

Transient renal dysfunction during initial inhibition of converting enzyme in congestive heart failure

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SUMMARY Treatment with captopril in resistant normotensive congestive heart failure is associated with a pronounced reduction in blood pressure, particularly after the first dose. The effects of this reduction on renal function were assessed in 10 patients at the beginning of and during chronic treatment (at one week and three months). Renal plasma flow and glomerular filtration rates were measured by isotope clearance during water diuresis. The first dose of captopril (25 mg) led to a pronounced fall in renal plasma flow and glomerular filtration rates together with a decrease in mean arterial pressure; this fall correlated with baseline plasma renin activity. These changes were paralleled by decreases in water and sodium excretion. In contrast, by the end of the first week of treatment a similar fall in mean arterial pressure occurred together with a pronounced increase in renal plasma flow; the glomerular filtration rate was maintained and there was no decrease in water and sodium excretion. This new response pattern recurred after three months of treatment.

The difference in response at different stages of treatment may reflect the balance between the different mechanisms influencing kidney dynamics in heart failure and their alteration by converting enzyme inhibition. The sustained increase in renal plasma flow during chronic treatment with captopril may account for the continued control of heart failure in these patients.

It is widely accepted that reduced cardiac output in heart failure activates multiple homeostatic mechanisms that serve to maintain blood pressure and preserve organ perfusion.¹⁻⁹ These mechanisms, however, may result in a further reduction in cardiac output and persistence of circulatory failure.¹⁰⁻¹⁹ Interruption of this cycle with vasodilator treatment has resulted in both clinical and circulatory improvement.¹⁶⁻²³ In particular, an appreciable improvement in renal haemodynamics has been reported with the use of alpha blockers,¹⁶⁻¹⁹ hydralazine,²⁰⁻²² nitroprusside,²⁰ and captopril.^{23 24}

Recently, however, considerable concern has arisen over the possible deleterious effect on renal function of a reduction in renal perfusion pressure by captopril, particularly in patients with congestive heart failure^{25 26} and renovascular disease.²⁷⁻³⁰ The obvious clinical relevance of these reports prompted us to

undertake the present study to define more clearly the sequence of changes in cardiac and renal haemodynamic indices during initial and chronic treatment with captopril and to examine the contribution of these renal changes to the therapeutic efficacy of captopril in congestive heart failure.

Patients and methods

Ten patients (nine men and one woman), with resistant congestive heart failure (NYHA class III-IV) secondary to either coronary atherosclerotic heart disease or primary myocardial disease participated in the study. Their heart failure had been resistant to conventional treatment with digitalis and diuretics together with either hydralazine or prazosin. Their ages ranged from 43 to 65 (mean \pm SD 56.6 \pm 2.1) years. The details of the study and possible side effects of the drug were explained to the patients, and all gave their written informed consent. The study protocol was approved by the Institutional Review Board of the Cleveland Clinic Foundation.

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STUDY PROTOCOL

Previous vasodilator treatment was stopped gradually whereas the diuretics and digoxin doses were kept constant. Patients were given a controlled diet as soon as they were admitted to hospital. After two to three days of stabilisation, all patients received a 2 g sodium diet. After an equilibration period of four to five days systemic haemodynamic indices were measured using radionuclide dilution curves using the Stewart Hamilton formula for cardiac output determination as described below. On the next day, renal haemodynamic indices were measured before and for two hours after the first dose of captopril (25 mg orally). Subsequently, the patients received 25 mg captopril three times daily. At the end of a week, while the patients were still taking the same controlled diet in hospital, systemic haemodynamic indices were measured two hours after their early morning dose of captopril. Renal function was re-evaluated on the next day—10 to 12 hours after the last dose of captopril. After the baseline renal measurements had been determined the next dose of captopril (25 mg) was given and measurements were repeated for two hours. The patients were then followed closely in the outpatient department, care being taken to maintain stable doses of digitalis, diuretic agents, and captopril. The patients were advised to continue the 2 g sodium diet.

Two to four months later (mean three months) the patients were readmitted to hospital and the same procedure was repeated. Systemic haemodynamic indices were measured on one day two hours after the morning daily dose of captopril; the next day the renal studies were performed at the same hour of the morning as previously (10 to 12 hours after the last captopril dose), and renal measurements were repeated for two hours. Body weight and urinary electrolyte excretion were measured daily in all patients throughout their stay in hospital.

HAEMODYNAMIC MEASUREMENTS

Systemic measurements were performed in the morning after an overnight fast—except for medications—and after resting supine for 30 minutes. Cardiac output and pulmonary mean transit time were determined in duplicate from radionuclide first pass dilution curves³¹; heart rate was determined from the electrocardiogram (lead II), and blood pressure using a sphygmomanometer. Ejection fraction was determined by the gated blood pool technique³² using the equilibrium phase of the same circulating isotope (technetium-99m labelled human "serum" albumin). Plasma volume was measured by radioiodinated (I^{125}) human serum albumin²⁹; total blood volume was calculated from the plasma volume and simultaneously determined haematocrit as described³³; results were calculated in ml/cm of height. Because analysis

included nine men and one woman intravascular volume was expressed as a percentage of the expected normal for our laboratory for each sex. Derived haemodynamic indices were calculated by standard formulas.³¹

RENAL FUNCTION TESTS

Renal haemodynamic indices, glomerular filtration rate, and electrolyte excretion were measured in the morning four to six hours after the last dose of digitalis and diuretics; captopril was withheld for 10 to 12 hours before the studies at the end of the first week (week 1) and third month (month 3) of follow-up. Patients were given water 15 ml/kg by mouth over one hour and allowed sufficient time to develop a water diuresis. Urine was collected with a bladder catheter and all urinary losses were replaced with distilled water by mouth. Glomerular filtration rate and renal plasma flow were measured by determining the clearance of iodine-125 radiolabelled iothalamate and iodine-132 radiolabelled hippuran respectively. After a priming dose of 0.5 μ Ci (0.02 MBq) per kg body weight of both isotopes iothalamate was infused at a constant rate of 0.25 μ Ci/min (0.01 MBq/min) and hippuran at 0.5 μ Ci/min (0.20 MBq/min) throughout the study. The isotopes were dissolved in 5% dextrose, and the rate of infusion was 1.0 ml/min. To avoid radioiodine uptake by other organs 10 drops of Lugol's solution were given by mouth 12 to 18 hours before the test. Serum and urine concentrations of each isotope were determined by isotope scintillation counting in a double well gamma counter with correction for spillover from I^{131} to I^{125} . Serum concentrations were determined at the beginning and at the end of each urine collection.

After a 45 minute equilibration period urine was collected during two 30 minute control periods. Thereafter, 25 mg of captopril was given orally, and urine was collected during four 30 minute clearance periods. Blood pressure was measured every five minutes. Samples for serum osmolarity were obtained at the beginning and end of each clearance period. Plasma renin activity, plasma aldosterone, plasma noradrenaline and adrenaline concentrations, and serum concentrations of angiotensin converting enzyme were determined before and one and two hours after the administration of captopril. Collected urine was assayed for the concentration of isotopes, urine osmolarity, and urinary content of sodium and potassium.

In three patients systemic haemodynamic indices were measured during the acute study at the same time as the renal haemodynamic indices by the thermoluminescence technique at right heart catheterisation with a Swan-Ganz catheter positioned in the pulmonary artery under fluoroscopic guidance. This meas-

urement was performed to confirm that the first dose of captopril had led to an increase in cardiac output in these patients, as reported previously both by our group and others.¹²

Calculations

Variation about the mean of the replicate values for the two control periods in the present study was 5.6% for the glomerular filtration rate and 5.8% for renal plasma flow (ERPF). Renal blood flow (RBF) was calculated from the following formula and expressed in l/min: $RBF = ERPF / (1 - Hct)$.

Renal vascular resistance (RVR) was calculated as $RVR = MAP / RBF$ where MAP (mean arterial pressure) was calculated from all the arterial pressures measured during a collection period.

ANALYTICAL METHODS

Isotope concentration was determined by a double well scintillation counter. Sodium and potassium concentrations (mmol (mEq)/l) were determined by flame photometry; serum and urine osmolarity were determined by an Advanced Instruments osmometer. Plasma renin activity was estimated by radioimmunoassay of angiotensin I generated during incubation of 1 ml of plasma for three hours at pH 5.7.³⁴ Plasma aldosterone concentration was determined by radioimmunoassay³⁵ and plasma catecholamine concentrations by a radioenzymatic method.³⁶ Angiotensin converting enzyme activity was determined by hydrolysis of a synthetic tripeptide after the method of Cushman and Cheung.³⁷

STATISTICAL ANALYSIS

Normality of sample distribution was assessed by the Wilk Shapiro test. The paired *t* test was used for comparing normally distributed samples. For non-

normally distributed samples Wilcoxon's sign rank test for paired data was used. Correlations were derived according to standard formulas. Values are expressed as means \pm standard error (SE). Sequential changes in hormonal measurements were examined by Dunnett's method.³⁸

Results

Demographic data and pretreatment data for each patient are shown in Tables 1 and 2, which also give the normal values for our laboratory. Cardiac index was reduced, pulmonary mean transit time prolonged, and ejection fraction impaired. Renal blood flow was reduced but glomerular filtration rate was little changed, reflecting an increased filtration fraction. Both effective renal plasma flow and glomerular filtration rate correlated with cardiac output ($r = 0.81$, $p < 0.01$, and $r = 0.69$, $p < 0.05$ respectively).

Plasma renin activity was increased in eight patients and low in two despite prolonged diuretic treatment and chronic decompensated congestive heart failure. Plasma aldosterone and plasma noradrenaline concentrations were increased. Blood volume varied from 85.7% to 155% of normal. None of these measurements correlated with systemic haemodynamic or renal function indices. Taken together pretreatment measurements indicated systemic and renal vasoconstriction associated with stimulation of the renin angiotensin system and an increase in circulating catecholamines.

FIRST DOSE EFFECTS

The peak effects of captopril on renal haemodynamic indices occurred 60 to 90 minutes after oral administration. This variation in time to peak effect in different patients could possibly be due to variable rates of drug absorption. The data reported are therefore

Table 1 Clinical and haemodynamic results before treatment in 10 patients treated with captopril for congestive heart failure

Case No	Age (yr) (sex)	NYHA class	Underlying cardiac disease	CI (l/min/m ²)	TPR (u/m ²)	MTT (s)	EF (%)
1	61 (M)	IV	CAD	1.5	52	19.5	14
2	43 (M)	IV	CAD	1.6	56	21.0	21
3	48 (M)	III	PMD	1.2	77	26.8	11
4	59 (M)	III	CAD	2.1	43	16.0	10
5	61 (M)	IV	CAD	1.4	54	23.3	17
6	63 (M)	III	CAD	1.5	61	25.5	24
7	54 (M)	III	CAD	1.1	89	27.0	9
8	65 (M)	IV	PMD	1.2	70	20.0	16
9	55 (F)	III	CAD	1.6	47	14.0	16
10	56 (M)	III	CAD	1.4	48	11.8	47
Mean \pm SE	56.6 \pm 2.1			1.46 \pm 0.08	59.7 \pm 4.6	20.5 \pm 1.6	18.5 \pm 8.5
Normal values: mean \pm SE				2.96 \pm 0.44	30.7 \pm 4.80	8.48 \pm 1.63	55 \pm 7.0

CI, cardiac index; NYHA, New York Heart Association classification; TPR, total peripheral resistance; CAD, coronary artery disease; MTT, mean transit time; PMD, primary myocardial disease; EF, ejection fraction.

Table 2 Pretreatment renal, humoral, and volume characteristics in patients treated with captopril for congestive heart failure

Case No	RBF (ml/min/ 1.73 m ²)	GFR (ml/min/ 1.73 m ²)	EF	RBF: CO ratio (%)	PRA (ng/ml/h)	Aldosterone (ng/dl)	Noradrenaline (ng/dl)	TBV (%)
1	249.7	52.8	0.31	9.3	7.9	39.5	520	134.9
2	554.5	126.2	0.40	19.9	20.0	25.3	307	123.3
3	332.2	81.5	0.43	15.6	7.0	58.6	1257	90.3
4	689.5	126.9	0.30	18.8	8.0	18.8	449	134.3
5	487.6	73.8	0.21	19.6	9.0	32.0	380	122.3
6	308.0	56.5	0.31	11.7	0.2	42.7	583	155.0
7	218.3	74.0	0.60	11.4	0.3	26.2	415	98.4
8	189.0	38.2	0.32	8.6	3.6	29.4	649	98.7
9	253.4	46.8	0.27	8.9	10.0	22.2	473	97.5
10	379.5	70.2	0.29	15.6	7.5	46.6	415	85.7
Mean±SE	366±51.5	74.6±9.6	0.35±0.03	13.9±1.4	7.36±1.78	34.13±3.95	544.8±85.1	114.0±7.2
Normal values: mean±SD	771±17.0	123±33	0.26±0.3	15.5	1.2±0.4	12.7±4.9	218±92	100

RBF, renal blood flow; GFR, glomerular filtration rate; EF, ejection fraction; CO, cardiac output; PRA, plasma renin activity; TBV, total blood volume.

Conversion: traditional to SI units—renin: 1 ng/dl≈0.8 mmol/l; aldosterone: 1 ng/dl≈0.03 nmol/l; noradrenaline: 1 ng/dl≈0.59 nmol/l.

those obtained at the time of the peak action of captopril on renal haemodynamic indices to allow for this variability.

Absorption of the drug and biochemical evidence of its action was shown by a reduction in angiotensin converting enzyme activity (76 ± 7 to 28 ± 6 nmol/ml/h, $p<0.01$), an increase in plasma renin activity (7.4 ± 1.7 to 39.7 ± 10 ng/ml/h (5.6 ± 1.3 to 30.5 ± 7.6 mmol/h), $p<0.01$), and a reduction in plasma aldosterone concentrations (28 ± 4 to 23 ± 5 ng/dl (0.8 ± 0.1 to 0.7 ± 0.2 nmol/l), $p<0.05$).

Systemic haemodynamic indices

The first dose of captopril led to a pronounced fall in mean arterial pressure (Table 3) with no appreciable change in heart rate. In the three patients studied using the thermodilution technique the reduction in

blood pressure was accompanied by a decrease in peripheral resistance (46 ± 5.4 u/m² to 33 ± 4 u/m²) and an increase in cardiac output (3.08 ± 0.3 l/min to 3.8 ± 0.2 l/min).

Renal function

Individual changes in mean arterial pressure and renal plasma flow are shown in Fig. 1. Whereas mean arterial pressure fell in all patients renal plasma flow decreased in eight and increased in two. The decrease in glomerular filtration rate was more pronounced than the reduction in renal plasma flow (Table 3), and as a result the calculated filtration fraction decreased. These changes were associated with a pronounced decrease in urinary flow rate and in water and electrolyte excretion.

Both the percentage change in renal plasma flow

Table 3 Acute effects of one dose of captopril (first dose) on renal function in patients with congestive heart failure. Values are means ± SEM

	Initial values (n=10)			Values after 1 week (n=7)			Values after 2-4 months (n=8)		
	Control	Captopril	p	Control	Captopril	p	Control* (at 3 months)	Captopril (next dose)	p
Mean arterial pressure (mm Hg)	88.7±3.6	79.8±3.7	<0.005	89±4	81±5	<0.01	89±5	79±6	<0.01
Effective renal plasma flow (ml/min)	248±39	173±30	<0.05	196±25	242±29	<0.01	274±47	332±70	<0.05
Glomerular filtration rate (ml/min)	82±12	46±7	<0.025	67±12	75±13	NS	78±11	81±10	NS
Filtration rate (ml/min)	0.35±0.03	0.28±0.02	<0.01	0.34±0.03	0.31±0.03	NS	0.30±0.02	0.27±0.03	<0.05
Renal vascular resistance (u/m ²)	280±42	347±52	NS	320±44	228±26	<0.02	234±33	172±23	<0.015
Urine flow (ml/min)	5.6±1.1	2.2±0.7	<0.02	6.0±1.4	7.5±1.7	NS	6.9±1.4	7.9±1.1	<0.05
Free water clearance (ml/min)	3.0±1.1	1.0±0.6	<0.01	3.8±1.1	4.8±1.3	<0.05	5.5±1.5	5.9±1.1	NS
Urinary sodium excretion (mEq/l/min)	87±40	29±19	<0.01	105±31	160±70	NS	135±71	134±61	NS
Urinary potassium excretion (mEq/l/min)	115±28	41±11	<0.01	82±17	61±13	NS	67±16	52±10	NS

*12 hours after last dose of captopril.

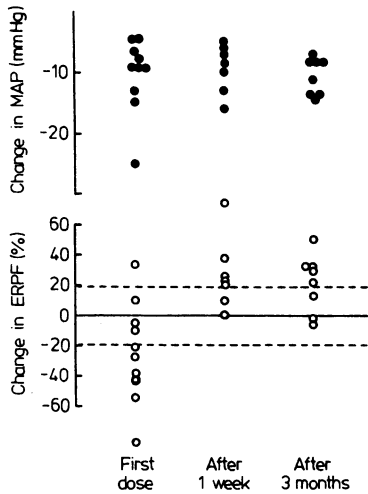


Fig. 1 Effects of captopril (25 mg) on mean arterial pressure (MAP) and renal plasma flow (ERPF) at various stages of treatment.

and the percentage change in glomerular filtration rate correlated with the percentage change in mean arterial pressure ($r=0.70$ and 0.64 respectively, $p<0.05$ for both). Baseline plasma renin activity correlated significantly with the peak effect of captopril on mean arterial pressure ($r=-0.63$, $p<0.05$), renal plasma flow ($r=-0.85$, $p<0.01$), and glomerular filtration rate ($r=-0.79$, $p<0.01$). One patient (Fig. 2) showed progressive azotaemia in the first three days of maintenance treatment with captopril associated with hypotension. Stopping captopril in this patient led to the recovery of renal function and natriuresis. A repeat challenge with the drug three weeks later led to a similar response; captopril treatment in this patient was therefore stopped.

EFFECT OF MAINTENANCE TREATMENT FOR ONE WEEK

Sodium excretion during the first week

Mean sodium excretion gradually rose after several days of treatment. The time delay for this to occur varied among patients (Fig. 3). For the group as a whole sodium excretion was unchanged during the first five days of treatment; an appreciable natriuresis occurred thereafter (Fig. 4).

Systemic haemodynamic indices

After one week of maintenance treatment there was a significant increase in resting supine cardiac output (from 2.5 ± 0.1 l/min in these seven patients to 2.9 ± 0.2 l/min, $p<0.05$). Heart rate was significantly reduced from 82 ± 5 beats/min to 74 ± 4 beats/min ($p<0.01$), and total peripheral resistance fell (from 64.0 ± 5.0

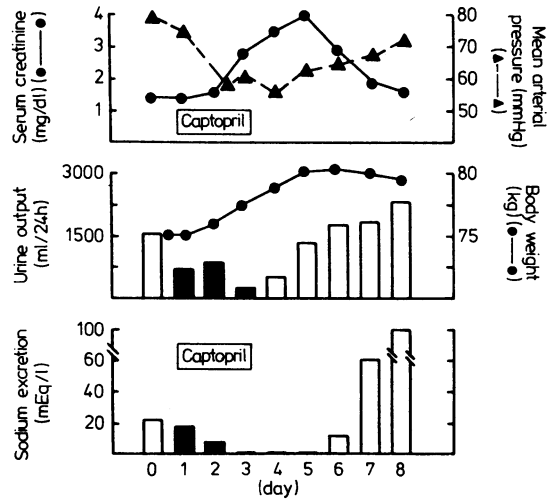


Fig. 2 Deterioration in kidney function in one patient after the first few doses of captopril. Serum creatinine increased gradually (day 2–5), while urine output and sodium excretion were reduced. Stopping captopril (day 5) resulted in a gradual reduction in serum creatinine to reach pretreatment values on day 8. Conversion from traditional to SI units—creatinine: $1 \text{ mg/dl} \approx 88.4 \text{ mmol/l}$; sodium: $1 \text{ mEq/l} = 1 \text{ mmol/l}$.

u/m^2 to $49.0 \pm 5.0 \text{ u/m}^2$, $p<0.005$). The slight decrease in mean transit time (20.8 ± 2.3 s to 17.8 ± 2.1 s) and body weight (72.1 ± 2.8 to 71.1 ± 2.7 kg) did not reach statistical significance.

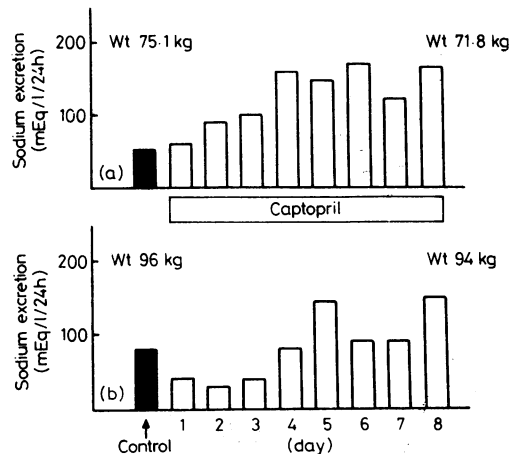


Fig. 3 Sodium excretion in the first eight days of treatment with captopril in two patients. In one patient (a) there was a rapid and progressive increase in sodium excretion, whereas in the other (b) sodium excretion decreased initially but then increased. Body weight fell significantly in both patients during follow up. Conversion from traditional to SI units—sodium: $1 \text{ mEq/l} = 1 \text{ mmol/l}$.

Renal function

Twelve hours after the last dose of captopril blood pressure and renal haemodynamic indices were essentially the same in these seven patients as those seen before the start of treatment with captopril (Fig. 1). Nevertheless, plasma renin activity was higher (12.3 ± 3.7 compared with 6.9 ± 2.5 ng/ml/h (9.4 ± 2.8 vs 5.3 ± 1.9 mmol/l/h), NS) and plasma aldosterone concentration lower (20.6 ± 4.1 compared with 35.8 ± 5.1 ng/dl (0.6 ± 0.1 vs 1.1 ± 0.1 nmol/l), NS) compared with pretreatment values. Angiotensin converting enzyme activity was still significantly reduced (42.5 ± 6.1 mmol/l/h compared with 78.3 ± 9.8 mmol/l/h, $p < 0.05$), suggesting that the effects of captopril had not entirely disappeared.

Administration of a single dose of captopril 25 mg orally under these conditions again lowered mean arterial pressure to the same extent (Fig. 1) in contrast with the acute first dose effect; however, renal plasma flow increased, and glomerular filtration rate (Table 3) was maintained. Filtration fraction decreased, but this change did not reach statistical significance ($p < 0.09$). Urine flow and urinary sodium excretion were maintained despite the fall in blood pressure. Urinary potassium excretion decreased slightly. Free water clearance was increased, and renal vascular resistance was reduced.

EFFECT OF MAINTENANCE TREATMENT WITH CAPTOPRIL (2-4 MONTHS)

Eight of the 10 patients were admitted to hospital two to four months after starting treatment with captopril for the re-evaluation of cardiac and renal function.

Systemic haemodynamics

Chronic treatment with captopril therapy in these patients led to a sustained increase in cardiac output from a pretreatment level of 2.8 ± 0.26 l/min to 3.9 ± 0.36 l/min ($p < 0.05$). Heart rate was slightly slower (85 ± 4 beats/min to 81 ± 5 beats/min, NS). Total peripheral resistance was still significantly reduced (61.0 ± 5.6 u/m² to 41.5 ± 4.1 u/m², $p < 0.05$). Pulmonary mean transit time was reduced to near normal values (upper limit 12 s) from 19.2 ± 2.3 s to 14.0 ± 1.2 s ($p < 0.05$). No significant changes were found in body weight (77.5 ± 3.6 kg vs 77.5 ± 3.7 kg). No correlation could be found between the haemodynamic changes at this stage and pretreatment values of plasma renin activity and plasma concentrations of aldosterone or noradrenaline.

Renal function

Twelve hours after the last dose of captopril angiotensin converting enzyme activity (72.3 ± 7.4 nmol/ml/h) and plasma renin activity (13.7 ± 3.3 ng/ml/h (10.5 ± 2.5 nmol/l/h)) were not different from pre-

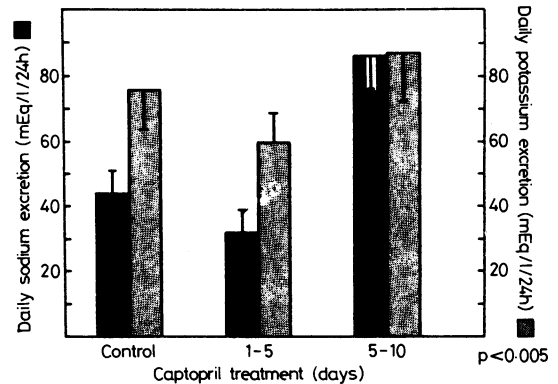


Fig. 4 Mean cumulative values for 24 hour excretion of sodium and potassium in 10 patients during the first 10 days of treatment with captopril. The initial reduction in urinary sodium was not maintained; a significant increase in sodium excretion occurred 5-10 days after the start of treatment. On the other hand, changes in urinary potassium were not significant. Bars represent mean (SEM). Conversion from traditional to SI units—sodium: 1 mEq/l = 1 mmol/l; potassium: 1 mEq/l = 1 mmol/l.

treatment values. Plasma aldosterone concentrations (18.0 ± 2.4 ng/dl (0.5 ± 0.07 nmol/l)), however, remained lower than the control values ($p < 0.02$). Renal blood flow and glomerular filtration rates were remarkably similar to the pretreatment values.

Administration of a single dose of captopril 25 mg orally (Table 3) reduced mean arterial pressure but again increased effective renal plasma flow; glomerular filtration rate was minimally altered (Table 3). Urine flow increased and free water clearance and urinary sodium excretion remained constant, which is similar to the pattern seen at one week.

Discussion

This study was designed to evaluate the effects of blood pressure reduction by captopril on renal function and to elucidate the possible role of renal mechanisms in the clinical improvement of cardiac failure seen during treatment with captopril. Our results indicate that the initiation of converting enzyme inhibition is often associated with a deterioration in renal blood flow and glomerular filtration rates and a reduction in water and electrolyte excretion rates. This association appeared to be closely related to the fall in systemic blood pressure, which was itself correlated with pretreatment values of plasma renin activity. In our patients blood pressures were relatively low, probably near the lower range of renal autoregulation in man. A further decrease may well have lowered perfusion pressures below the limits of effective

autoregulation at which the flow becomes directly related to the perfusion pressure. Patients with severe congestive heart failure may be particularly sensitive to blood pressure reduction because of the intrarenal distribution of blood flow which favours juxtamedullary rather than cortical nephrons. Under conditions of reduced perfusion pressure, the renin content of all glomeruli, including the deep nephrons, increases.^{39 40} These deep nephrons are thought to be less able to autoregulate flow and hence may be especially vulnerable to falls in perfusion pressure, as seen in this study.

Our findings contrast with the small changes seen at comparable levels of pressure during nitroprusside infusion.²⁰ This contrast implies that factors other than pressure alone were playing a role in the renal response to converting enzyme inhibition. Intrarenal angiotensin II may protect glomerular filtration in the face of sodium depletion^{41 42} and circulatory failure^{1 20} by acting preferentially on efferent arterioles and increasing the filtration fraction.^{43 44} A fall in systemic blood pressure and interruption of efferent arteriolar constriction by angiotensin II would appreciably lower glomerular transcapillary hydrostatic pressure and reduce filtration. Furthermore, suppression of renin-angiotensin activity appears to impair glomerular autoregulation.²⁶

Whatever the exact mechanism the fall in renal perfusion may cause appreciable clinical azotaemia as shown in at least one patient (Fig. 2). In this case, the use of captopril was limited by the progressive rise in serum creatinine concentration and the fall in urine flow and sodium excretion over several days. This occurred on two separate occasions and was reversed after the drug had been stopped. Although the extent of that response was exceptional, it does indicate a potential danger; the close correlation between pretreatment values of plasma renin activity and the immediate fall in blood pressure and renal plasma flow might help to identify patients at risk of this complication.

These findings are similar to those seen in patients with congestive heart failure by Pierpont and Cohn²⁵ and in patients with renal artery stenosis^{26 30} when taking captopril but contrast with those of Creager *et al.*,²³ who found improved renal perfusion with the start of treatment. Different patient populations and study protocols may be responsible for the discrepancy in findings; of particular importance in this respect is the fact that we continued diuretic treatment in our patients, whereas in those of Creager *et al.*²³ it was stopped 48 hours before treatment with captopril.

Recovery and improvement in renal haemodynamic indices and function were evident by one week and at two to four months of treatment with captopril. These

changes were associated with an improvement in cardiac index. Similar decrements in blood pressure in response to the same (25 mg) dose of the drug were associated with a well maintained glomerular filtration rate, water and electrolyte excretion, and an actual increase in measured renal plasma flow. These laboratory findings were supported by the clinical improvement noticed in the symptoms related to congestive heart failure, the clearing of oedema, and the improvement in systemic haemodynamic function. During chronic treatment stable weights were maintained despite higher daily sodium excretion, indicating that the patients were able to achieve sodium balance and effective natriuresis despite lower arterial pressures and a higher sodium intake than previously.

Differences between the first dose effects of converting enzyme inhibition and those after long term treatment suggest that an alteration had occurred in the balance of forces determining renal function. Although the sustained moderate rise in cardiac output was associated with a relatively stable ratio of renal blood flow to cardiac output, there was no obvious direct relation between changes in renal blood flow and in cardiac output during treatment. Whether part of the long term improvement in renal response was related to a redistribution of intrarenal flow to cortical areas favouring sodium excretion is admittedly a speculative, albeit attractive, hypothesis. The effects of an agent such as captopril could reasonably be expected to depend on the interplay of several opposing factors including the effects of decreasing angiotensin II, changes in cardiac performance, and possibly the non-angiotensin mediated effects of the drug.^{45 46}

The transient nature of the deterioration in renal function and the sustained improvement with continued treatment stress the need for careful early evaluation of patients with cardiac failure treated with captopril. Moreover, the similarity in renal haemodynamic indices between the pretreatment values and those obtained after withholding the drug for 10 to 12 hours suggests that to maintain improvement doses should be given at closer intervals to prevent periods of reduced renal perfusion. Experience with these patients indicates that a persistent rise in plasma renin activity or a reduction in angiotensin converting enzyme values 10 to 12 hours after the last dose did not mean a similar persistence of renal haemodynamic effects; the latter may fall to pretreatment values more rapidly than these humoral indices.

The complex pattern of findings in this study underlines the importance of sequential determinations of renal and systemic haemodynamic indices in the evolution of cardiac decompensation and its response to treatment. The multiplicity of factors evident in the long term follow up of patients undergoing

Table 4 Sequential renal haemodynamic studies. Figures are means \pm SE (n=6)

Indices of renal function	Before captopril	At 1 week*	At 3 months†
Mean arterial pressure (mm Hg)	91 \pm 5	82 \pm 7**	83 \pm 8*
Glomerular filtration rate (ml/min)	82 \pm 14	78 \pm 13	83 \pm 11
Effective renal plasma flow (ml/min)	215 \pm 32	256 \pm 34**	291 \pm 31*

**p>0.05, *p<0.05.
†2 hours after dose.

captopril treatment^{12,47} is matched by the complexity of responses seen in renal function. If the effect of captopril were to be judged only from a comparison of pretreatment values with those obtained after a week or three months of treatment (Table 4) the conclusion would have been simple (improved systemic and renal blood flow) but probably incomplete. Our comparison of immediate responses to the same dose at different periods of treatment (Table 3) suggests that intrarenal adjustments occur that allow improved renal perfusion and sodium excretion at reduced systemic blood pressures.

These studies show that haemodynamic indices and renal function deteriorate transiently immediately after the inhibition of angiotensin converting enzyme in patients with refractory normotensive congestive heart failure. Some renal adaptation to allow natriuresis and restore glomerular filtration then appears to develop since chronic treatment led to clinical and renal functional improvement despite the lowered blood pressure. Failure to achieve such an adaptation may rarely prove to be a limiting factor to such treatment, in which case progressive prerenal azotaemia could preclude the successful use of captopril.

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