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Contents

Characterization of the ANF system in patients with cirrhosis of the liver

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Summary

Defects of the ANF system in cirrhosis could not be demonstrated in terms of an absolute deficiency of plasma levels or evidently major abnormalities of processing in patients with cirrhosis. In the present study the responsiveness of the ANF system to acute volume stimulation by water immersion, the diuretic and natriuretic effects of ANF infusion were examined. Stimulation of ANF release by 1 h immersion was significantly blunted in 10 cirrhotic patients with ascites (increase of plasma ANF by 46 ± 18%), whereas 11 cirrhotics without ascites showed a 104 ± 16% increase, similar to the 117 ± 29% stimulation in 25 healthy controls. Immersion increased urinary volume by 3.6 ± 0.6, 2.0 ± 0.8, and 0.7 ± 0.4 ml/min, and urinary sodium excretion by 146 ± 38, 75 ± 43, and 43 ± 19 µmol/min in controls, cirrhotics without ascites, and cirrhotics with ascites, respectively. Infusion of ANF for 30 min prompted an increase in diuresis and natriuresis in seven cirrhotic patients, which was less marked in patients with ascites as compared to patients without. Thus, the stimulus-response coupling for ANF may be impaired in patients with cirrhosis and ascites.

Introduction

The pathophysiology of renal sodium retention and ascites formation in patients with cirrhosis of the liver has become rather perplexing. There is increasing evidence that activation of the renin-aldosterone system is just one of several factors involved in the impaired volume regulation of cirrhosis. For many years, a deficiency of a putative natriuretic hormone in cirrhosis has been postulated, but never satisfactorily demonstrated. Therefore, investigations on the role of the novel atrial natriuretic factor (ANF) (7) in cirrhosis have been anticipated.

The first communication on ANF plasma levels in cirrhosis showed that there is no absolute deficiency of this novel natriuretic and diuretic hormone in patients with cirrhosis (9). These findings have been confirmed by several groups, reporting ANF plasma levels in patients with cirrhosis and ascites equal to or higher than normal (11).

However, the immunoreactive ANF in plasma of patients with cirrhosis might include different molecular species with altered biological activity, as has been suggested in patients with congestive heart failure (3). By high performance gel permeation chromatography only negligible amounts of immunoreactivity coeluting with precursor forms of

ANF 99-126 have been detected (2). Thus, no evidence for major abnormalities of processing of ANF was found in cirrhosis.

Neither basal plasma levels nor characterization of immunoreactivity necessarily reflect the functional status or the compensatory reactivity of the ANF system. Therefore, in the present study responsiveness of the ANF system to volume stimulation was investigated. Head out of water immersion (WI) in a thermoneutral bath has been shown to induce central hypervolemia with atrial distention and to prompt natriuresis and diuresis (4). Epstein and others have demonstrated in numerous investigations that WI is a useful tool for the study of volume regulation (5): it increases central volume by shifting blood from peripheral vessels thus obviating the necessity of infusing volume expanders that might alter plasma composition. We demonstrated that WI rapidly increases ANF plasma levels in healthy human subjects (10). In the present study WI was used to investigate the response of ANF to acute volume stimulation in patients with cirrhosis.

Infusion of ANF has been shown to induce diuresis and natriuresis in healthy subjects (15). The initial observation of a diuretic effect of ANF in a patient with cirrhosis and refractory ascites (8) prompted us to investigate the renal response to ANF infusion in cirrhotic patients.

Patients and methods

Water immersion: 25 healthy controls and 21 patients with cirrhosis, 10 with ascites and 11 without ascites were investigated after informed consent had been obtained. There was no evidence for cardiovascular, renal, or pulmonary disease in control or patients. No diuretics had been given to any subject for one week preceeding the study. Subjects were on a hospital diet containing approximately 150 meq sodium/day and were prohibited alcohol, tobacco, tea, and coffee the day before and during the experiment. In the morning after complete emptying of the bladder, a catheter was placed in a forearm vein, subjects were given 400 ml of water orally and were seated next to a tank with thermoneutral (34.5 ± 0.2°C) water. After 1 h the subjects were immersed up to their necks in the water bath, maintaining the same position for 1 h. This was followed by another hour of sitting outside the tank. Throughout the investigation 200 ml/hour of water were given orally to ensure adequate urine flow. Urine obtained by spontaneous emptying of the bladder was collected before (0), after 60 min (60 min) and 60 min subsequent to (120 min) the end of immersion. Blood samples were obtained at 0.60 and 120 min.

ANF infusion: ANF (Bissendorf, West Germany) was infused (50ng/kg/min) into a forearm vein of seven patients with cirrhosis, three without and four with ascites in the supine position, (the patients bladder were emptied 1h before starting the infusion) urine was collected immediately before, 1 and 2 h after the start of the infusion. Plasma samples were collected before, 30 min and 2 h after start of the infusion. ANF was determined in extracted plasma samples as described before (2). Plasma renin activity was measured by RIA (16). Data are given as mean and standard error. Data were evaluated statistically by paired or unpaired Students *t*-test.

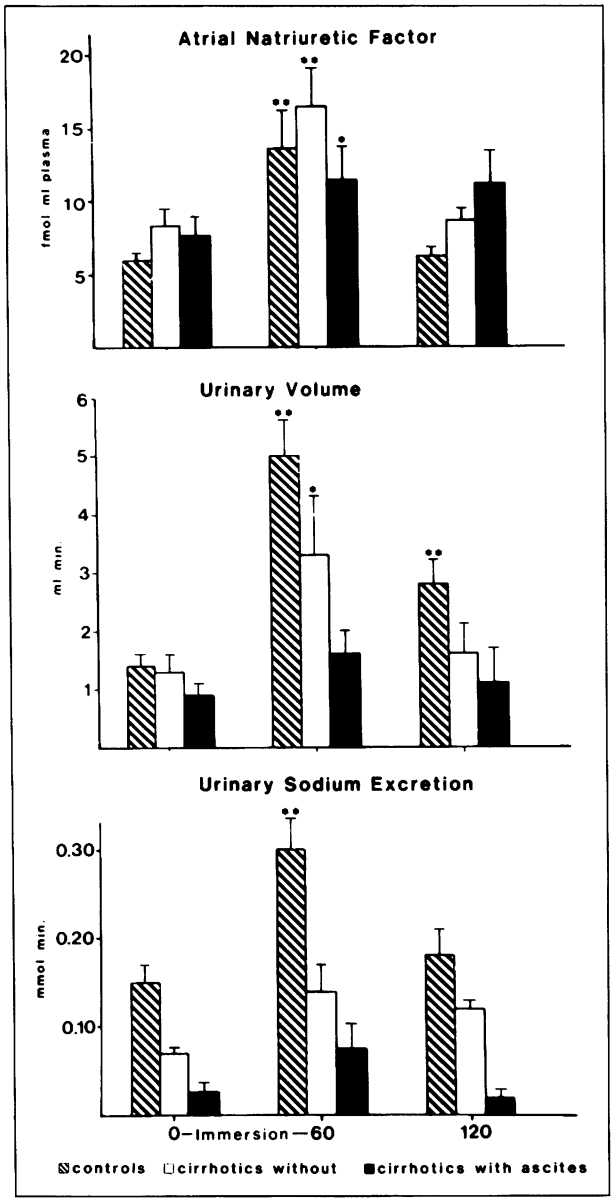

Fig. 1. Plasma levels of Atrial Natriuretic Factor, urinary volume and urinary sodium excretion before (0 min), after 1 hour (60 min) and 1 hour subsequent to (120 min) the end of water immersion in 25 healthy controls, 11 cirrhotic patients without and 10 cirrhotic patients with ascites. * $p < 0.05$, ** $p < 0.01$ as compared to baseline levels

Results

Volume stimulation by water immersion caused a rise of plasma ANF from 6.0 ± 0.6 to 13.6 ± 2.6 fmol/ml in healthy subjects and from 8.5 ± 1.3 to 16.5 ± 2.6 fmol/ml in cirrhotic patients without ascites; increases were significant at the $p < 0.01$ level. In cirrhotics with ascites stimulation of ANF from 7.7 ± 1.3 to 11.4 ± 2.3 fmol/ml was significantly ($p < 0.05$) blunted as compared to cirrhotics without ascites (Fig. 1).

The renal response to immersion is illustrated in Fig. 1. Mean increases in urinary volume were found to be 3.64 ± 0.60 ml/min in controls, 2.02 ± 0.81 ml/min in cirrhotics without ascites, and only 0.68 ± 0.35 ml/min (not significantly different from baseline values) in cirrhotics with ascites. Similar differences were observed in urinary sodium excretion: immersion induced a rise by 146 ± 38 µmol/min in controls, by 75 ± 43 µmol/min in cirrhotics without ascites, and by only 43 ± 19 µmol/min in cirrhotics with ascites. Increases in both cirrhotic groups did not reach the level of significance.

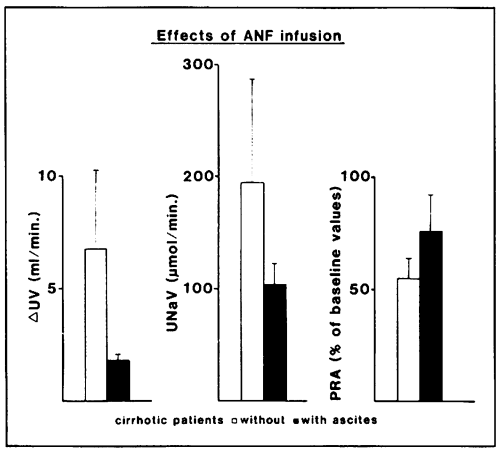

Fig. 2. Increase of diuresis and natriuresis 1 hour after the beginning of a 30 minute infusion of ANF and suppression of plasma renin activity after 30 minutes of infusion in 3 cirrhotic patients without and 4 cirrhotic patients with ascites

Infusion of ANF markedly stimulated diuresis and natriuresis in the hour subsequent to the beginning of the infusion. After another hour renal parameters returned to baseline levels. In patients without ascites the effects were stronger than in patients with ascites (Fig. 2): urinary volume increased by 6.8 ± 3.6 as compared to 1.8 ± 0.3 ml/min, sodium excretion increased by 195 ± 93 as compared to 105 ± 19 µmol/min. Plasma renin activity in patients without ascites decreased from 13 ± 11 to 7 ± 5 ng AI/ml/h; and a similar suppression from 27 ± 21 to 16 ± 10 ng AI/ml/h was seen in patients with ascites.

Discussion

The observation that water immersion significantly increases ANF plasma levels in a large number of healthy subjects is in accordance with previous results from our laboratory (10) and has been confirmed by other investigations (1,6,13,14). Similar increases were observed in patients with cirrhosis of the liver without ascites. In cirrhotics with ascites, however, stimulation of ANF release into the plasma was found to be significantly reduced after 1 h of immersion. This might be due to a decreased volume stimulus in these patients. However, plasma renin activity as an indicator of centrally effective volume decreased in cirrhotics with ascites by a ratio not different from that in cirrhotics without ascites or controls (unpublished observations). Furthermore, central hemodynamics and intracardiac pressures are influenced by water immersion independent of the degree of ascites (12). Thus, a blunted increase of atrial pressure as a stimulus for ANF release does not seem a likely explanation for the observed blunted ANF stimulation in these patients. Therefore, a defective ANF synthesis or release might be suspected in these patients.

The blunted ANF stimulation was paralleled by reduced increases of urinary sodium excretion and urinary volume following immersion in cirrhotics with ascites. While this might suggest a (patho-)physiological role of ANF in volume regulation, no correlations of either basal or stimulated ANF with renal response could be found. In view of the involvement of several other hormonal systems in volume regulation, however, this finding is not surprising.

Furthermore, at comparable baseline plasma levels of ANF, excretion of sodium was diminished in cirrhotic patients as compared to controls, and in patients with ascites as compared to patients without ascites. The renal response to stimulation by water immersion was less marked than the increase of ANF in the cirrhotic groups. These findings might be consistent with the increased activitiy of sodium retaining principles, counteracting the renal action of ANF, or blunted responsiveness of the kidney to ANF in cirrhosis.

Infusion of ANF at a rather low dose induced a marked diuresis and natriuresis in patients with cirrhosis, with a less marked response of the patients with ascites. This might have been due to the lowering of systematic blood pressure by ANF, causing a reflectory increase of renin activity, counteracting the renal effects of ANF. However, with the dose applied no marked decreases of blood pressure were seen and plasma renin activity was suppressed in both cirrhotic groups. Thus, a reduced activity of the renal receptor-effector coupling must be taken into consideration in patients with decompensated cirrhosis.

This study demonstrates a blunted response of ANF release to water immersion in patients with cirrhosis of the liver and might indicate a reduced renal response to ANF in patients with ascites, thus, suggesting a role for this novel hormone in the impairment of acute volume regulation in cirrhosis.

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