AII is known to be a renal vasoconstrictor while prostaglandins (PG) are renal vasodilators. Much animal data suggests that PGs act in a counter regulatory manner against AII's vasoconstrictive effect especially against its effect on the renal afferent arteriole. In support of this, we recently found in normal man that indomethacin alone had no effect on RBF or GFR but it markedly augmented the AII induced fall in RBF and GFR (Motwani & Struthers, 1992).

The clinical relevance of this relates to the fact that diuretics increase AII levels and the coprescription of diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) is very common. This is especially so in the elderly where a degree of renal dysfunction is often accepted as the inevitable consequence of old age whereas it may often be of iatrogenic origin due to diuretics and NSAIDs.

Atrial natriuretic factor and cyclosporin

Cyclosporin has revolutionised organ transplantation but it is also of major value in many non-transplant patients such as those with early diabetes mellitus. How-

ever its use is severely limited by its adverse effects especially in the non-transplant group. There would therefore be great value if we could blunt the toxic effects of cyclosporin.

The toxic effects of cyclosporin are now known to be initiated by renal vasoconstriction which leads to sodium retention, hypertension and renal tubular toxicity. Interestingly atrial natriuretic factor (ANF) has an intriguing array of effects which make it look as though it were 'tailor made' to reverse the adverse effects of cyclosporin. The relevant properties of ANF are that it dilates precontracted renal vessels, it is natriuretic and it is hypotensive in its own right.

We therefore infused ANF into seven patients with renal transplants who were on chronic cyclosporin treatment. ANF increased urine sodium, urine volume and renal blood flow and decreased systolic BP but the most gratifying effect was a 33% increase in GFR which persisted after the ANF infusion was terminated (Lang *et al.*, 1992b).

It must be confessed however that ANF is only one of many renal vasodilators which has shown some success against cyclosporin. The other agents are dopamine, calcium antagonists, ACE inhibitors, sympatholytic agents and prostaglandin analogues. We are currently engaged in comparing the relative efficacy of all of those renal vasodilators against cyclosporin.

Brain natriuretic peptide (BNP)

ANF was sequenced in 1984 but it is now apparent that it is only one member of a large family of natriuretic peptides. Brain natriuretic peptide (BNP) was sequenced in 1988 and C type natriuretic peptide (CNP) in 1990. Although BNP was found originally in the brain, it is found in larger quantities in the heart.

We examined BNP release in a series of studies. Chronic salt loading over 5 days did indeed increase BNP levels (Lang *et al.*, 1991a). Haemodialysis over 3–5 h decreased plasma BNP levels (Lang *et al.*, 1992c). In contrast, intravenous saline loading over a few minutes in normal volunteers increased only plasma ANP levels but not plasma BNP levels.

The metabolism/clearance of BNP is harder to study in man. By analogy, ANF is known to be cleared by two mechanisms: the neutral endopeptidase enzyme and specific ANF clearance receptors. To examine the former, we administered a neutral endopeptidase inhibitor (candoxatril) to patients with chronic heart failure (CHF) and found that it did indeed increase plasma BNP levels (Lang *et al.*, 1991b). To examine whether clearance receptors were involved, we had to use an indirect approach whereby we infused ANF into CHF patients to a level (400 pmol l^{-1}) which was well above the K_D for the clearance receptor ($10\text{--}100 \text{ pmol l}^{-1}$). This ANF infusion should fully occupy the clearance receptors and yet plasma BNP levels did not change (Lang *et al.*, 1992d). In support of this finding, Mukoyama *et al.* (1991) recently found that BNP bound to ANF clearance receptors with only 7% of the affinity that ANF had. Overall therefore BNP would appear to be cleared by the neutral endopeptidase mechanism but only to a small extent, if at all by ANF clearance receptors.

Cardiac death and ACE inhibitors

Several recent large scale studies have shown convincingly that ACE inhibitors reduce the death rate in CHF patients (CONSENSUS, 1987). This has quite rightly had a major impact on the therapy of CHF but this kind of observation may well yield even more important information. If ACE inhibitors reduce the death rate, then we might be able to use this kind of observation to learn more about the actual mechanism of cardiac death in CHF patients.

What other factors are known to be associated with cardiac death? It was shown many years ago that plasma noradrenaline was positively related to the CHF death rate (Cohn *et al.*, 1984). The problem with these kind of data is that plasma NA may simply be a marker of disease severity but, for the sake of argument let us assume that noradrenaline is intrinsically harmful to the heart. This is not too hard to believe since NA is arrhythmogenic, it makes platelets clump together and blocking NA with β -blockers improves mortality post myocardial infarction. We therefore decided to put these two observations together and see whether an ACE inhibitor altered the myocardial uptake or clearance of NA. We injected tritiated NA into the right ventricular cavity in anaesthetised rats *in vivo*. This model is akin to ischaemia or infarction where there is a large release of NA which then has to be metabolised and/or taken back up into myocardial tissue. In this animal model, we found that AII inhibited while captopril increased the myocardial uptake and clearance of NA. It may therefore be that the cardioprotective effect of ACE inhibitors is due at least in part to their encouraging the local uptake of NA into myocardial cells where it is then metabolised and inactivated. We also have some preliminary evidence that aldosterone rather than angiotensin II is the active substance causing myocardial NA uptake which is not that surprising since corticosterone, with a structure similar to aldosterone, is the classically used inhibitor of uptake₂. Indeed many years ago, aldosterone was shown to increase ectopic activity in a dose dependent manner after coronary ligation in dogs (Arora & Somani, 1962) and it may now be that this was due to aldosterone blocking myocardial NA uptake and the persistence of NA in the myocardial cavity.

Hypotensive effect of ACE inhibitors in CHF

When ACE inhibitors were introduced in CHF, it was common practice to admit patients to hospital for 2–3 days to start therapy. The obvious question to answer was whether the drug could be initiated as an outpatient, the limitation to that being that one could only observe the BP response to the first dose as an outpatient. The main point of concern was whether any patients would have a small BP fall to the first dose but a large BP fall to some subsequent dose. We found that this was unlikely since in a group of 40 CHF patients, there was a significant correlation between the BP fall to the 1st dose of captopril and the BP fall to the 4th dose of captopril. We also found that the size of the BP fall was the same whether the starting dose was 6.25 mg or 25 mg of captopril. In

a further series of CHF patients, we measured extra cellular fluid volume (ECFV) radioisotopically prior to captopril and found that the largest BP falls were indeed found in those patients with a low ECFV (<95% predicted).

Renal function after an ACE inhibitor in CHF

We measured RBF and GFR before and after two doses of captopril in a large group of CHF patients. The response was variable depending on the starting GFR level. In those patients with a GFR >80 ml min⁻¹, captopril had little effect on RBF or GFR. In those with a starting GFR of 45–80 ml min⁻¹, captopril increased RBF but reduced GFR by 7 ml min⁻¹ on average. In those patients with a starting GFR of <45 ml min⁻¹, captopril had no effect on RBF but decreased GFR by a larger margin than the group with a starting GFR of 45–80 ml min⁻¹.

An important aspect of angiotensin II in the kidney of CHF patients is that AII appears to exert a biphasic effect on urinary sodium output. In the glomerulus, AII helps maintain the GFR by maintaining efferent arteriolar tone: this in turn helps boost urine sodium output. By contrast in the tubules, AII exerts an antinatriuretic effect tending to decrease urine sodium output. Incidentally in normal man, only the latter tubular effect applies as the GFR in a normal person does not need endogenous AII to maintain it in the normal range. Therefore in normal man, an ACE inhibitor increases urine sodium output by acting only on the tubules whereas in CHF, an ACE inhibitor has a relatively neutral effect on urine sodium output because the fall in GFR is compensated for by an increase in tubular sodium output. This biphasic effect was most clearly seen in our studies in the group of CHF patients with a starting GFR of <45 ml min⁻¹. Despite a pronounced fall in GFR after captopril, there was no overall change in urine sodium output. This tubular increase in sodium output presumably helps to prevent these patients retaining fluid and developing pulmonary oedema even when the ACEI has reduced the GFR to a large extent.

In CHF, ACE inhibitors are often prescribed with frusemide and here the biphasic effect of AII is even more prominent since frusemide itself often produces a further increase in AII. We speculated that it might be possible to use a low dose of an ACE inhibitor and dissociate the glomerular and tubular effects of AII. Our aim would be to abolish the harmful effect of ACEI on the glomerulus while retaining the beneficial effect on the tubules. We found this indeed to be the case in that 1 mg of captopril doubled the natriuretic effect of frusemide and did so purely by acting on the tubules with no effect at all on the GFR (Motwani *et al.*, 1992). By contrast, a standard (25 mg) dose of captopril reduced the natriuretic effect of frusemide mainly because of a pronounced fall in GFR which on this occasion was not compensated for adequately enough by the tubules. This 1 mg/25 mg comparison with captopril does not suggest that we should use lower doses of captopril in all patients but it does suggest that this might be a useful strategy in the subgroup of oedematous patients who turn out to be resistant to large doses of diuretics.

Conclusion

I would like to finish on a philosophical note about the relationship between the kidney and the cardiovascular system (CVS). The naive view of this relationship is that the kidney is a passive overflow pipe at the end of the CVS. I adhere more to the 'nephrocentric view' that the kidney regulates and protects itself very carefully (auto-regulation) and does so often at the expense of the CVS. This is particularly obvious in CHF where AII overproduction protects the GFR at the expense of the CVS. (One can assume that AII overproduction is harmful to

the CVS in CHF since ACE inhibitors reduce cardiac death in CHF.) Therefore with regard to the kidney and the CVS, it may be that it is more a case of the tail wagging the dog rather than the other way round.

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References

- Arora, R. B. & Somani, P. (1962). Ectopic arrhythmia provoking action of aldosterone. *Life Sci.*, **5**, 215–218.
- Cohn, J. N., Levine, T. B., Olivari, M. T., Garberg, V., Lura, D., Francis, G. S., Simon, A. B. & Rector, T. (1984). Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *New Engl. J. Med.*, **311**, 819–823.
- CONSENSUS Trial Study Group (1987). Effect of enalapril on mortality in severe congestive heart failure. *New Engl. J. Med.*, **316**, 1429–1435.
- Lang, C. C., Choy, A. M., Henderson, I. S., Coutie, W. J. & Struthers, A. D. (1992c). The effect of haemodialysis on plasma levels of brain natriuretic peptide in patients with chronic renal failure. *Clin. Sci.*, **82**, 127–131.
- Lang, C. C., Coutie, W. J., Khong, T. K., Choy, A. M. & Struthers, A. D. (1991a). Dietary sodium loading increases plasma brain natriuretic peptide levels in man. *J. Hypertension*, **9**, 779–782.
- Lang, C. C., Henderson, I. S., McTier, R., Stewart, W. K. & Struthers, A. D. (1992b). Atrial natriuretic factor improves renal function and lowers systolic BP in renal allograft recipients treated with cyclosporin. *J. Hypertension*, **10**, 482–483.
- Lang, C. C., Motwani, J., Coutie, W. J. & Struthers, A. D. (1991b). Influence of candoxatril on plasma brain natriuretic peptide in heart failure. *Lancet*, **ii**, 255.
- Lang, C. C., Motwani, J., Coutie, W. & Struthers, A. D. (1992d). Brain natriuretic peptide clearance in chronic heart failure: evidence for a neutral endopeptidase mechanism but against an ANP clearance receptor mechanism. *Clin. Sci.*, (in press).
- Lang, C. C., Rahman, A. R., Balfour, D. J. K. & Struthers, A. D. (1992a). Prazosin blunts the antinatriuretic effect of angiotensin II in man. *J. Hypertension*, (in press).
- Motwani, J. G. & Struthers, A. D. (1992). Interactive effects of indomethacin, angiotensin II and furosemide on renal haemodynamics and natriuresis in man. *Current advances in ACE inhibition*, eds Sever, P. S. & McGregor, G. A., (in press).
- Motwani, J. G., Fenwick, M., Morton, J. J. & Struthers, A. D. (1992). Frusemide induced natriuresis is augmented by ultra low dose but not by standard doses of captopril in chronic heart failure. *Circulation*, (in press).
- Mukoyama, M., Nakao, K., Hosoda, K., Suga, S., Saito, Y., Ogawa, Y., Shirakami, G., Jougasaki, M., Obata, K. & Yasue, H. (1991). Brain natriuretic peptide as a novel cardiac hormone in humans. *J. clin. Invest.*, **87**, 1402–1412.
- van Hooft, I. M. S., Grobbee, D. E., Derkx, F. H. M., de Leeuw, P. W., Schalekamp, M. A. D. H. & Hofman, A. (1991). Renal haemodynamics and the renin angiotensin aldosterone system in normotensive subjects with hypertensive and normotensive parents. *New Engl. J. Med.*, **324**, 1305–1311.
- Woods, K. L. (1991). Possible pharmacological actions of magnesium in acute myocardial infarction. *Br. J. clin. Pharmacol.*, **32**, 3–10.

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