RENIN, ALDOSTERONE, URINARY SODIUM AND WEIGHT CHANGE IN CIRRHOTIC PATIENTS WITH ASCITES AND SODIUM RESTRICTION

M. PERPÉTUA ROCHA, RICARDO GORJÃO, D. GARCIA, C. SIQUEIRA, L. FARO, J. PINTO CORREIA

Dept. of Medicine II and Center of Gastroenterology. University Hospital of Santa Maria. Lisboa. Portugal

SUMMARY

To study the relationship between Plasma Renin Activity (PRA), Plasma Aldosterone Concentration (PAC) and Urinary Sodium Excretion in 24 h volume (UNaV), and to determine the prognostic value of these variables in relation to the response to sodium restriction, we studied 25 patients who had liver cirrhosis and non complicated ascites. A wide variation was found both in basal values and after sodium restriction, in PRA (13.7 ± 15.8 and 13.5 ± 14.7 ng/ml/h) and PAC (377.6 ± 437.5 and 441.1 ± 439.1 pg/ml); UNa V was very low in both occasions (27 ± 33.8 and 16.7 ± 14.2 mmol). A positive correlation between PRA and PAC was found when the sodium intake was in the range of 44 ± 10 mEq/day, but not with severe sodium restriction. No negative correlation was found between PAC and UNa V, suggesting that other factors besides Aldosterone, are important in the sodium retention found in these patients. All patients with an initial high UNa V (> 30 mmol/24 h) have low PRA and PAC and lose weight; the opposite is not true. This study confirms that PAC is not the only factor in the renal sodium handling in cirrhotic patients with ascites, and indicate that UNa V is of prognostic value for the response to dietary sodium restriction.

RESUMO

Renina, Aldosterona, excreção urinária de sódio e variação ponderal em doentes cinóticos com ascite e restrição de ingestão de sódio

Pretendeu-se estudar, em 25 doentes com cirrose hepática e ascite não complicada, a correlação entre os valores da renina (PRA) aldosterona (PAC) e sódio urinário (UNAV) e determinar o seu valor prognóstico em relação à resposta destes doentes de sódio na dieta. Houve uma grande variação nos valores obtidos em condições basais assim como após a restrição de sódio, quer no PRA (13,7+15,8 e 13,5+14,7 ng/ml/h) quer no PAC (377,6+437,5 e 441,1+439,1 pg/nl), a excreção de sódio urinário foi baixa em ambas as determinações (27+33,8 e 16,7+14,2 nmol). Encontrou-se uma correlação positiva entre PRA e PAC quando a ingestão de sódio era de 44+10m Eq/dia, o que não se verificou com a restrição de sódio mais marcada. Não houve correlação negativa entre PAC e UNAV, sugerindo que outros factores além da aldosterona intervêm na retenção de sódio observada nestes doentes. Todos os doentes com uma excreção urinária de sódio inicial alta (30nl/24h), tiveram valores baixos de PRA e PAC e perderam peso; o oposto não é verdadeiro. Este estudo confirma que o PAC não é o único factor no manuseamento renal de sódio em doentes com cirrose hepática e ascite, indicando que a excreção urinária de sódio tem valor prognóstico em relação à resposta do doente ascítico à restrição de sal na dieta.

INTRODUCTION

Plasma Renin and Aldosterone are said to be increased in cirrhotics with ascites. [1,2,3] Other authors (Wilkinson and Roger Williams, 1980),[4, 5] however have shown that PRA and PAC are normal in two thirds of these patients, independent of their positive sodium balance. Most studies show a correlation between PRA, PAC and UNa V in cirrhotic patients with fluid retention.[2, 4, 5, 6] On the other hand, in groups of patients with different degree of sodium retention, statistically significant differences were observed in Renin, Aldosterone and Urinary Sodium.[2]

The present study was undertaken to determine the activation of the Renin-Aldosterone-System (RAS), the relationship between PRA, PAC and UNa V, and their prognostic value for the response to sodium intake restriction in cirrhotics with uncomplicated ascites.

MATERIAL AND METHODS

The study was made in 25 patients with alcoholic liver cirrhosis and ascites, 17 males and 8 females. Criteria for selection of patients were: age under 60; clinical or histological data supporting the diagnosis of alcoholic cirrhosis; ascites; absence of arterial hypertension or renal, cardiac, respiratory or endocrinologic disorders. Laboratorial criteria for inclusion in the study included also a plasma creatinine concentration lower than 97.5 μ mmols per liter.

The first evaluation was performed after a period of 5 days of bed rest and diet with 44 mEq of sodium daily: a 24 h urine volume was collected for the determination of sodium and creatinine excretion; after 6 hours in supine position fasting blood samples were collected in prechilled tubes with sodium EDTA, centrifuged, aliquated and stored deep frozen (—20. °C) for the determination of PRA, PAC,

Received: June 16, 1985

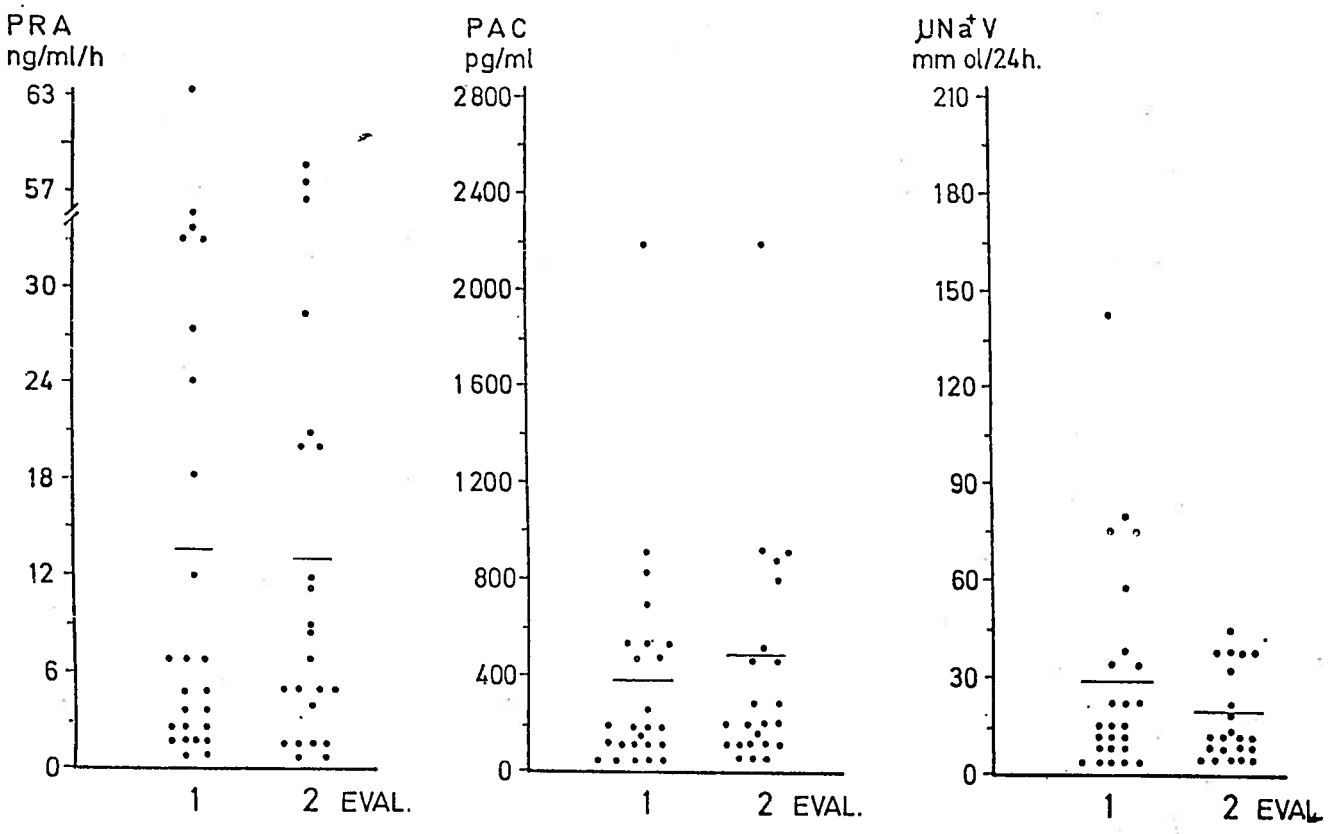

Figure 1: Results of PRA and UNa V on both evaluations; PRA:1st eval. m: 13.7 ± 15.8; 2nd eval. m: 13.5 ± 14.7 ng/ml/h. PAC lst eval. m: 377.6 ± 437.5; 2nd eval. m: 377.6 ± 437.5; 2nd eval. m: 441.1 ± 439.1 pg/ml. UNa V: lst eval. m: 27 ± 33.8; 2nd eval. m: 16.7 ± 14.2 mmol/24h.

plasma electrolytes and creatinine were obtained too; patients weight was recorded.

A diet containing 22 mEq sodium daily was then started, and the same determinations were made on the 8th day (2nd evaluation). No drugs were given during the study. Two patients were lost to 2nd evaluation because they have been discharged from the hospital before the 7th day.

PRA and PAC were measured by radioimmunoassay[7] (Angiotensin I radioimmunoassay Kit — Cis sorin) — Aldosterone radioimmunoassay Kit — Cis sorin). Normal values in our laboratory for subjects at rest in supime position are: PRA = 0.24-3, 24 ng/ml/h; PAC = 12-125 pg/ml. All values were measured twice. The coefficient of variation in within — assay and between — assay for PRA and PAC were respectively 5.8-7.5 %, 9.8-12.2 % for PRA, 7.3-8.2 % 11.0-13.1 % for PAC.

Urinary sadium excretion (24h urine) was measured by iome selective method (Astra Beckman), with normal volue: 100-260 mmol/24h.

RESULTS

On the first evaluation (Fig. 1), mean PRA was 13.7 ∓ 15.8 ng/ml/h (range 0.1 to 62.6 ng/ml/h); the levels were normal (< 3.24 ng/ml/h) in 8 patients and elevated above the normal range in 17 patients. Mean PAC was 377.6 ∓ 437.5 pg/ml (range 45 to 2100 pg/ml); the levels were normal (< 125 pg/ml) in 5 patients and elevated in 20 patients. Mean UNa V was 27 ∓ 33.8 mmol/24 h (range 1 to 140 mmol/24 h); all patients but one (the one with 140 mmol/24 h) have shown very low levels of urinary sodium excretion.

On the 2nd evaluation (Fig. 1), mean PRA was 13.5 ∓ 14.7 ng/ml/h (range 0.1 to 54.3 ng/ml/h); the levels were normal (<3,24ng/ml/h) in 6 patients and elevated in 17 patients. Mean PAC was 441.1 ∓ 439.1 pg/ml (range 43 to 1990 pg/ml); The levels were normal (< 125 pg/ml) in 4 patients and elevated in 19 patients. Mean UNa V was 16.7 ∓ 14.2 mmol/24 h (range 2 to 51 mmol/24 h).

Between the 1st and 2nd evaluation 11 patients put on weight (mean: 827.2 g) and 14 patients lost weight (mean: 1317 g).

PRA was found to be directly related to PAC (Fig. 2), at the first evaluation (r: 0.45, $p < 0.05$); no correlation was found at the 2nd evaluation (r: 0.39, $p > 0.05$). But there was no significative difference between the two evaluations in relation to the mean values of PRA and PAC.

On both evaluations a negative correlation was found between PRA and UNa V (1st = r: − 0.41, $p > 0.05$/2nd = r: — 0.54, $p < 0.01$) but not between PAC and UNa V (Ist = r - 0.31, $p > 0.05$/2nd = r: - 0.28, $p > 0.05$).

According to Fig. 1, there is an increased number of patients below 6 ng/ml/h of PRA, 400 pg/ml of PAC, 30 mmol/24 h of UNa+ V, and a widespread dispersion above those values. These data make possible to draw a line at the above mentioned values.

In relation to the 1st evaluation there are the following further observations (Table 1): all patients with high PRA (>6 ng/ml/h) and/or high PAC (> 400 pg/ml) had UNa V < 30 mmol/24 h but no correlation was found between these values of PRA and UNa V (r: — 0.02,

$p > 0.05$), or PAC and UNa V (r: 0.29, $p > 0.05$); these patients have a variable weight change.

All patients with UNa V < 30 mmol/24 h, have impredictable weight change without relation with the values of PRA or PAC, which are very variable, but all with UNa V > 30 mmol/24 h have low PRA and low PAC and have lost weight. There was no changes on plasma Na+ levels from the first to second evaluation, neither correlation with PAC or PRA.

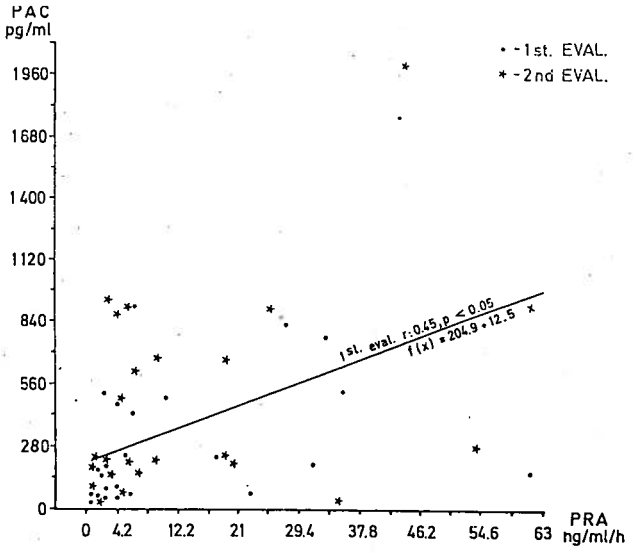

Figure 2: Relationships between PRA and PAC on both evaluations. On the 1st, a positive correlation was found (r: 0.39, $p > 0.05$). on the 2nd, no correlation was found (r: 0.39, $p > 0.05$).

TABLE 1 **On the 1st evaluation, all patients with high PRA and/or high PAC had low UNa V; all patients with high UNa V have lost weight**

	PRA		PAC	
	> 6	< 6	> 400	< 400
PATIENTS	12	13	9	16
U_{Na^+V} > 30 / WEIGHT CHANGE	0 / -	8 / 8↓	0	8 / 8↓
U_{Na^+V} < 30 / WEIGHT CHANGE	12 / 9↑ 3↓	5 / 2↑ 3↓	9 / 8↑ 1↓	8 / 3↑ 5↓

DISCUSSION

The results of the present study confirm that PRA and PAC are quite frequently elevated in cirrhotics with ascites.[1, 2, 3] In spite of this, some authors found normal values of these variables in two thirds of these patients,[4, 5] showing a nonstimulated RAS. These different findings lend support to the two most accepted theories about ascites formation:[4, 5, 7] traditional v.s. over-flow theory. The first theory supports that a sequestration of fluid in the splanchnic territory with reduced effective plasma volume would be the most important signal for activation of RAS with the consequent sodium retention and ascites formation.[8] However some studies show that no correlation can be established between PRA and renal plasma flow (or effective renal plasma flow) or glomerular filtration rate.[2] The second theory, proposed by Lieberman,[3, 4, 9] supports that in other cases the primary event is excessive sodium retention by the kidneys, with a resultant expansion of plasma volume. These patients have a normal PRA and PAC ,they might have either a deficiency of natriuretic factor or an increased renal tubular sensitivity to aldosterone; probably both concepts are true, according to the patients. It seems that several factors may stimulate renin secretion in patients with cirrhosis and ascites: intrarenal redistribution of blood flow, [4,10]hyponatraemia,[4] alterations in splanchnic haemodinamics,[2] humoral agents produced by the liver,[2] neurogenic splanchno--renal reflex.[2] When there is a normal PAC most authors evoke mechanisms other than aldosterone to explain sodium retention, like failure of the natriuretic factor [9, 11, 12] or alterations in the proximal reabsortion of sodium with decreased distal delivery of filtrated and reduced free water excretion.[1, 11]

We could not confirm early observations [2, 5] of positive correlation between PRA and PAC, when patients were submitted to severe sodium restricion. The explanation is difficult to ascertain unless we admit other factors of aldosterone secretion control like sodium and potassium concentration in the extra celular fluid.

A negative correlation was found between PRA and UNa V, but not between PAC and UNa V. These findings were described in several studies;[1, 9, 10] the relation PRA--UNa V may be explained by decrease delivery of sodium to the distal tubule, a strong stimulus to renin production via the macula densa.[10] The absence of relationship PAC-UNa V in our study demonstrates the interference of other factors besides PAC on renal sodium handled in cirrhotic patients with ascites. There is some evidence [11] of a more important sodium reabsortion in the proximal than distal tubule, this may play a fundamental role in pathogenesis of sodium retention in these patients with normal or low PAC.

More than the plasma values of both hormones, urinary sodium excretion appears as the only factor with prognostic value in relation to the response to a sodium restriction diet. As a matter of fact, all patients with UNa V > 30 mmol/24 h lost weight, independently of their initial values of PRA or PAC; patients with UNa V < 30 mmol/24 h can have unpredictable behaviours, either respond to sodium restriction or not, independently of their PRA and PAC values. So urinary sodium excretion is an important (and easy) measurement in these patients because it is an important prognostic marker in relation to the response to sodium restriction diet. Probably those with high sodium excretion will be the patients with better homeostatic mechanism and so better survival rates as shown previously by Rodés and al.[6]

REFERENCES

1. RASOFF, L.; HONTEN, R.: Studies of Renin and Aldosterone in Cirrhotic Patients with Ascites. *Gastroenterology*, 1975; 69: 698-705.
2. BOSCH, M.; ARROYO, V.; RODÉS, J.: Hepatic Haemodynamics and the Renin-Angiotensin-Aldosterone System in Cirrhosis. *Gastroenterology*, 1980; 78: 92-9
3. WONG, P. Y.; CARROL, R. E.; LIPINSKY, L.; CAPONE, R.: Studies on the Renin-Angiotensin-Aldosterone system in patients with cirrhosis and Ascites: effect of saline and albumine infusion. *Gastroenterology*, 1979; 77: 1171-6.
4. WILKINSON, S. P.; WILLIAMS, R.: Renin-Angiotensin-Aldosterone System in Cirrhosis. *Gut.*, 1980; 21: 454-54.
5. GONVERS, J. J.; BRUNNER, H. R.: Ascite Cirrhotique et Sistheme Renine-Aldosterone. *Schweiz Med. Wschr.*, 1980; 110: 869-71.
6. ARROYO, V.; BOSCH, Y.; RODÉS, J.: Plasma Renin activity and urinary Sodium excretion as prognostic indicators in non azotemic Cirrhosis with ascites. *Ann. of Int. Med.*, 1981; 94: 198-201.
7. DUARTE, C. G.: Renal Function Tests 2nd ed. Little, Brown and Company, 1980.
8. OTERO, L.; GONZALEZ, M.; PESQUENA, F. B.; ANDRADE, C. F.; DIEZ, A. C.; KERN, F. A.: La actividad de renina plasmática in la Cirrosis Hepática. Su relacion con el flujo plasmático renal eficaz. *Med. Clin.*, 1977; 68: 339-42.
9. EPSTEIN, M.: Deranged Sodium Homeostasis in Cirrhosis. *Gastroenterology*, 1979; 76: 622-35.
10. ROSOFF, L. SHERLOCK, S.: Renal Haemodynamics and the Renin-Angiotensin System in Cirrhosis. *Dig. Dis. and Scienc.*, 1976; 24: 25-32.
11. NACCARATO, R.; MESSA, P.; D'ANGELO, A.; FABRIS, A.; CHIARMONTE, M.; GREGALIN.; ZANON, G.: Renal handling of sodium and water in Early Chronic Liver Diseases. *Gastroenterology*, 1981; 81: 205-10.
12. EPSTEIN, M.: Natriuretic Hormone and the Sodium retention of Cirrhosis. *Gastroenterology*, 1981; 81: 295-9.

Pedido de Separatas:
J. Pinto Correia
Serviço de Medicina II
Hospital de Santa Maria
1600 Lisboa. Portugal