Aldosterone related blood volume expansion in cirrhosis before and during the early phase of ascites formation

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SUMMARY Thirty-seven patients with liver cirrhosis (16 without ascites: group 1; 21 with untreated ascites at the first onset; group 2) were studied during controlled sodium intake (40 mmol/day). Renal plasma flow, glomerular filtration rate, urinary sodium excretion, plasma sodium and potassium, plasma renin activity, plasma aldosterone concentration, blood volume, and arterial pressure were evaluated. All the patients had normal renal perfusion, plasma sodium and potassium, and arterial pressure. Mean plasma renin activity and plasma aldosterone concentration were significantly depressed in group 1 (p<0.001, p<0.005 respectively) compared with 21 normal controls in identical experimental conditions. This was possibly a consequence of expanded blood volume (p<0.001 compared with controls) which was directly correlated with plasma aldosterone concentration (p<0.001). In group 2 plasma renin activity and plasma aldosterone concentration were normal in over 50% of cases. Blood volume was lower than in group 1 (p<0.002), but again related to plasma aldosterone concentration (p<0.01). In both groups plasma aldosterone concentration was hyperbolically and inversely correlated with urinary sodium excretion, but the two curves were progressively shifted to the left in respect to controls suggesting an enhanced renal tubular sensitivity to the hormone. The results suggest that aldosterone related renal sodium retention, with consequent blood volume expansion, occurs before ascites formation. The mineralocorticoid activity of aldosterone is amplified by an enhanced sensitivity of renal tubules which appears to increase as the disease progresses.

Recent studies performed under controlled experimental conditions in cirrhotic patients without or with untreated ascites, have shown that plasma renin and aldosterone are usually reduced in compensated patients and are often normal in the presence of ascites. These findings have been confirmed by others, suggesting that a different approach to the traditional theory of ascites formation had to be taken into account. The depression of renin-angiotensin system in cirrhotics without ascites has been attributed to extracellular fluid expansion, which implies that sodium retention must precede ascites formation. Even if some authors question a central role for aldosterone in promoting renal sodium retention in cirrhosis with ascites, a close inverse relationship between the rate of urine sodium excretion and both urine aldosterone 18-glicuronide excretion and plasma aldosterone have generally been found in these patients.

The relationship, however, between plasma aldosterone concentration and renal sodium handling in patients with cirrhosis without ascites has not been selectively investigated and it is not clear therefore whether the mineralocorticoid hormone holds a basic role for renal sodium retention preceding ascites formation as well.

In the present study plasma renin activity, plasma aldosterone concentration, blood volume, renal function, plasma electrolytes, arterial pressure, and their interrelationship were assessed in patients with cirrhosis of the liver with and without untreated ascites, in order to evaluate the role of aldosterone in the development of renal sodium retention, and the consequent blood volume expansion during the early stages of the disease.
Methods

Patients
Thirty-seven patients with cirrhosis of the liver were studied. There were 25 men and 12 women, their age ranged from 32 to 71 years (median 51 years). The diagnosis had been established by laparoscopy and liver biopsy (22 cases), liver biopsy alone (11 cases), and laparoscopy alone (four cases). The nature of liver disease was alcoholic (15), post-necrotic (16), nine being HBsAg positive) and cryptogenic (six). Portal hypertension was indirectly established in all patients by the presence of oesophageal varices by means of endoscopy and/or abnormalities of the portal vein and its collaterals by means of laparoscopy and/or ultrasonography.

The patients were divided into two groups, according to the following criteria: Group 1: compensated cirrhosis. The absence of ascites was ascertained by ultrasonography or laparoscopy; previous ascites was excluded by close questioning. Sixteen patients fulfilled these criteria; one of them showed clinical evidence of grade I hepatic encephalopathy. Group 2: cirrhosis with ascites at the first onset. This group included 21 subjects showing ascites with a negative history of previous oedema and/or abdomen swelling and had not been treated with diuretics. Grade I hepatic encephalopathy was present in three cases and grade II in one. The distribution of age, sex, and cause of cirrhosis was comparable in the two groups. No patients had recent gastrointestinal bleeding requiring blood transfusions, or showed features of intrinsic renal disease or heart failure.

Protocol of Study
Immediately after admission to the hospital the patients were placed on the same 1900 calorie diet, containing 60 g protein, 60 g lipids, 280 g carbohydrates, 40 mmol sodium, and 80 mmol potassium daily.

This 'equilibration period' lasted six days and the patients were studied on the morning of the seventh day, starting at 10 am, after overnight fasting, and one hour of bed rest. During this period the patients did not receive diuretics, corticosteroids, prostaglandin inhibitors, amines, and other drugs known to influence renal function or the renin-angiotensin-aldosterone system.

Determinations
1. Na-thiosulphate and p-aminohippurate clearances
After the administration of a 20 ml/kg body weight water load over one hour, an intravenous loading dose of sodium thiosulphate (1·6 ml/kg bw of a 10% solution) was given, followed by constant infusion at 1·6 ml/min rate. An infusion of a 20% solution of p-aminohippurate, in order to maintain plasma concentrations of 2-5 mg/100 ml, started at the same time.

After an equilibration time of 30 minutes, three clearance periods of 30 minutes were performed. At the midpoint of each clearance period peripheral venous blood samples were taken and tested for Na-thiosulphate and p-aminohippurate; at the first midpoint, blood samples for sodium, potassium, plasma renin activity, and aldosteronaemia determinations were also taken. At the end of the clearance periods urine was collected by voluntary voiding (in four occasions an indwelling bladder catheter was used), and the same parameters, except for renin and aldosterone, were evaluated.

Na-thiosulphate (14) and p-aminohippurate (15) were determined by standard techniques. The values given for clearances were obtained by calculating the mean of three clearance periods. Na-thiosulphate clearance values were considered representative of glomerular filtration rate and p-aminohippurate clearance representative of renal plasma flow. Plasma and urine sodium and potassium were determined by flame photometry.

2. Plasma renin activity and plasma aldosterone concentration determinations
Blood samples for plasma renin activity and aldosterone were collected in ice-cooled polyethylene tubes with disodium EDTA as anticoagulant (1 mg/ml of blood). Plasma renin activity was determined by radioimmunoassay for angiotensin I and calculated by the difference between angiotensin I present in 1 ml of plasma incubated with dimercaprol and 8-hydroxyquinolone for three hours at 37°C, pH 6·6, and that present in 1 ml of plasma maintained at 4°C under the above conditions. Angiotensin I was evaluated using a commercial kit from Lepetit SpA. Plasma renin activity values were expressed as ng/ml/h (angiotensin I generation rate). Plasma aldosterone concentration was evaluated by radioimmunoassay using commercial kit from Abbot. Aldosterone values were expressed as pg/ml.

Values for 21 healthy control subjects under identical conditions of sodium intake ranged from 0·68 to 1·99 ng/ml/h (x: 1·37±0·39 SD ng/ml/h) for plasma renin activity and from 32 to 150 pg/ml (x: 98·8±32·43 pg/ml) for aldosteronaemia.

3. Other determinations
Blood volume was calculated according to the technique described by Eisenberg. The ideal body
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weight of patients with ascites was assessed according to Lorentz’s formula
P = T − 100 − (T − 150)/4, where P = body weight, and T = height in centimetres. Blood
volume values were expressed as ml/kg bw. (Values obtained in 11 healthy volunteers ranged from 58 to
85 ml/kg; ± 67.36±8.27 ml/kg).

Daily urinary sodium excretion was evaluated by determining sodium content by means of flame
photometry in a urine sample from a 24 hour collection (\(U_{NaV} = \text{mmol/24 h}\)). Arterial pressure
was estimated by sphygmomanometry

4 Statistical analysis

Results are shown as mean ± SD. In order to evaluate the significance of the differences observed
between the two groups a Student’s t test was performed. Linear functions were used for para-
metrically distributed variables to derive correlation coefficients. If the variables were logarithmically
distributed, the logarithm was used. The analysis of covariance was applied to test differences of the
linear regressions among the patient groups and controls.

Results

Group 1: compensated cirrhosis (Table). The patients showed glomerular filtration rate (114.37±24.94 ml/min), renal plasma flow (697.31±168.14 ml/min), plasma sodium (139.26±3.23 mmol/l), and potassium concentrations (4.22±0.70 mmol/l) and arterial pressure (123±12±11.67 mmHg) within normal limits.

Plasma renin activity was depressed in all but three patients; the difference with mean values of cirrhotics and controls was statistically significant (p<0.001). Plasma aldosterone concentration was reduced in five cases; the remaining 11 showed a tendency to be grouped in the lower level of the normal range so that the cirrhotics’ mean plasma aldosterone concentration was significantly reduced compared with controls (p<0.005). Most patients appeared to be in sodium balance (urinary sodium excretion from 38 to 49 mmol/day), but five showed a clear negative balance (from 55 to 90 mmol/day), and two a positive one (24 and 27 mmol/day). Finally, 12 subjects had expanded blood volume, the remaining four being within the normal range; its mean value was significantly increased in respect to normal subjects (p<0.001).

Group 2: cirrhosis with ascites at the first onset (Table). Again glomerular filtration rate (91±52±26.71 ml/min), renal plasma flow (617.10±95.55 ml/min), plasma sodium (138.57±5.44 mmol/l), and potassium (4.16±0.54 mmol/l) concentrations and arterial pressure (106.43±39.43 mmHg) were not altered in this group considered as a whole. Their mean values were lower than group 1, but the difference reached statistical significance only for glomerular filtration rate (p<0.02).

The mean values of plasma renin activity and plasma aldosterone concentration were significantly higher than in group 1 (p<0.001 and p<0.007 respectively), but it should be noted that over 50% of patients (nine for plasma renin activity and 10 for plasma aldosterone concentration) showed values within the normal range or even slightly reduced (two patients). When compared with our normal controls, the plasma renin activity in patients of group 2 was significantly increased (p<0.001), but plasma aldosterone concentration was not. All subjects were avidly retaining sodium and showed a positive sodium balance. Blood volume was normal in 14 cases, increased in three, and depressed in four, and its mean value appeared to be close to normal and significantly reduced compared with group 1 (p<0.002).

INTERRELATIONSHIP BETWEEN RENIN-
ALDOSTERONE AXIS, SODIUM EXCRETION AND
BLOOD VOLUME

(a) Determinants of urinary sodium excretion.

Log plasma aldosterone concentration inversely correlated with hourly log urinary sodium excretion in both groups, but the relationship was far more significant in group 2 (\(r=-0.59; \ p<0.05; \ r=-0.94; \ p<0.001\)). The weaker correlation observed in group 1 was owing to the fact that at least three patients showed abnormally high plasma aldosterone concentration in respect to corresponding sodium excretion (Fig. 1). In addition the linear aldosterone/urinary sodium excretion relationship
Fig. 1 Correlation between aldosteronaemia and hourly urinary sodium excretion (U\textsubscript{Na}V) in controls and patients. Progressive significant shift to left of regression line is evident for groups 1 and 2 compared with controls.

appeared progressively and significantly shifted to the left in the two groups compared with the values observed in normal subjects (group 1 vs controls: p<0.01; group 2 vs controls: p<0.001; group 2 vs group 1: p<0.001) (Fig. 1).

(b) Determinants of blood volume. Blood volume was significantly correlated with log plasma aldosterone concentration in group 1 (r=0.80; p<0.001) and, to a lesser extent, in group 2 (r=0.66; p<0.01) (Fig. 2).

(c) Renin-aldosterone axis: a significant correlation between plasma renin activity and plasma aldosterone concentration (log values) was only obtained in group 2 (r=0.87; p<0.001).

(d) Factors influencing the renin-angiotensin system: plasma renin activity was inversely correlated with renal plasma flow (r=-0.49; p<0.05), glomerular filtration rate (r=-0.77; p<0.001), plasma sodium concentration (r=-0.89; p<0.001), and arterial pressure (r=-0.56; p<0.01) only in group 2.

Breaking down this group into patients with (4.03±1.21 ng/ml/h) and those without (1.41±0.54 ng/ml/h; p<0.001) raised plasma renin activity, no significant differences were found in blood volume, arterial pressure, and plasma potassium concentration, whereas plasma sodium concentration, glomerular filtration rate and renal plasma flow were significantly reduced in the former (134.50±3.44 mmol/l; 77.60±15.57 ml/min; 576.0±62.40 ml/min respectively) compared with the latter (142.45±3.42 mmol/l, p<0.001; 110.54±21.55 ml/min, p<0.001; 654.45±107.39 ml/min, p<0.001).

Discussion

The possibility that patients with liver cirrhosis show reduced plasma renin activity was first reported by Wilkinson et al.\textsuperscript{1} Other studies followed\textsuperscript{2} and our findings further support the fact that this condition is peculiar for cirrhotics without ascites. As pointed out by Wilkinson et al\textsuperscript{1} a reduced renin substrate availability should be ruled out in these patients and an active suppression of the renin-angiotensin system by expanded blood volume, which is a major determinant of plasma renin activity,\textsuperscript{1} appears to be the most likely explanation for this suppression. Interestingly, such a suppression persists even in the presence of at least one activating factor such as portal hypertension, which has been shown to correlate directly with plasma renin activity in cirrhotics.\textsuperscript{6} In the same study, however, by extrapolating the data of compensated cirrhotics from the whole group of patients, no correlation between these variables was evident.

The lack of inverse correlation between blood volume and plasma renin activity is not surprising as we can assume that a variable and unmeasurable fraction of blood volume was subtracted from the "effective" volume within the splanchnic circulation.
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because of portal hypertension. This concept also applies to patients of group 2, whose mean blood volume was significantly reduced compared with compensated cirrhotics. The finding of blood volumes within the normal range in the majority of our patients with ascites appears to be in contrast with the findings of some authors who have reported expanded plasma volumes in cirrhosis with ascites.2 It is possible that plasma volume measurements in cirrhotics with ascites are artificially high, due to leakage of labelled albumin into the ascites or hepatic lymph during the mixing time. Such an event, however, should not significantly affect the results, as it has been shown by Lieberman and Reynolds17 that simultaneous measurements of plasma and blood volumes in patients with cirrhosis and ascites are comparable. Therefore this discrepancy cannot be fully explained. The reduction of blood volume, however, in cirrhotics with ascites, observed by us, compared with compensated patients, could well explain the fact that patients of group 2 had normal or increased plasma renin activity.

The disappearance of a 'suppressing factor', such as the expanded blood volume, could allow a full-blown response by the renin-angiotensin system when other activating factors are present. In our experience, arterial pressure, and, above all, renal plasma flow, glomerular filtration rate, and plasma sodium concentration, appeared to be the most important factors in this group, confirming the findings reported by others.751820

As with plasma renin activity, plasma aldosterone concentration too has been described as often reduced in cirrhosis, especially in compensated patients.23 In our study the mean values in group 1 were significantly reduced compared with control subjects. It should also be pointed out that 12 out of 21 patients in group 2 had an aldosterone plasma concentration within the normal range or even slightly reduced, so that the mean concentration of plasma aldosterone was not significantly different from that of controls. In spite of that, plasma aldosterone concentration was significantly and inversely correlated with hourly urinary sodium excretion in both groups which proved to be a very important factor in influencing the renal sodium handling of these patients. Similar results have been obtained in patients with cirrhosis with ascites22 or with and without ascites considered as a single group.36

The significant correlation between plasma aldosterone concentration and blood volume has not been previously documented. The gap between measured and effective blood volume should not affect such a relationship, as the aldosterone dependent fluid retention should be distributed in the whole extracellular fluid, whereas the haemodynamically effective blood volume only influences renin release. It can, therefore, be suggested that, in cirrhosis, mineralocorticoid activity is a major determinant of extracellular fluid volume by way of renal sodium retention. This observation, along with the finding of reduced (group 1) or often normal (group 2) plasma aldosterone concentration, would seem to imply an increase in sensitivity of renal tubules to mineralocorticoid activity, as described in dogs with constriction of the thoracic segment of the inferior vena cava22 and suggested by Wilkinson et al3 in patients with cirrhosis. The present evidence of a significant progressive shifting to the left of the relationship plasma aldosterone concentration/urinary sodium excretion in the two groups of cirrhotics compared with controls is in keeping with this concept and suggests that such an abnormality increases as the disease progresses. Another explanation, which should not exclude the suggested tubular hypersensitivity, would be a deficiency of natriuretic factor synthesis and/or release. In fact it has been shown that cirrhotics may be unable to escape from the sodium retention induced by exogenous mineralocorticoids23 and to increase the renal excretion of a natriuretic substance when given an intravenous saline load.24

The increased blood volume of patients in group 1 and the presence of at least two patients of this group in positive sodium balance suggest that aldosterone dependent sodium retention is present before ascites formation and this assumption concurs with the overflow theory of ascites formation.8 The lower blood volume in patients of group 2 could be a sign of compartmentalisation within the peritoneal cavity of the retained fluids. This condition, as reported above, could account both for the normal or increased plasma renin activity found in this group and for the positive sodium balance seen in all the patients with ascites. On the contrary, five patients of group 1 showed a negative sodium balance and three a ratio plasma aldosterone concentration/renal sodium excretion abnormally raised compared with the other subjects with compensated cirrhosis, suggesting that periodic equilibration of extracellular fluid is possible at this stage of the disease. In fact the lack in natriuretic escape is not the rule for compensated cirrhotics as some of them can escape at least partially the effects of exogenous mineralocorticoid administration.2325

A positive relationship between plasma renin activity and plasma aldosterone concentration in patients with ascites has been reported by many others.246 The lack of a relationship between these variables in group 1 is most likely because of the
very low plasma renin activity concentrations, close to the limit of method sensitivity, even if it can not be excluded that when the renin-angiotensin system is depressed, other regulating factors become prevalent in the control of aldosterone secretion. In this respect it is useful to remember that the acute suppression of renin-angiotensin activity, by beta-blocking drugs\textsuperscript{11} or 1-sarcosine 8-isoleucine angiotensin II,\textsuperscript{26} has not been followed by expected changes in plasma aldosterone concentration.

In conclusion, the present study suggests that aldosterone dependent sodium retention, with consequent blood volume expansion, precedes ascites formation in cirrhosis. The sodium retaining activity of the hormone is amplified by an enhanced sensitivity of renal tubules, which appears to increase as the disease progresses.

References


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