

AMERICAN SOCIETY OF HYPERTENSION SYMPOSIUM SERIES

Vol. 1: *Biologically Active Atrial Peptides*

B. M. Brenner and J. H. Laragh, editors, 614 pp., 1987.

Vol. 2: *Advances in Atrial Peptide Research*

B. M. Brenner and J. H. Laragh, editors, 652 pp., 1988.

AMERICAN SOCIETY OF HYPERTENSION SYMPOSIUM SERIES
VOLUME 2

Advances in Atrial Peptide Research

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Raven Press  New York

008 000000
006 102800

6962747

Raven Press, 1185 Avenue of the Americas, New York, New York 10036

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Made in the United States of America

Library of Congress Cataloging-in-Publication Data

Advances in atrial peptide research.

Advances in atrial peptide research / editors, Barry M. Brenner, John H. Laragh.

p. cm. — (American Society of Hypertension symposium series ; v. 2)

Based on a congress held in May 1987 in New York City.

Includes bibliographies and index.

ISBN 0-88167-405-2

1. Atrial natriuretic peptides—Physiological effect—Congresses.

I. Brenner, Barry M., 1937- . II. Laragh, John H., 1924- .

III. Series.

[DNLM: 1. Natriuretic Peptides, Atrial—congresses. W1 AM787 v.

2 / QU 68 A244]

QP572.A86A84 1988

612'.12—dc19

DNLM/DLC

for Library of Congress

88-6730

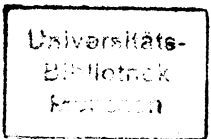
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9 8 7 6 5 4 3 2 1



Q = 78 4112

Acknowledgments

The Editors are privileged to have again played a role in the organizational and scientific aspects of the Second World Congress and wish to express their gratitude to the many authors for their excellent contributions and splendid cooperation. We also gratefully acknowledge the invaluable efforts of the many professionals at Wyeth-Ayerst Laboratories and Raven Press, without whose interest and support these scientific proceedings would not be possible.

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IMPAIRED STIMULATION OF ANF IN PATIENTS WITH CIRRHOSIS AND ASCITES

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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 of the role of atrial natriuretic factor (ANF) in cirrhosis have been eagerly awaited.

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 (1). These findings have been confirmed by several groups, reporting ANF plasma levels in patients with cirrhosis and ascites equal to or higher than normal (2).

However, the immunoreactive ANF in plasma of patients with cirrhosis might comprise 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 (4). 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 water immersion (WI) into a thermoneutral bath has been shown to induce central hypervolemia with atrial distension and to prompt natriuresis and diuresis (5). Epstein and others have demonstrated in numerous investigations that WI is a useful tool for the study of volume regulation (6): 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 (7). In the present study WI was used to investigate the response of ANF to acute volume stimulation in patients with cirrhosis.

PATIENTS AND METHODS

Twenty-five healthy controls and 21 patients with cirrhosis, 10 with and 11 without ascites, were investigated after informed consent had been obtained. There was no evidence for cardiovascular, renal, or pulmonary disease in controls or patients. No diuretics had been given to any subject for 1 week preceding 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 assumed a seated position next to a tank with thermoneutral ($34.5 \pm 0.2^\circ\text{C}$) water. After 1 hr the subjects were immersed to their neck into the water bath, maintaining the same position for 1 hr. This was followed by another hour of sitting outside the tank. Throughout the investigation, 200 ml/hr 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 WI. Blood samples were obtained at 0, 60 min, and 120 min. ANF was determined in extracted plasma samples as described before (4).

Data are given as mean and standard error. Data were evaluated statistically by paired or unpaired Students *t*-test.

RESULTS

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

Renal response to immersion is illustrated in Fig. 1B and C. 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 $\mu\text{mol}/\text{min}$ in controls, by 75 ± 43 $\mu\text{mol}/\text{min}$ in cirrhotics without ascites, and by only 43 ± 19 $\mu\text{mol}/\text{min}$ in cirrhotics with ascites. Increases in both cirrhotic groups did not reach the level of significance.

DISCUSSION

The observation that WI significantly increases ANF plasma levels in a larger number of healthy subjects is in accordance with previous results from our laboratory and has been confirmed by other investigators (8–11). Similar increases were observed in patients

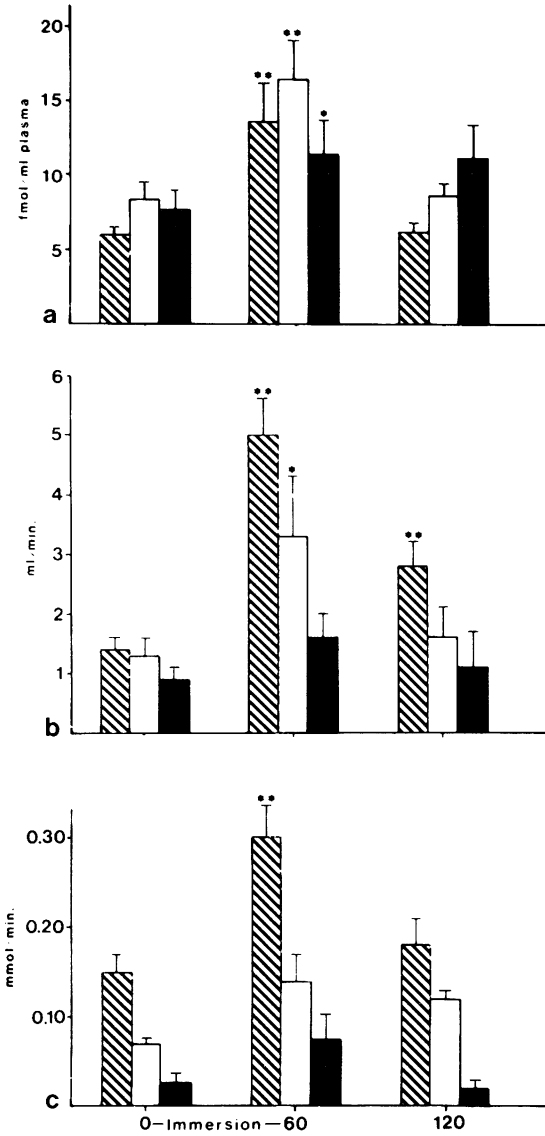


FIG. 1. Plasma levels of atrial natriuretic factor (A), urinary volume (B), and urinary sodium excretion (C) before (0 min), after 1 hr (60 min), and 1 hr subsequent to (120 min) the end of water immersion in 25 healthy controls, 11 cirrhotic patients without ascites, and 10 cirrhotic patients with ascites. (*) $p < 0.05$, (**) $p < 0.01$, as compared to baseline levels.

with cirrhosis of the liver without ascites. In cirrhotics with ascites, however, stimulation of ANF release into plasma was found to be significantly reduced after 1 hr 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 WI independent of the degree of ascites (12). Thus, 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 defect of ANF synthesis, release, or metabolism might be suspected in these patients.

The blunted ANF stimulation is paralleled by reduced increases of urinary sodium excretion and urinary volume following immersion in cirrhotics with ascites. Although 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 increased activity of sodium retaining principles, counteracting the renal action of ANF, or a blunted responsiveness of the kidney to ANF in cirrhosis.

This study demonstrates a blunted response of ANF release to WI in patients with cirrhosis of the liver and ascites and might suggest a role for this novel hormone in impairment of acute volume regulation in cirrhosis.

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