Gastroenterology

Official Journal of the American Gastroenterological Association

W. B. Saunders Company
The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106-3399

NOTICES

Brief notices of interest to a substantial number of our readers are published in GASTROENTEROLOGY. Notices must be typewritten double-spaced and submitted in triplicate. Notices received less than 5 months before the issue of publication cannot be guaranteed an appropriate publication date. Direct all Notices to: Nicholas F. LaRusso, M.D., Editor, GASTROENTEROLOGY, Mayo Foundation, 200 First Street S.W., Rochester, Minnesota 55905.

FALK SYMPOSIA NOS. 72 AND 73

Symposium 72, "IV International Symposium on Inflammatory Bowel Diseases," will take place September 6–8, 1993. "Short Chain Fatty Acids," symposium 73, will be held September 9–11, 1993. Both congresses will be in Strasbourg, Germany.

Contact: Falk Foundation e.V., Leinenweberstraße 5, W-7800 Freiburg, Germany; or call (49) 761-13034-0; or fax (49) 761-13034-59.

SECOND INTERNATIONAL CONFERENCE OF GASTROENTEROLOGY

This conference will be held in Hong Kong August 27–29, 1993, and in Chengdu August 27–September 2, 1993.

For information and application, please contact: Conference Secretariat, Room 1611-13, World Finance Center, North Tower, Harbour City, Kowloon, Hong Kong; or call (852) 736-7837; or fax (852) 376-0329.

INTERNATIONAL CONFERENCE ON ENDOTOXINS AMSTERDAM IV

This conference will take place in Amsterdam, The Netherlands, August 17–20, 1993.

Contact: Dr. S. J. H. van Deventer, Conference Secretary, Department of Hematology (G-1-112), Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; or call (31) 20-5669111; or fax 09 (31) 20-5664440.

THE AGA 1993 FALL POSTGRADUATE COURSE

The topic for this course is "A Comprehensive Update and Review of Gastroenterology and Hepatology." It will be held September 9–12, 1993, in Chicago, Illinois. CME Credit (24.5 hours, Category I) will be offered.

Contact: Registration Manager, SLACK Incorporated, 6900 Grove Road, Thorofare, New Jersey 08086-9447; or call (609) 848-1000; or fax (609) 848-5274.

THE LEEDS COURSE IN CLINICAL NUTRITION

This event will take place September 7–10, 1993, in Leeds, England.

Contact: Mrs. Hilary L. Helme, Dept of Continuing Professional Education, Continuing Education Building, Springfield Mount, Leeds LS2 9NG, England; or call (44) 532-333233.

SECOND ANNUAL SCIENTIFIC MEETING OF THE DYSPHAGIA RESEARCH SOCIETY

Abstracts of scientific works in physiology/pathophysiology of swallowing and dysphagia-related topics are invited for presentation. This meeting will be held October 22–24, 1993, in Lake Geneva, Wisconsin. Deadline for submission of abstracts is September 1, 1993.

Contact: Dysphagia Research Society, Administrative Office, c/o Reza Shaker, M.D., GI Section/111C, VA Medical Center, 5000 West National Avenue, Milwaukee, Wisconsin 53295; or call (414) 384-2000, ext 6943; or fac (414) 384-8480.

14TH INTERNATIONAL CONGRESS OF LYMPHOLOGY

The following conferences will be held in Washington, D.C. "Frontiers in Lymphology" (Part 1) will be held September 20–21, 1993, and "Lymphology in 1993" (Part 2) will be held September 22–26, 1993.

Contact: 14th ICL Congress Secretariat, c/o M. H. Witte, M.D., Attention: Grace Wagner, Program Coordinator, Department of Surgery/General, University of Arizona College of Medicine, 1501 North Campbell Avenue, Tucson, Arizona 85724; or call (602) 626-6118; or fax (602) 626-0822.

ASPEN BILE ACID/CHOLESTEROL/ LIPOPROTEIN CONFERENCE

This conference will take place August 21–24, 1993 in Aspen, Colorado. Deadline for applications is May 30, 1993.

Contact: Mrs. Bernie C. Kern, 501 Madison Street, Denver, Colorado 80206; or call (303) 325-0330; or fax (303) 355-0739.

15TH ANNUAL ASPEN CONFERENCES ON PEDIATRIC DISEASE

This conference will be held July 26–30, 1993, in Aspen, Colorado. Twenty-five hours of Category I credit will be offered.

Contact: Institute for Pediatric Medical Education, 6604 Landon Lane, Bethesda, Maryland 20817; or call/fax (301) 229-8338.

AUTHOR INDEX TO VOLUME 104

KEY TO ABBREVIATIONS

aga—American Gastroenterological Association
br—Book Reviews
cr—Case Reports
cch—Clinical Challenges
ceig—Commemorative Essays in Gastroenterology
c—Correspondence
e—Editorials
paps—Policy and Position Statement
ss—Selected Summaries
srr—Special Reports and Reviews
tmig—This Month in Gastroenterology
vodd—Viewpoints on Digestive Diseases

SUBJECT INDEX TO VOLUME 104

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CENTRAL BLOOD VOLUME IN CIRRHOSIS

Henriksen J, Bendtsen F, Gerbes A, et al. (Departments of Clinical Physiology and Hepatology, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark; Department of Internal Medicine and Endocrinology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; and Department of Medicine II Klinikum Grosshadern, Ludwig Maximilian University, Munich, Germany). Estimated central blood volume in cirrhosis: relationship to sympathetic nervous activity, β-adrenergic blockade and atrial natriuretic factor. Hepatology 1992;16:1163–1170.

The dispute between the "overflow" and "underfill" theories of early pathophysiology in cirrhosis shows no signs of early resolution. Regardless of what the initial events might be, however, in the more advanced stages of cirrhosis the clinical picture suggests a maldistribution of blood volume. The authors of the present article have been interested in determining the volume of blood contained in the heart, lungs, and central arterial tree, which they have termed the estimated central blood volume (ECBV). The present study from Copenhagen is an attempt to quantify the ECBV and

to look for correlations with sympathetic nervous activity, atrial natriuretic factor (ANF) levels and the effects of adrenergic blockade on these parameters. This is one of a series of studies by a group of investigators that has had a long-term interest in the hemodynamic abnormalities associated with cirrhosis.

Nineteen patients (17 male) with biopsy-proven cirrhosis were studied and compared with 16 subjects (12 male) with normal hepatic function. Nine other subjects served as controls for assay of arterial and renal venous catecholamines. The cirrhotic patients were roughly equally divided into Child–Turcotte groups A–B and C. Patients and controls underwent catheterization of the right atrium as well as the hepatic and renal veins. An arterial catheter was positioned at the bifurcation of the aorta. Total plasma volume, whole blood volume, and cardiac output were determined as previously described (Gastroenterology 1989;97:1506–1513) by the same group of investigators. The hepatic gradient was determined by direct measurement.

The ECBV is calculated by multiplying the cardiac output by the mean indicator transit time. The latter figure is the mean time of indicator sojourn in the central vascular bed. This is estimated from the time-weighted area under the arterial indicator curve following an injection of ^{125}I-labelled albumin at the junction of the inferior vena cava and the right atrium with arterial sampling at the level of the aortic bifurcation. Plasma catecholamines and ANF levels were determined by standard methods (Gut 1984;25:1034–1043; Liver 1986;6:361–368).

There was a significant difference in the ECBV between cirrhotics (22.9 mL/kg) and controls (27.2 mL/kg). As would be expected from this finding, the mean central circulation time was less in the cirrhotic patients (14.0 seconds ± 4.1) compared with the controls (20.0 seconds ± 6.1). There was an inverse relationship between the hepatic gradient, which reflects portal pressure, and the ECBV. The cirrhotics had an increase in total plasma volume along with a decrease in mean arterial blood pressure and systemic vascular resistance. Arterial plasma norepinephrine (but not epinephrine) levels were significantly increased in the patients (3.08 vs. 1.36 nmol/L). There was an inverse correlation between norepinephrine levels and ECBV. Plasma ANF levels were normal in both patients and controls. β-blockade caused the expected decrease in heart rate and cardiac output while the central circulation time increased, thereby leaving the ECBV unchanged. Arterial catecholamines rose after propranolol administration, but there was no correlation with the ECBV.

Comment. The main conclusions of this article are that at some stage of cirrhosis, not necessarily at its inception, there is a maldistribution of blood with a relative deficiency of plasma volume in the ECBV associated with a rise in the levels of norepinephrine. The authors suggest that these changes are causally related, because there was a strong inverse relationship between ECBV and renal vein catecholamines. There are several other studies confirming the elevation of norepinephrine in cirrhosis (Lancet 1986;(Oct): 939–992) and (N Engl J Med 1982;309:1152–1157). The authors contend that this central underfilling contributes directly to the enhanced sympathetic activity with renal sympathetic overactivity causing reduced renal blood flow and increased sodium and water retention in established cirrhosis. This interpretation is in keeping with the authors' previous work in which an hypothesis is suggested for the early changes in cirrhosis. They have postulated an initial decrease in peripheral resistance (of unknown cause), which then leads to peripheral sequestration of fluid, a decrease in ECBF, under perfusion of baro- and volume receptors with consequent increase in sympathetic activity and associated salt and water retention. Although this is an attractive theory, there are a number of factors it does not explain such as the role of other salt-retaining hormones and the surprising lack of effect of β-blockade on the ECBV in spite of major hemodynamic shifts. This might raise the question of how definite an entity the ECBV is because its determination is based on catheter placement, which must be somewhat arbitrary. Rector (Gastroenterology 1988;95:1658–1663) reported that left atrial size was actually greater in cirrhotics, whereas both left and right atrial pressures were similar in cirrhotics with and without ascites. This would appear to excuse the heart of any "central underfilling" in cirrhosis. Because there is no evidence of differences in pulmonary vascular capacity, this leaves only the aorta as a possible site for the decreased ECBV. One could also point out that there is no present explanation for the initial decrease in peripheral resistance postulated by the authors, but this, perhaps, is not too different from the situation with the classic "overflow" theory in which the early message from the liver to the kidney remains a postulate rather than a measurement.

The lack of any demonstrable role for the ANF in this theory is surprising. ANF has been reported to be low, normal, and high in cirrhosis. Unless these discrepancies are all due to technical errors (unlikely), this suggests that ANF levels may fluctuate at various stages of cirrhosis, and our separation into "compensated" and "decompensated" is too crude to detect these changes. A recent study by Angeli et al. (Hepatology 1992;16:1389–1394) has shown several subgroups of cirrhotics in which ANF levels correlate with various hormone patterns. The present study shows convincingly that plasma- and blood-volume distribution in cirrhosis is abnormal. Most physicians will have little argument with the findings showing that cirrhotics have a high cardiac output, low peripheral resistance, and too much blood in the peripheral vessels and splanchnic bed with too little in the large central arteries, because all these determinations fit well with clinical observation. Whether increased sympathetic tone is an etiological factor in these changes, however, remains at best an hypothesis.

J. G. SWEETING, M.D.

Reply. We would like to thank Dr. Sweeting for his comments on our report regarding central blood volume and sympathetic overactivity in cirrhosis (Hepatology 1992;16:1163–1170). We fully agree that the dispute between the "overflow" and "underfill" theories of early pathophysiology in cirrhosis seems to have no easy solution.

Dr. Sweeting raises the question of how definite an entity the central and arterial blood volume (ECBV) is and excludes the heart of any "central underfilling" based on a previous paper by Rector and Hossak (Gastroenterology 1988;95:1658–1663). ECBV (determined according to the kinetic theory as mean transit time in the central circulation multiplied by cardiac output) is the

blood volume in the heart cavities, lungs, and central arterial tree, i.e., the volume of blood contained within the arterial tree up to points that are temporally equidistant from the heart to the aortic bifurcation. The aortic bifurcation is arbitrary, but this was applied in cirrhotics as well as in controls. Rector and Hossak (Gastroenterology 1988;95:1658–1663) and Rector et al. (Gastroenterology 1990;99:766–779) have reported increased left atrial diameters in patients with cirrhosis and a nonsignificant increase in right ventricle diameter. However, taking a close look at their values obtained by echocardiography the average increase in the cardiac chambers is only 16 mL compared with controls (Hepatology 1991;13:1261). This is indeed a low difference compared with our decrease in ECBV (300 mL). Moreover, it should be recalled that volume detection by echocardiography has a relatively low accuracy (Am J Cardiol 1983;52:1249–1257). Thus, if the presence of ascites changes the configuration of the heart, volume measurement by standard echocardiographic procedures may not be correct (Hepatology 1990;11:662–667). Altogether, the findings referred to by Dr. Sweeting do not provide convincing points against our data.

ANF plasma concentrations are the result of both release and clearance (Life Sci 1990;47:1173–1180). Thus, alterations of ANF clearance by the liver and splanchnic circulation (Hepatology 1992;16:790–793) may counteract changes of ANF release in cirrhosis, resulting in unchanged plasma concentrations. Furthermore, the missing relation to ANF in our study may in part be due to the fact that 58% of the patients received diuretics, which are likely to influence the circulating levels of ANF. Moreover, the ANF data by Angeli et al. (Hepatology 1992;16:1389–1394) mentioned by Dr. Sweeting support our contention of a marked underfilling in decompensated cirrhosis.

We agree that there is no good present explanation for the decrease in systematic vascular resistance, but a number of potent vasodilators are increased in patients with cirrhosis (Lancet 1984;1:1480–1483; Gut 1988;29:1167–1172; J Hepatol 1991;12:118–123).

Finally, the enhanced sympathetic nervous activity is, most likely, a consequence of central and arterial underfilling, not an etiological factor.

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