Elevated Plasma Norepinephrine Concentrations in Decompensated Cirrhosis
Association with Increased Secretion Rates, Normal Clearance Rates, and Suppressibility by Central Blood Volume Expansion

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SUMMARY. Plasma norepinephrine concentrations are elevated in patients with decompensated cirrhosis, and correlate inversely with urinary sodium and water excretion. Increased plasma norepinephrine concentrations may result from a decreased metabolic clearance rate or an increased secretion rate, possibly in response to a decreased “effective arterial blood volume.” If the latter hypothesis is correct, plasma norepinephrine might be expected to be suppressed when central blood volume is expanded by head-out water immersion. In the present study, plasma norepinephrine secretion and clearance rates were determined by infusion of tritiated norepinephrine. Norepinephrine secretion rates were elevated in eight cirrhotic patients as compared to control subjects (1.50 ± 0.25 vs. 0.26 ± 0.08 µg/m² per min, P < 0.001), whereas clearance rates were similar (3.13 ± 0.48 vs. 2.60 ± 0.28 liters/min, NS). Baseline plasma norepinephrine concentrations were markedly elevated in the cirrhotic patients (830 ± 136 vs. 185 ± 12 pg/ml, P < 0.001). Head-out water immersion significantly suppressed plasma concentrations of both norepinephrine (704 ± 72 to 475 ± 70 pg/ml, P < 0.005) and epinephrine (121 ± 33 to 57 ± 10 pg/ml, P < 0.05) in all seven patients studied. We conclude that the high circulating catecholamine concentrations in cirrhosis are secondary to increased secretion, rather than to decreased metabolic clearance, and are suppressible by central blood volume expansion.

RECENT studies in which a sensitive radioenzymatic method was used have demonstrated elevated concentrations of plasma norepinephrine (NE) in decompensated cirrhotic patients (Henriksen et al., 1981; Bichet et al., 1982; Ring Larsen et al., 1982). Results of such studies have also demonstrated that the inability to excrete a water load provides a reliable means to delineate those cirrhotic patients who will have the highest plasma concentrations of NE (Bichet et al., 1982). These so-called “non-excretor” patients also have other hormonal indicators of a decrease in effective arterial blood volume (EABV), including elevated plasma concentrations of renin, aldosterone, and vasopressin (Bichet et al., 1982).

These findings have supported the “underfilling” hypothesis of sodium and water retention in cirrhosis (Better and Schrier, 1983). Moreover, since considerable experimental results indicate that the non-osmotic release of vasopressin is mediated by alterations in baroreceptor activity, it has been proposed that diminished afferent vagal and glossopharyngeal neural traffic to the central nervous system initiates both vasopressin release (Schrier et al., 1979) and increased efferent sympathetic activity. Since it has been demonstrated that neural alterations in baroreceptor activity in normal subjects are associated with parallel changes in plasma NE (Grossman et al., 1982), the proposal has been made that the elevated plasma concentrations of NE in cirrhotic patients result from increased NE secretion rates.

Alternatively, diminished NE clearance rates may account for, or substantially contribute to, the increased plasma NE concentrations in non-excretor cirrhotic patients. The viability of this possibility is supported by the observation that these “non-excretor” patients with decompensated cirrhosis exhibit a significantly higher incidence of ascites and hypoalbuminemia than the cirrhotic patients who can excrete a water load normally (Bichet et al., 1982). Thus, at least the hepatic component of NE clearance could theoretically be substantially diminished in the non-excretor patients. However, studies by Ring Larsen et al. (1982) documented normal hepatic NE extraction in decompensated cirrhotic patients.

The present study was therefore undertaken to examine the whole-body NE secretion and clearance rates in non-excretor cirrhotic patients. Since volume and/or baroreceptor-mediated increases in NE plasma concentrations should diminish during improvement in EABV, the effect of head-out water immersion (HWI) on plasma catecholamine concentrations was also examined.
Methods

Eight patients with decompensated cirrhosis (clinical ascites present) were admitted to the Clinical Research Center of the University of Colorado Health Sciences Center. Their ages ranged from 36 to 63 years, mean 52.8 ± 2.9 years. Seven of the patients were male. Five days prior to study, all drugs were discontinued and the patients were placed on a 40 mEq/day sodium diet. Fluid intake was unrestricted. The normal subjects were 7 healthy volunteers (6 male), on no medication, and ranged in age from 22 to 48 years (mean 30 ± 3.2 years). Informed consent was obtained from all subjects, and the research protocol was approved by the Human Research Committee of this institution.

NE kinetics were determined by a method slightly modified from that of Esler et al. (1980). Tritiated NE, levo [7,8-3H;N]3,4-(OH)2C6H3CH(OH)CH2NH2, with specific activity 20–40 Ci/mmol (New England Nuclear) was diluted in 0.02 n sterile acetic acid and sterilized by millipore filtration. A 100-μCi aliquot of this solution was added to 150 ml of sterile 5% dextrose in water and infused intravenously at a constant rate of 0.35 μCi/min for 90 minutes. The average total tritiated NE dose was 54 μCi. The dose of NE given was 0.002 μg/kg/min, an amount insufficient to elevate blood pressure, heart rate, or total plasma NE level. Serial 6-ml blood samples were drawn at 10-minute intervals during the [3H]NE infusion from an indwelling intravenous catheter in the contralateral forearm, and were assayed for total NE and [3H]NE. The mean of these 10 determinations was taken as the baseline NE concentration for each subject.

During steady state conditions, the infusion rate of [3H]NE equals its rate of removal from the plasma. Since the infusion dose is assumed to be too low to affect endogenous clearance rate, the clearance rate of endogenous NE equals the clearance of [3H]NE, which is expressed by the following equation:

\[ \text{Clearance} = \frac{\text{[3H]NE infusion rate (dpm/min)}}{\text{Steady state plasma [3H]NE (dpm/ml)}} \]

The apparent secretion rate (ASR) of NE into the plasma is calculated as:

\[ \text{ASR} = \frac{\text{[3H]NE infusion rate (dpm/min)}}{\text{Specific activity of plasma [3H]NE (dpm/pg)}} \]

where specific activity of plasma [3H]NE (dpm/pg) = [plasma [3H]NE (dpm/ml)/[total plasma NE (pg/ml)]].

Plasma [3H]NE activity for clearance rate and apparent secretion rate calculations was derived by alumina extraction of the plasma obtained at 70, 80, and 90 minutes (Esler et al., 1980). [3H]NE concentration was determined by liquid scintillation counting of the perchloric acid extract. The counting efficiency of the Packard liquid scintillation counter was 60%, and [3H]NE concentrations (cpm/ml) were corrected to obtain dpm/ml. Mean percent recovery of [3H]NE from the plasma was 64.0 ± 2.5%.

Endogenous plasma NE concentrations and the NE concentrations of the perchloric acid extracts were measured by a modification (Bichet et al., 1982) of the radioenzymatic method of Peuler and Johnson (1977). The method of Peuler and Johnson (1977) served as his own control, and was studied on two occasions in the same semirecumbent position, at the same time of day. On each occasion, the patient received a standard 20 ml/kg water load intravenously over 30 minutes, before study. On one of the two occasions, in a random sequence, the patient was studied during HWI for 5 hours. Blood for NE and E determinations was drawn hourly during the two experiments. The plasma NE and E concentrations were then compared in the same patient with and without increased EABV secondary to HWI.

Statistical Analysis

Unpaired Student’s t test was used to compare baseline NE levels, NE clearance, and secretion rates in cirrhotic patients with those of normal subjects. Paired Student’s t test was utilized to compare catecholamine levels with and without water immersion. The results are expressed as the mean ± SEM. The null hypothesis was rejected if the P value was less than 0.05.

Results

Water Load Excretion

The mean percent excretion of the 20 ml/kg water load during control conditions in the eight cirrhotic patients was 33 ± 10% in 5 hours. The range was 9.0–60.0%. Therefore, each of the patients fulfilled the criterion for being labeled as a “non-excretor” (Bichet et al., 1982): that is, none of the patients were able to excrete 80% of the administered water load within 5 hours.

Plasma NE Concentrations

The mean plasma NE concentration in the seven normal subjects was 185 ± 12 pg/ml, and was 830 ± 136 pg/ml in the eight cirrhotic patients, P < 0.001 (Fig. 1).
Plasma NE Clearance Rates

In Figure 2 are shown the plasma NE clearance rates in the normal subjects and the cirrhotic patients. The mean clearance rate in the normal subjects was 2.60 ± 0.28 liters/min and was 3.13 ± 0.48 liters/min in the cirrhotic patients; these values were not significantly different.

Plasma NE Secretion Rates

The plasma NE secretion rates in the normal subjects and cirrhotic patients are shown in Figure 3. The mean NE secretion rate was 0.26 ± 0.08 μg/m² per min for the control subjects and was 1.50 ± 0.25 μg/m² per min for the cirrhotic patients, P < 0.001. There was a significant correlation between plasma NE concentrations and NE secretion rates as analyzed by linear regression analysis. In the 15 subjects (seven control and eight cirrhotic patients), the r value was 0.68 and the P value was <0.01. (plasma [NE] = 760 X apparent secretion rate – 180.)

Effect of HWI on Plasma NE

In each of seven patients studied, plasma NE concentrations were suppressed during HWI (Fig. 4). The mean plasma NE concentrations were suppressed from 704 ± 72 to 475 ± 70, P < 0.005. The plasma E concentrations were also suppressed by HWI from 121 ± 33 to 57 ± 10 pg/ml, P < 0.05 (Fig. 5). Furthermore, HWI resulted in an increase in the percent excretion of the administered water load to 65.7 ± 6.0% in 5 hours (P <0.05), consistent with our previous experience (Bichet et al., 1982; Shapiro et al., 1984).

Discussion

Although there have been conflicting results in early studies in which less sensitive methods were used (Shaldon, 1962; Joly et al., 1967), more recent studies of cirrhotic patients by sensitive radioenzymatic technique have demonstrated significantly increased plasma NE concentrations (Henriksen et al., 1981; Bichet et al., 1982; Ring Larsen et al., 1982; Epstein, 1983). Moreover, decompensated cirrhotic patients have the highest NE levels, and also demonstrate more hyponatremia and higher plasma concentrations of arginine vasopressin, renin, and al-
dosterone than compensated cirrhotics who excrete a water load normally (Bichet et al., 1982). The results of the present investigation confirm those of previous studies from our laboratory in demonstrating significantly elevated plasma NE concentrations in non-excretor cirrhotic subjects. This study also extends these findings in delineating the relative contributions of altered NE clearance and secretion to the elevated plasma NE concentrations found in these patients.

Since the normal liver contains large quantities of monoamine oxidase and catechol-o-methyl transferase, decompensated cirrhotic patients might be expected to have a deficiency of these enzymes and, thus, impaired catecholamine clearance. Alternatively, or in addition, if the peripheral vasodilation, splanchnic venous pooling, and diminished oncotic pressure mediate a decrease in EABV in decompensated cirrhosis, then volume- and/or baroreceptor-mediated increases in NE secretion may cause an increase in plasma NE concentrations.

The results demonstrate that NE clearance is not diminished in patients with advanced cirrhosis, compared to normal subjects. Our clearance data are concordant with the results of Ring Larsen et al. (1982), who found normal hepatic extraction of NE in cirrhotic patients. In contrast, NE secretion rates were significantly increased in these decompensated cirrhotic patients. The elevated plasma NE concentrations in these patients are therefore more compatible with increased adrenergic activity and NE release, rather than diminished hepatic NE clearance. Moreover, in concert with the aforementioned elevations of plasma renin, aldosterone, and vasopressin, these results provide further support for the underfilling hypothesis of sodium and water retention in advanced cirrhosis. These findings are consistent with the findings of others (Ring Larsen et al., 1982; DiBona, 1984) which suggest that efferent sympathetic nerve activity is enhanced in decompensated cirrhosis, as a response to a decreased "EABV." This increased sympathetic tone seems likely to contribute to the renal vasoconstriction that characterizes this disorder (Better and Schrier, 1983; DiBona, 1984).

The underfilling hypothesis was examined further in the present study by measuring plasma NE concentrations in the same patients in the presence and absence of central blood volume expansion. If volume- and/or baroreceptor-mediated increases in adrenergic activity are triggered by a diminished EABV and account for the increased plasma NE concentrations, then central blood volume expansion should tend to reverse this sequence and lower plasma NE concentration. In preliminary studies in our laboratory, central blood volume expansion using HWI decreased plasma NE in four patients (Bichet et al., 1983). However, these results were not confirmed in a larger group of cirrhotic patients from another laboratory (Epstein et al., 1983). In the latter study, however, the level of decompensation of these patients was not rigidly defined. As indicated above, those cirrhotic patients who are unable to excrete a standard water load normally demonstrate the highest plasma NE concentrations, as well as other hormonal evidence of a decreased EABV. In the present study, each of the seven non-excretor patients demonstrated a suppression of plasma NE during HWI, a technique that has been previously documented to increase intracardiac pressures and cardiac index, presumed evidence of enhanced EABV (Bichet et al., 1983; Shapiro et al., 1984).

Although advancing age has been noted to increase plasma NE levels, its contribution appears to be quantitatively small (Ziegler et al., 1976). Specifically, Lake et al. (1977) reported that plasma NE levels increased by approximately 25% between the ages of 30 and 50 years, in a population of 67 hypertensive and 84 normotensive subjects. In the present studies, although the normal subjects were younger than the cirrhotic patients by the approximate margin noted above, the difference in plasma NE levels was much more pronounced than that anticipated from age alone. It therefore seems reasonable to maintain that the age difference between the cirrhotic and normal subjects cannot account for the 300—400% higher mean NE level in the cirrhotic group.

Although accepted as a valid index of overall sympathetic activity (Grossman et al., 1982), the plasma NE concentration does not delineate either the stimulus to secretion or its organ source. Sympathetic nervous discharge to different organs is non-uniform, and determinations of organ-specific sympathetic nervous function, via measurement of NE across isolated vascular beds, provides more specific information (Folkow et al., 1983; Esler, 1984). Ring Larsen et al. (1982) have measured renal arteriovenous differences of NE and have detected higher renal arterial-to-venous increments, as well as lower renal blood flows, in decompensated cirrhotic patients compared to normal subjects. Thus, the importance of the contribution of efferent renal sympathetic nerve activity to the renal vasoconstriction and, hence, sodium and water avidity of decompensated cirrhosis, has become increasingly evident (DiBona, 1984).

Our studies were designed to examine total peripheral activity rather than the secretion or clearance of NE across specific vascular beds. In this regard, Goldstein (1983) has proposed that the concept of venous plasma NE concentration, representing a mean sympathetic activity of multiple vascular beds, is analogous to total peripheral resistance, a useful index of the overall status of the peripheral circulation, but lacking in regard to information about specific vascular beds.

In summary, non-excretor decompensated cirrhotic patients consistently demonstrate increased plasma NE concentrations. These elevated NE con-
centrations are associated with increased NE secretion rates and normal NE clearance, as compared to normal subjects. The suppressibility of plasma NE and E with HWI provides further evidence that a decreased EABV is the stimulus for enhanced NE secretion in decompensated cirrhosis.

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