Systemic and Renovascular Hypertension

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JACKSON, B., FRANZE, L. and WHITTY, M. Systemic and Renovascular Hypertension. Tohoku J. Exp. Med., 1992, 166 (1), 155-164 — To ascertain the contribution of systemic hypertension in the progression of renal failure, we have studied the effects of pharmacological treatment of hypertension in rats with the remnant kidney model of renal insufficiency, streptozotocin diabetes, or nephrotoxic serum nephritis. Treatment with the angiotensin converting enzyme (ACE) inhibitor enalapril lowered systemic blood pressure in the remnant kidney and diabetic animals, but did not lower blood pressure in rats with nephrotoxic serum nephritis. Proteinuria was reduced in all three models, and creatinine clearance improved in the remnant kidney and diabetic animals, when compared with untreated controls. In the remnant kidney and diabetic models systemic blood pressure was lowered to a similar degree by treatments with a calcium blocker, with no improvement in either proteinuria, or glomerular filtration rate. Further studies of the long-term effects of enalapril have been undertaken in rats with the two kidney one clip model of hypertension. Rats treated with enalapril had a lower blood pressure and improved survival over one year of treatment, compared with untreated rats. After 1 year of treatment however the clipped kidney was small and fibrotic, and non functional. Following withdrawal of enalapril therapy there was no functional improvement of the clipped kidney. The possibility that ACE inhibitors have a specific intra-renal effect reducing the rate of progression of renal disease now needs confirmation in human studies. In renovascular hypertension however, intra-renal changes induced by ACE inhibitors may cause irreversible renal damage. —— chronic renal failure; diabetic nephropathy; hypertension; nephrotoxic serum nephritis; renovascular hypertension

The contribution of systemic hypertension to the progression of renal failure is controversial. Systemic hypertension is common in chronic renal failure, and may contribute to the progression of glomerular injury (Del Greco et al. 1975). It is well known that malignant hypertension leads to progressive renal failure, where fibrinoid necrosis of the arterioles is associated with progressive loss of renal function, and eventual endstage renal failure. The treatment of severe accelerated hypertension is associated with improvement in renal function, however the effect of antihypertensive therapy on renal functional impairment associated with milder forms of systemic hypertension is still not clear. Studies of blood pressure treatment have yielded conflicting results. In some risk factor surveys, systemic

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hypertension has been reported as a risk factor for progression of renal disease, whilst others have been unable to confirm these observations (Hamilton et al. 1964; Veterans Administration Cooperative Study Group on Antihypertensive Agents 1967; Berry and Hawkins 1984; Van Der Peet et al. 1977).

Progressive loss of renal function however appears to be an inevitable consequence in most patients with established renal failure. Regardless of the primary insult renal failure appears to be progressive, after a certain degree of reduction in the number of functioning nephrons. This phenomenon is well documented across a broad spectrum of clinical disease, both in animal models of renal failure and human disease (Chanutin and Ferris 1932; Mitch et al. 1976; Purkerson et al. 1976; Rutherford et al. 1977; Hostetter et al. 1981). Recently investigators have suggested that adaptive changes in the residual functioning nephrons lead to an increase in glomerular capillary pressure and flow, and that these intra renal hemodynamic changes may mediate progressive structural and functional glomerular injury (Brenner 1985; Meyer et al. 1985).

To ascertain if systemic hypertension is a factor contributing to the progression of chronic renal disease we have studied the effect of pharmacological treatment of systemic hypertension in rats with several models of renal disease; the remnant kidney model (Jackson et al. 1986a; Jackson and Johnston 1988), streptozotocin induced diabetes mellitus (Jackson et al. 1986b; Whitty and Jackson et al. 1988), and nephrotoxic serum nephritis (Jackson et al. 1988).

Studies in the remnant kidney model of renal failure

Subtotal nephrectomy was established in Sprague-Dawley rats by selective infarction of 7/8 of one kidney, and surgical excision of the other. One week later rats were matched for plasma creatinine concentration, and allocated to treatment with enalapril (5 mg/kg/day) or felodipine (30 mg/kg/day by gavage), or to a no treatment group. Over the subsequent 5 weeks of treatment blood pressure was reduced in both the enalapril and felodipine treatment groups when compared with the untreated animals. A similar degree of blood pressure reduction was achieved both with the angiotensin converting enzyme inhibitor and the calcium blocker.

Plasma creatinine concentration fell towards normal in the enalapril treated group, but remained elevated in the felodipine group comparable with that of the untreated group. Urinary protein excretion 6 weeks after subtotal nephrectomy was reduced in the enalapril treated group but increased in the felodipine group, compared with the untreated group. Renal injury was assessed using a histological score of glomerular sclerosis. Glomerular sclerotic changes were marked in the untreated animal and were significantly reduced in the enalapril treated animals, but not in the felodipine treated group (Jackson et al. 1986a; Jackson and Johnston 1988).

These results in rats with the remnant kidney model of renal failure suggest
that angiotensin converting enzyme inhibitor treatment had a specific beneficial effect over and above the control of systemic blood pressure. Micro-puncture studies have demonstrated that residual glomeruli in rats with a reduced renal mass have an increased glomerular hydrostatic pressure. Furthermore, in studies during angiotensin converting enzyme inhibitor therapy, glomerular hypertension has been reduced by converting enzyme inhibitor therapy in rats with the remnant kidney model of renal failure. The intra renal effect of angiotensin converting enzyme inhibitor therapy thus appears to limit glomerular injury in these animals (Dean et al. 1974; Hostetter et al. 1981; Brenner 1985; Meyer et al. 1985).

Studies in the streptozotocin model of diabetes mellitus

We have studied Sprague-Dawley rats, subjected to unilateral nephrectomy, and rendered diabetic by streptozotocin (70 mg/kg intraperitoneal). One month after induction of diabetes rats were matched by serum creatinine concentration and randomized to an untreated, enalapril treatment, or to a verapamil treated group. A further group of non diabetic rats that had undergone unilateral nephrectomy was followed as a control group. Diabetic rats developed a modest increase in systolic systemic blood pressure, relative to non diabetic uninephrectomized rats. Treatment of the diabetic rats with enalapril, or verapamil was introduced 1 month after induction of diabetes, and reduced the systemic blood pressure to a comparable degree in each group, and to a level similar to that of the non diabetic rats. Creatinine clearance was elevated by some 30% in untreated diabetic rats 1 month after streptozotocin administration, compared with non diabetic rats. The creatinine clearance remained elevated over the next 2 months. Treatment with enalapril reduced the elevated creatinine clearance of diabetic rats, but this was unaltered by treatment with verapamil. Urinary protein excretion was significantly elevated in diabetic rats when compared with non diabetic animals. Urinary protein excretion in the third month after induction of diabetes was reduced by enalapril treatment but not by verapamil treatment (Jackson et al. 1986b; Whitty and Jackson 1988).

Thus, despite equal lowering of systemic blood pressure, angiotensin converting enzyme inhibitor therapy had a specific renal effect over and above the effect of systemic blood pressure reduction. Hyperfiltration was minimized, and urinary protein excretion was reduced in angiotensin converting enzyme inhibitor treated animals, but these parameters were unaltered by calcium inhibitor treatment.

Micropuncture experiments have demonstrated glomerular hemodynamic changes of hyperfiltration, and raised glomerular hydrostatic pressure in rats with streptozotocin diabetes. Treatment with angiotensin converting enzyme inhibitors has been shown to ameliorate these intra renal haemodynamic changes. Angiotensin converting enzyme inhibitor thus appears to produce a specific intra renal effect beneficial to rats with diabetic nephropathy, over and above the effects
on systemic blood pressure (Zatz et al. 1985, 1986).

**Studies in the nephrotoxic serum nephritic model of renal failure**

The third model of progressive renal failure we studied in the rat was that of nephrotoxic serum nephritis. Sprague-Dawley rats underwent unilateral nephrectomy, were presensitized to sheep gamma globulin, and 1 week later injected with nephrotoxic serum with antiglomerular basement membrane antibody activity. Rats developed progressive renal failure over the next six weeks, associated with systemic hypertension, and heavy proteinuria.

Animals were treated with enalapril, and compared with an untreated group. In this study angiotensin converting enzyme (ACE) inhibitor therapy did not alter systemic systolic blood pressure, and did not influence progression of renal failure, however, a significant reduction of urinary protein excretion was noted (Jackson and Debrevi 1988).

The intra renal and glomerular hemodynamic changes of nephrotoxic serum nephritis have been measured by Neugarten et al. (1985). They demonstrated that single nephron glomerular filtration rate was maintained primarily by an increase in glomerular capillary pressure. They also demonstrated that a reduction of the systemic blood pressure with reserpine, hydralazine and hydrochlorothiazide reduced protein excretion, and ameliorated structural changes, in association with a return of glomerular hemodynamic parameters towards normal.

In the chronic puromycin aminonucleoside nephropathy model of renal disease, Marinides (1987) has shown that ACE inhibitor treatment failed to effect the degree of proteinuria, or glomerular injury as assessed histologically. It thus appears that in some animal models of renal injury in the rat systemic blood pressure reduction does not necessarily lead to preservation of renal structure and function.

The apparent differences in outcome between different modes of antihypertensive therapy do however appear to relate to differences in their intra renal effect. Intra renal hemodynamic parameters documented by micropuncture that are associated with progressive renal failures have been modulated by dietary protein restriction, with amelioration of progression of renal damage (El-Nahas et al. 1983; Brenner 1985; Kenner et al. 1985). It is interesting to note that systemic blood pressure effects have also been dissociated from the preservation of renal structure and function, during dietary protein restriction, as this has little effect of systemic blood pressure. Micropuncture studies have in general supported the speculation that an elevated glomerular capillary pressure is a critical determinant in the progression of renal failure, with documentation that maneuvers that reduce glomerular capillary pressure are associated with an improved renal course. Micropuncture data has however been obtained from superficial glomeruli in anaesthetized animals, so it thus not unexpected that the intra renal renin-angiotensin system is stimulated, and glomerular filtration appears to be
maintained by angiotensin mediated efferent arteriolar constriction. The intra renal mechanism of action of angiotensin converting enzyme inhibitors is however far from simple (Zusman 1984). Whilst angiotensin II constricts the efferent arteriole, and contributes to the maintenance of glomerular capillary pressure and glomerular filtration, it has may other actions within the kidney. These include effects on mesangial cell contraction (Raij and Keane 1985), macro-molecular uptake (Hall 1986), tubular sodium reabsorption, and medullary blood flow (Chou et al. 1986). Modulation of any of these functions might alter the rate of progression of renal injury in progressive renal failure. Furthermore, the renin angiotensin system interreacts with the renal kallikrein-kinin system (Johnston et al. 1983), and the prostaglandin system (Heller and Horacek 1986), which may also be involved in an intra-renal effect of angiotensin converting enzyme inhibitor therapy.

It is tempting to speculate that in progressive renal failure in humans, that treatment of hypertension with angiotensin converting enzyme inhibitors may confer a specific preservation of renal function. Although benefit from ACE inhibitor therapy has been shown in several animal models of renal injury, this is not a universal observation. Observations in the dog with an advanced degree of renal mass reduction have not demonstrated a tendency for renal failure to progress (Bourgoignie et al. 1987), so there may be major differences between species in the behaviour of residual nephrons in renal insufficiency. Studies of dietary protein reduction in patients with chronic renal failure have however yielded similar clinical benefits to those observed in animal studies, though the precise role of protein restriction in progressive chronic renal failure remains controversial (Giordano 1982; Maschio et al. 1982; Klahr et al. 1983; Mitch 1984). Early studies of angiotensin converting enzyme inhibitor therapy in patients with chronic renal disease have shown marked benefits (Taguma et al. 1985), however the demonstration of a specific therapeutic advantage of angiotensin converting enzyme inhibitors over and above conventional forms of systemic blood pressure treatment has yet to be demonstrated.

**Studies in renovascular hypertension**

Renovascular hypertension is a common secondary form of hypertension, for which the angiotensin converting enzyme inhibitors offer specific medical therapy. Whilst control of systemic blood pressure has been very effective with ACE inhibitor treatment in renovascular hypertension, acute compromise of renal function has occurred in some cases (Jackson et al. 1984). We conducted a retrospective analysis of 32 patients with renovascular hypertension treated with an angiotensin converting enzyme inhibitor, and noted acute deterioration of renal function in 6 patients. Acute renal failure developed in 3 patients with bilateral renal artery stenosis, and in 3 patients with a single kidney with renal artery stenosis. In all 6 patients acute renal failure resolved following withdrawal of
angiotensin converting enzyme inhibitor therapy. In 1 patient captopril was reintroduced on two subsequent occasions, and was associated with acute deterioration, then recovery, of renal function following drug withdrawal (Jackson et al. 1986c).

In prospective studies we (1986c), and others (Wenting et al. 1984), have shown that in addition to the well described compromise of renal function during angiotensin converting enzyme inhibitor therapy in patients with bilateral renal artery stenosis, or stenosis to a single functioning kidney, loss of renal function can also be demonstrated in patients with unilateral renal artery stenosis, and a normal kidney. Using 99mTc-DTPA renal clearance, studies before and during prospective therapy with angiotensin converting enzyme inhibitors showed a reduction of glomerular filtration rate during angiotensin converting enzyme inhibitor therapy on the stenosed kidney side, and an increase in glomerular filtration rate in the kidney on the normal side, in patients with unilateral renovascular disease.

In our study two patients were studied before, during, and after ACE inhibitor therapy over a 3 months period (Jackson et al. 1986c) with withdrawal of angiotensin converting enzyme inhibitor therapy associated with a return of renal function to pretreatment levels. The reversible nature of functional renal impairment during angiotensin converting enzyme inhibitor therapy over the longer term is however not known.

To examine this further we have treated rats with the two kidney one clip model of renovascular hypertension over a 12 month period, with the angiotensin converting enzyme inhibitor enalapril. In this study (Jackson et al. 1988) rats were randomized to a no treatment group, treatment with enalapril, or treatment with the vasodilator minoxidil. Rats treated with enalapril had a improved survival, compared with untreated controls, and the minoxidil treated rats. Blood pressure control was however not equivalent with minoxidil, which though it lowered the blood pressure compared with untreated animals, did not achieve levels equivalent to those during enalapril treatment.

After 12 months of therapy total renal function in surviving rats was similar in all 3 groups, however there were marked differences between the function of the clipped and unclipped kidneys, in all 3 groups. In surviving untreated rats renal function was similar on each side, and renal size was reduced on the clipped side. Histological examination revealed changes of severe hypertensive vascular injury in the unclipped kidney, with minimal evidence of vascular injury on the clipped side. Surviving animals treated with angiotensin converting enzyme inhibitor had marked atrophy of the clipped kidney. Histological examination revealed marked changes of tubular atrophy and interstitial fibrosis, associated with glomerular shrinkage and fibrosis. Split kidney function studies showed the small clipped kidney was without glomerular filtration, and an increase in glomerular filtration rate was noted on the non clipped side. In the minoxidil treatment
group surviving rats had moderate vascular injury evident on histological examination of the unclipped kidney. The clipped kidney however contributed some 50% of the total renal function, and on histological examination had minimal evidence of damage. In these animals it thus appears that treatment with the angiotensin converting enzyme inhibitor improved survival, but was associated with fibrotic atrophy of the clipped kidney. Enalapril therapy was withdrawn in 5 animals, and 2 weeks later renal function studies performed. There was no functional improvement of the clipped kidneys, which on histological examination were indistinguishable from animals studied during enalapril therapy.

The hemodynamic effects of angiotensin converting enzyme inhibitors in the clipped kidney of two kidney one clip hypertensive animals has been well described (Levenson and Dzau 1987). Most studies have however been acute, and note complete functional reversal of effects following withdrawal of angiotensin converting enzyme inhibitor therapy. Gröne and Helmchen (1986) have studied two kidney one clip rats after 2 weeks of therapy with enalapril, and noted prominent tubular atrophy in the clipped kidney of the enalapril treated group. A group treated with dihydralazine, studied in parallel, had comparable systemic blood pressure reduction, but did not develop tubular atrophy. The tubular changes in the enalapril treatment group were accompanied by a reduction in renal function, compared with the hydralazine treated group. Following removal of the clip and the non clipped kidney, and cessation of enalapril therapy, glomerular filtration rate returned, accompanied by regeneration of tubular epithelial cells. Michel and co authors (1987) have studied the effects of 5 weeks therapy in two kidney one clip renovascular hypertension in rats. They demonstrated marked shrinkage of the clipped kidney in the ACE inhibitor treated group, and on histological examination found diffuse ischaemic changes with shrunken glomeruli, and renal tubular atrophy.

The effects of ACE inhibitor therapy on renal function may not be specific to this class of blood pressure reducing agents. Patients with bilateral renovascular disease treated with other blood pressure reducing agents may also develop acute renal compromise. Textor et al (1985), studied patients with renovascular disease during acute blood pressure reduction with nitroprusside and showed that a critical perfusion pressure, within the range achieved in clinical practice with conventional agents, was required for the maintenance of renal function.

When ACE inhibitor therapy is used in the treatment in renovascular hypertension renal function should be carefully monitored, as the long term effects of ACE inhibitor therapy on the function of the kidney with renal artery stenosis is not known. Where surgery or angioplasty are not possible and in patients with total occlusion of one renal artery the efficiency of longterm therapy with ACE inhibitors relative to conventional antihypertensive drugs is uncertain.

The possibility that ACE inhibitors have a specific intra renal effect that reduced the rate of progression of experimental renal disease is an exciting
prospect, and now needs direct clinical confirmation in formal prospective controlled studies. The same intrarenal hemodynamic consequences of ACE inhibition may however be detrimental in renovascular hypertension, where the intrarenal hemodynamic effects may cause irreversible renal damage during chronic therapy. This potential effect of the ACE inhibitors also needs critical study by prospective controlled clinical trials.

Acknowledgments

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References

ACE Inhibition and the Kidney


