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Portal pressure, renal function and hormonal profile after acute and chronic captopril treatment in cirrhosis

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Summary. The acute effects of captopril in cirrhosis are well known but there are few descriptions of the pattern of response to chronic administration of captopril in this disease. Nine nonuraemic cirrhotic patients with ascites and portal hypertension were studied after 1 week on fixed sodium and water intake (balance diet) and following acute and chronic treatment with captopril (three doses of 25 mg every 30 min and 75 mg · day^{-1} for three weeks, respectively).

Whilst on the balance diet, 7/9 patients were unable to excrete the amount of sodium ingested. After the acute administration of captopril, a significant reduction was seen in arterial blood pressure (86.9 vs 77 mm Hg), with no change in the intra-hepatic pressures (free suprahepatic pressure, FSHP: 15.0 vs 12.1 mm Hg and wedged suprahepatic pressure, WSHP: 22.9 vs 20.7 mm Hg).

After chronic captopril treatment, a drop was observed in portal pressure (FSHP: 9.4 mm Hg and WSHP 18.8 mm Hg, NS) and the arterial pressure returned to its basal level.

The plasma aldosterone concentration decreased, whilst noradrenaline and dopamine increased significantly, the latter more than the former, leading to a reduction in the noradrenaline/dopamine ratio (14.5 vs 5.0). Seven out of nine patients showed enhanced natriuresis and the remaining two, who previously had had a positive sodium balance failed to do so. These haemodynamic, hormonal and renal changes were interpreted as evidence of blockade of angiotensin II generation by captopril, and also as a homoeostatic response by the sympathetic nervous system.

Key words: Cirrhosis, Captopril; portal pressure, dopamine, noradrenaline/dopamine, natriuresis, hepatic haemodynamics, aldosterone, sodium balance, renal function

Most patients with hepatic cirrhosis develop portal hypertension and sodium and water retention, all significant in the prognosis of the disease [1]. Characteristic haemodynamic changes in the syndrome include relative arterial hypotension, peripheral vasodilatation and decreased vascular responsiveness to pressor hormones [2]. Increases in catecholamines, antidiuretic hormone and in the renin-angiotensin-aldosterone axis, characterise the hormonal profile in these patients [2]. A number of reports have recently appeared on the use of converting enzyme inhibitors in diverse diseases, most related to arterial hypertension [3], cardiac failure [4] or the cirrhotic oedematous ascitic syndrome [5]. In the latter condition, the response of renal function is controversial, as Caramelo et al. [5] reported a beneficial effect of chronic captopril administration upon sodium and water excretion, whereas others have demonstrated that angiotensin II infusion promotes a natriuretic response in some decompensated cirrhotic patients [6].

The overall pattern of hormonal changes after chronic converting enzyme inhibition in these patients is poorly established, since most studies have only described the acute effects of converting enzyme inhibition [3, 4, 5, 7].

The purpose of the present study was to elucidate the haemodynamic, hormonal and renal responses to chronic administration of captopril in cirrhotic patients with a moderate to marked oedematous syndrome.

Subjects and methods

Nine male cirrhotic patients, aged 33 to 63 y (mean 53 y), with a moderate to marked ascitic oedematous syndrome were studied. All showed clinical evidence of portal hypertension (collateral circulation, vascular spiders and oesophageal varices), low serum sodium and normal creatinine (Table 1). There were no signs of digestive bleeding, encephalopathy or fever after admission or during the study. Other causes of ascites (carcinoma, infection or pancreatic disease) were ruled out. None of the patients had a Le Veen shunt. The diagnosis of hepatic cirrhosis was made by liver biopsy and the causes were: alcoholism (7 cases), post necrotic HBs Ag (1 case) and cryptogenetic (1 case). As shown in Table 1 the patients may be considered to belong to Types "B" or "C", respectively, or to Stages 2 to 3 of the Child and McDermott classifications.

Medication was discontinued a week before the study, and the patients were started on a fixed sodium and water intake

Table 1. Routine analyses and clinical data on admission

Pat. no.	Serum Na mEq·l^{-1}	Serum creatinine mg·dl^{-1}	Oedema	Ascites[a]	Serum album in g%
1	136	0.77	+ + + +	Massive	3.5
2	134	0.80	+ + + +	Massive	4.1
3	128	0.75	+ + + +	Massive	3.1
4	137	0.70	+ + + +	Massive	3.2
5	129	1.08	+ +	Moderate	4.0
6	135	0.57	+ + + +	Massive	3.1
7	130	1.2	+ + + +	Massive	3.15
8	128	0.60	+ +	Moderate	4.0
9	131	0.57	+ + + +	Massive	3.5

Bilirubin		Transaminases		Alkaline phospha-tase	Pro-thrombin time
Total mg%	Direct mg%	SGOT U·l^{-1}	STGP U·l^{-1}	U·l^{-1}	%
4.53	2.80	125	75	400	90
2.08	1.28	170	69	88	45
4.27	2.92	70	36	119	41
1.14	0.43	13	3	70	80
1.56	0.61	73	40	60	67
4.05	1.95	170	80	106	47
2.88	1.59	59	50	32	64
3.26	2.47	106	42	104	54
2.38	0.86	66	18	235	46

[a] None of the patients had hydrothorax. Normal serum albumin 3.8–5 g%

(40 mEq Na and 1 l tap water per day). This diet was maintained throughout the study. Intrahepatic haemodynamic measurements and evaluation of renal function and hormonal profile were made after 7 days on the balance diet (control condition) and were repeated after the administration of captopril.

Haemodynamic studies

The studies were performed at the imaging diagnostic unit with the patients supine. They were catheterised according to the Seldinger technique, using a # 7 French catheter, through the femoral vein under radiographic control. The catheters was placed in the right suprahepatic vein and its position was checked by injection of radiological contrast medium (Hypaque). Free (F) and wedged (W) pressures were measured under control conditions and after the administration of 25 mg captopril, three times every 30 min (acute captopril treatment); systemic arterial blood pressure was simultaneously recorded by the conventional technique. This investigation was repeated after 3 weeks of chronic administration of captopril 25 mg t. d. s. (chronic captopril treatment). No adverse effect was observed during the study. Preliminary investigations in other patients not included in the study had not revealed any adverse effects of the drug at this dose. Mean arterial pressure (MAP) was calculated using the formula: diastolic pressure + [(systolic pressure – diastolic pressure)/3].

Evaluation of renal function

Twenty-four h creatinine clearance, water and electrolyte excretion, and plasma and urine osmolality, were determined on admission, after the first week on the balance diet, and after the chronic captopril administration. Patients who excreted more or less sodium than the amount ingested in the balance diet are called salt tolerant (ST) and salt intolerant (SI), respectively [8]. Those in whom sodium excretion was increased after chronic captopril are called captopril responders (CR), while those who failed to respond are called captopril non-responders (CRN). Na and K were measured by flame photometry using Li as the internal standard osmolality by the freezing point method and creatinine by the Jaffé method.

Hormonal profile

Haemodynamic studies were carried out at 08.00 h after a 12 h fast. Peripheral venous blood samples were taken under control condition for measurement of plasma renin activity (PRA), plasma aldosterone concentration (PAC) and catecholamines, namely adrenaline (A), noradrenaline (NA) and dopamine (DA). Samples were also obtained to repeat these measurements after chronic captopril administration. Both samples, i. e. those collected control condition and after chronic captopril administration, were taken while patients were on the fixed sodium and water diet. 24 h urine samples were also collected for urinary kallikrein (UK) determination. PRA and PAC were measured by radio immunoassay and catecholamines by the modified radioenzymatic method of Da Prada and Zurcher [9]. UK was determined by the amidolytic method, using the S 2266 synthetic substrate from KABI.

Results are expressed as mean with (SEM). The analysis of significance employed Student's t test for paired values and/or one way analysis of variance with Tukey's test. The Pearson correlation coefficient was also calculated when necessary [10].

Patients gave their written consent to the studies. The protocol was approved by the Clinical Investigation Committee of the Hospital and was in accordance with the Helsinski ethical guide-lines.

Results

Routine analyses on admission showed increased SGOT (from 13 to 170 mUI·ml^{-1}) which diminished during hospitalisation (19–54 mUI·ml^{-1}). The serum albumin concentration was within the normal range (3.54 (0.14) g%; Table 1).

Haemodynamic studies (Fig. 1)

Two patients refused to undergo catheterisation at any time and further 3 did so sporadically. Thus, 6/9 patients were studied under control conditions and after acute captopril administration, and 5/9 under control conditions and after chronic captopril treatment.

After the balance diet, acute captopril administration failed to induce significant changes either in free suprahepatic (FSHP) or in the wedged suprahepatic pressure (WSHP); the values were 15.0 (1.8) to 12.1 (0.9) and 22.9 (2.7) to 20.7 (2.4) mm Hg. Calculated wegded hepatic venous pressure gradient WSHP – FSHP) was 7.58 (1.5) and 8.58 (2) mm Hg, respectively (NS). MAP fell significantly from 86.9 (2.6) to 77 (1.9) mm Hg, $P < 0.05$.

When captopril was given for 3 weeks, FSHP showed a significant decrease from the control value (15.0 (1.8) to 9.4 (0.5) mm Hg; ($P < 0.05$), while WSHP fell less, to 18.8 (2.9) mm Hg (NS); the calculated pressure gradient (9.32 (2.71) mm Hg) was not significantly different from control. Over the three weeks, MAP returned to the initial value (80.2 (3.7) mm Hg). Cardiac rate remained unchanged throughout the study (control phase

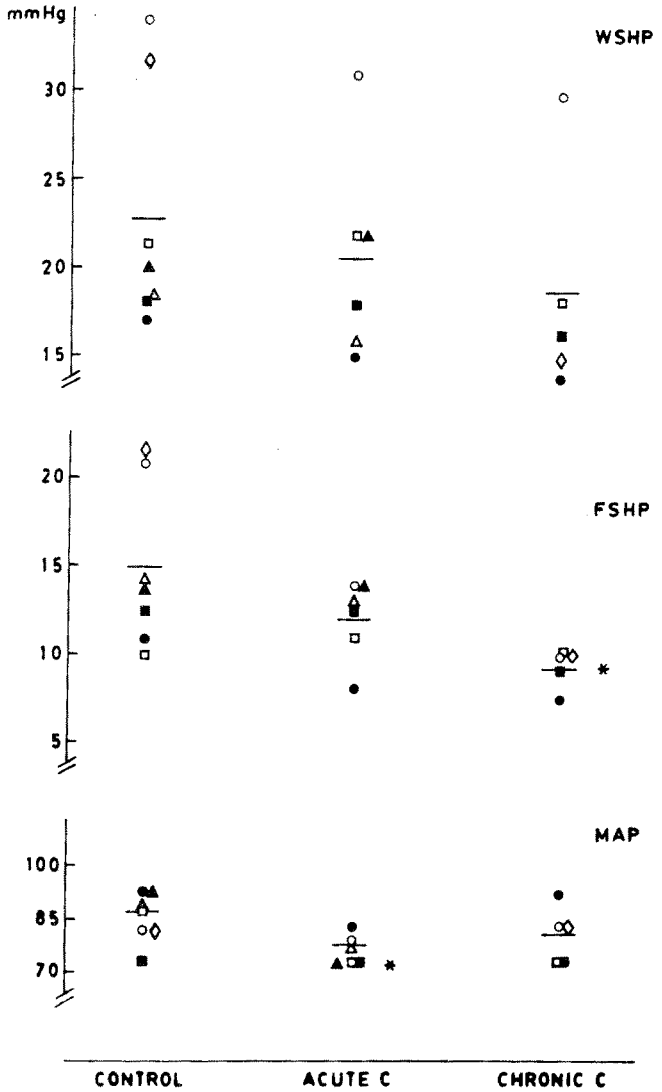

Fig. 1. Wedged (WSHP) and free suprahepatic pressures (FSHP) and mean arterial pressure (MAP) in the control condition and after acute (Acute captopril) and chronic (Chronic captopril) captopril administration. For the acute captopril phase, the last of the three measurements is given. Each symbol represents an individual patient. Horizontal bars indicate mean value for each group. Significant differences from control, obtained by analysis of variance, are indicated by an asterisk

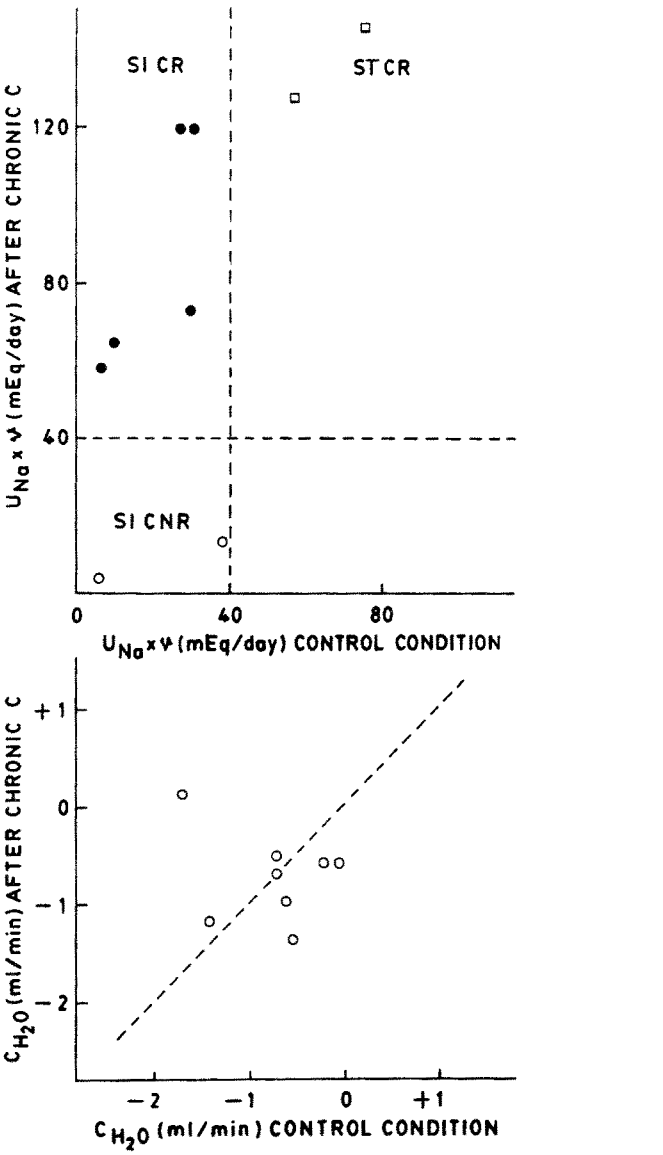

Fig. 2. Upper panel shows individual sodium excretion in the control condition and after chronic captopril treatment. Broken lines indicate amount of sodium excretion expected from intake (40 mEq/day). Black dots (●) indicate salt intolerant captopril responder patients; open circles (○) salt intolerant captopril non-responders, and open squares (□) salt tolerant captopril responders. Lower panel shows water excretion (C_{H_2O} ml/min) in the control condition and after chronic captopril administration. The line of identity is indicated by the broken line

75 (3.5) beats·min^{-1}, acute captopril 77.7 (5.4) beats ·min^{-1} and chronic captopril 74.2 (5.8) beats·min^{-1}).

Renal function

On admission, all patients showed normal plasma creatinine (0.78 (0.07) mg%), sodium 132 (1.2) mEq·l^{-1} and plasma osmolality 285 (5.2) mOsm·kg^{-1} H_2O (Table 1). Urinary osmolality was 468 (88) mOsm·kg^{-1} H_2O and the 24 h urine volume was 1620 (295) ml. Following the first week on 40 mEq daily sodium intake (control condition), 7/9 patients excreted less sodium than the amount ingested (SI), whereas the other two excreted more than 40 mEq (ST; Fig. 2, upper panel). Mean daily urine volume (1340 (100) ml) and osmolality (583 (80.3) mOsm·kg^{-1} H_2O) did not change significantly in any patient. The calculated mean free water clearance (CL_{H_2O}) was −0.68 (0.3) ml·min^{-1}. Sodium and plasma osmolality increased slightly (135 (1.8) mEq·l^{-1} and 292 (5.9) mOsm·kg^{-1} H_2O, respectively).

After three weeks on captopril (Fig. 2, upper panel), sodium excretion had increased significantly in 7 patients, from 36.7 (9.5) to 103 (13.8) mEq per day ($P < 0.001$); they were CRs. In the other two patients sodium excretion remained unchanged (CNRs). Mean daily urine volume and osmolality failed to change significantly but there was an increase in CL_{H_2O} in two patients (from −0.7 to −0.5 and from −1.4 to −1.2 ml/min) and in another a net im-

Table 2. Hormonal and Sodium handling response to chronic captopril treatment

Pat. no.	PRA ng Ang I · ml^{-1} · h^{-1}		PAC ng · 100 ml^{-1}		UK nKat · day^{-1}		Sodium excretion after	
	Basal	Chronic Cap	Basal	Chronic Cap	Basal	Chronic Cap	Diet	Chronic Cap
1	0.9	1.9	84	15	29.7	37.2	SI	CR
2	0.7	1.2	13	14	26.7	3.3	SI	CR
3	16.0	22.0	59	39	3.8	3.0	SI	CR
4	19.0	16.0	34	58	7.7	16.7	SI	NCR
5	12.0	19.0	39	17	8.8	5.7	ST	CR
6	19.0	16.0	100	55	17.8	3.9	SI	CR
7	16.0	15.0	54	39	ND	ND	SI	CR
8	6.8	5.0	50	42	3.4	12.2	ST	CR
9	4.2	4.0	16	22	50.1	60.5	SI	NCR

Cap, captopril; ND, not done; SI, salt intolerant; ST, salt tolerant; CR, captopril responders; NCR, captopril non-responders

provement was found in urine free dilution (from CL_{H_2O} / −1.7 to 0.1 ml · min^{-1}; Fig. 2, lower panel).

Total body weight diminished after chronic captopril treatment in all but two patients, who were CNRs. Weight loss started 48 to 72 h after chronic captopril treatment and reached 3–4 kg at the end of the study. No change in plasma potassium concentration was found at any time during the study.

Hormonal profile

Under control conditions, PRA in relation to natriuresis was high in 5/9 patients and was low or within the normal range in the other four subjects.

On chronic administration, PRA dropped slightly in 5 patients and increased in the other four patients (Table 2). Changes in PRA were not correlated with the observed changes in sodium excretion.

PAC was high in 7/9 patients, and in the other two it remained within the normal range. After three weeks of captopril administration, the high initial PAC had diminished significantly in 6 patients and had increased in one. At most, a slight increase was observed in the other two subjects, who had had normal initial values (Table 2). Patients able to decrease ($n = 6$) or stabilise ($n = 1$) their PAC after chronic captopril treatment (from 57 (10.8) to 31.6 (6.1) ng%, $P < 0.05$), were those who responded to treatment with a natriuresis. PAC was increased in the other two patients, who were unable to excrete sodium after captopril. However, under control conditions, a positive correlation was observed between aldosterone and WSHP ($r = 0.82$, $P < 0.05$) but not between aldosterone and FSHP, or captopril treatment, neither acute nor chronic (Fig. 3).

Under control conditions, UK excretion in relation to natriuresis was within the normal range in 4/8 patients and was low in further 4/8. After chronic captopril administration, UK was diminished in half of the 8 patients. There were no correlation between PAC and UK, PAC but not UK was raised in 7/9 patients (Table 2).

Under control conditions, A and NA were 134 (38) and 417 (58) pg · ml^{-1}, respectively, well above the values obtained in non-cirrhotic catheterised controls. DA was within the normal range (77 (22) pg · ml^{-1}). After chronic administration of captopril, the response of the catecholamines varied according to the ability of the patients to handle sodium intake during the balance period (Fig. 4, left panel). Those who excreted less sodium than the amount ingested (SI), showed no change in A (158 (76) to 133 (22) pg · ml^{-1}) but presented a significant increase in NA (433 (64) to 693 (92) pg · ml^{-1} ($P < 0.05$)) and DA (63 (28) to 119 (22) pg · ml^{-1} ($P < 0.025$)). In patients able to excrete more sodium than the amount ingested (ST), all three cathecholamines were decreased after captopril. The NA/DA ratio (Fig. 5, right panel) was significantly reduced after captopril, from 14.5 (4.65) to 5.0 (0.77; $P < 0.025$), in the SI group. In the two ST patients, the mean ratio was 10.9 before captopril and 15.2 after the treatment.

Discussion

The results show that captopril given chronically to cirrhotic patients induced a decrease in FSHP and WSHP without changing the intrahepatic pressure gradient,

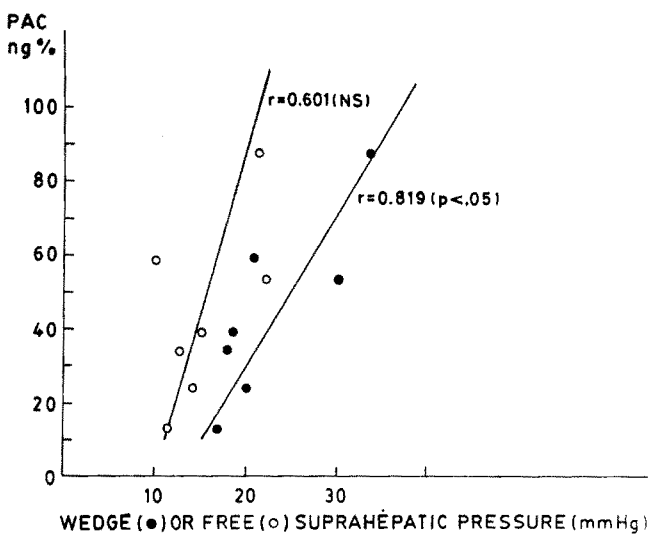

Fig. 3. Correlation between plasma aldosterone concentration (PAC) and wedge (●) and free (○) suprahepatic pressures (mm Hg) under control condition. Each symbol represents an individual patient. Values for suprahepatic pressure are the mean of three determinations. The correlation coefficient and level of significance are indicated for each pressure

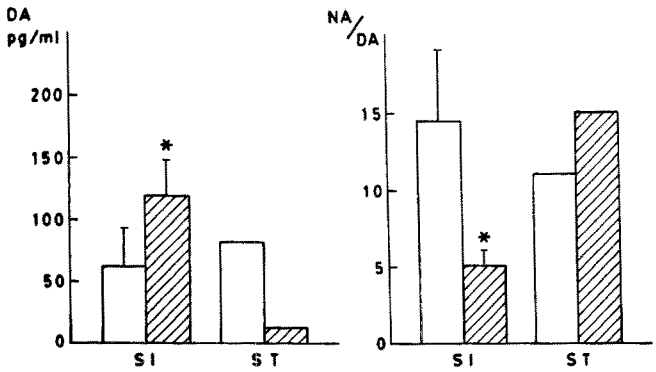

Fig. 4. Free dopamine (DA) (left panel), and noradrenaline (NA)/dopamine (DA) (right panel) in the control state (open bars) and after chronic captopril administration (closed bars) in salt intolerant (SI) and salt tolerant (ST) patients. The asterisk indicates a significant difference ($P < 0.05$) vs control

while systemic blood pressure and heart rate remained unaltered. The data also demonstrate that in patients unable to handle their sodium intake, dopamine level and sodium excretion were increased after chronic captopril administration. Other findings, such as the type of the hormonal profile, interrelation between aldosterone and portal pressure and haemodynamic changes after acute captopril treatment, have previously been described [1, 2, 7, 11–13].

The decrease in intrahepatic pressures observed after chronic captopril administration may be interpreted as a specific effect of the drug on hepatic venous resistance rather than as a secondary response to changes in cardiac output or liver perfusion. If the hepatic venous resistance were under the influence of the renin-angiotensin-aldosterone system, inhibition of converting enzyme should diminish pressure in the hepatic vascular bed [1, 12]. The drop in intrahepatic pressures after chronic captopril treatment may also result from the decrease in ascites following natriuresis, but similar hepatic haemodynamic changes were observed in a patient in whom there was no reduction in ascites or natriuresis. After the treatment, the increase in plasma catecholamine levels, particularly dopamine, was unexpected, since a decrease in plasma catecholamines is observed after chronic captopril administration in congestive heart failure and severe hypertension. In such clinical settings peripheral vasoconstriction is present [3, 4], whereas while marked vasodilatation is found in cirrhosis [14]. Thus, the increase in plasma catecholamine levels observed after chronic captopril administration may be a compensatory response to inhibition of a vasoconstrictor system, most probably renin-angiotensin.

The increased sodium excretion observed in most of the patients after chronic captopril administration was presumably due to the decrease in aldosterone caused by angiotensin blockade [15], or to alteration in sympathetic outflow as reflected by the changes in circulating catecholamine levels. Experimental studies in denervated animals have shown that sodium excretion is directed related to urinary DA and is inversely related to NA excretion. However, the role of endogenous circulating DA in renal sodium handling is controversial [16]. During chronic salt loading, the excretion of sodium, DA and NA was increased, rise being greater in the case of DA. Such findings were attributed not only to local dopamine production but also to an increase in renal sympathetic outflow [17]. Further an increase in urinary sodium excretion beyond the glomerular filtration rate due to dopamine in normal man and cirrhotic patients [19], as well as in experimental animals [18], has been well documented. After chronic captopril treatment, an increase in plasma DA was found, which lead to a decrease in the NA/DA ratio. The changes in plasma DA were quantitatively small and could not account for the large, expected increase in the urinary excretion of DA. It is tempting to speculate that the increase in plasma DA reflected increased renal production of DA. On the other hand, in vitro studies have shown that captopril may directly affect dopamine production by inhibiting dopamine-beta-hydroxylase enzyme activity [20]. The improvement in urine diluting ability recorded in three patients may be interpreted as the result of an antagonism between captopril and antidiuretic hormone operating at a central or tubular level [21, 22]. Neither the classic interrelation between UK and PAC under basal conditions nor the increase in UK after kininase II inhibition was observed in the present patients [23–25]. In such cases UK levels would probably be related to intrarenal haemodynamics rather than to mineralocorticoid activity [26]. Probably after captopril treatment, opposing stimuli affected UK release, namely enhancement when kininase was inhibited, and inhibition when PAC was diminished. In other experimental conditions captopril administration has no effect on UK excretion [27].

Although it is generally accepted that high renin and aldosterone are present in hepatic cirrhosis when certain variables, such as sodium intake, postural changes and the use of diuretics are controlled, only 20 to 40% of patients show this pattern [2]. Whilst on the balance diet, most of the present patients (65%) showed a raised PRA level and a close correlation between PRA and PAC. After chronic captopril administration, patients with activation of the renin-angiotensin-aldosterone system maintained the PRA but showed a lower PAC. Although there are almost no data available about similar findings in cirrhotic patients, McCaa et al. [28] reported that in normal dogs on a low sodium diet, chronic converting enzyme inhibition induced a drop in PAC with almost no change in PRA. This response may also be due to inhibition of renin generation by increased angiotensinogen, as suggested by others [29].

Overall, the haemodynamic, hormonal and renal changes could be interpreted as evidence of blockade of angiotensin II generation by chronic captopril treatment, and also as a homeostatic response of the sympathetic nervous system.

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