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Alterations in isoprenaline sensitivity in patients with cirrhosis: evidence of abnormality of the sympathetic nervous activity

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1 Isoprenaline sensitivity and plasma catecholamine concentrations were studied to assess the sympathetic nervous activity in 13 patients with alcoholic cirrhosis and were compared with five controls.

2 In patients with cirrhosis, the dose of isoprenaline required to increase the resting heart rate by 25 beats min^{-1} (chronotropic dose 25 or CD_{25}) ranged from 2.50 to 34.73 μg (median: 4.47 μg) and was significantly higher than in controls (range: 0.66 to 2.76 μg, median: 1.34 μg).

3 In cirrhotic patients, CD_{25} values were significantly correlated with plasma albumin concentration, resting heart rate and wedged hepatic venous pressure.

4 In patients with cirrhosis, plasma noradrenaline concentrations ranged from 192 to 978 pg ml^{-1} (median: 444 pg ml^{-1}) and adrenaline concentrations ranged from 5 to 183 pg ml^{-1} (median: 47 pg ml^{-1}). No correlation was found between noradrenaline or adrenaline concentrations and CD_{25} values in cirrhotic patients.

5 In conclusion, in patients with cirrhosis, β-adrenoceptor responsiveness assessed by isoprenaline sensitivity is altered.

Keywords isoprenaline cirrhosis sympathetic system haemodynamics catecholamine portal pressure

Introduction

The hyperkinetic circulatory state characterized by increased heart rate and cardiac output and decreased systemic vascular resistance, is common in patients with cirrhosis (Kowalski & Abelmann, 1953; Even *et al.*, 1966; Valla *et al.*, 1984a). Accurate causes and mechanisms of this syndrome have not, however, been clarified (Valla *et al.*, 1984a). In these patients, the sympathetic nervous system may be involved since its activity is enhanced. At the present time, the sympathetic nervous activity of these cirrhotic patients has only been assessed by plasma catecholamine determination (Ring-Larsen *et al.*, 1982; Henriksen *et al.*, 1984; Keller *et al.*, 1984) and by responsiveness to reflex stimulations (Lunzer *et al.*, 1975; Bernardi *et al.*, 1982). In the present study performed on a group of cirrhotic patients, the sympathetic nervous activity was evaluated by the isoprenaline test which is recognized to be a validated method for measuring β-adrenoceptor responsiveness (George *et al.*, 1972; Cleaveland *et al.*, 1972; London *et al.*, 1976; Vestal *et al.*, 1979). Moreover, the results of this test have been compared with basal plasma catecholamine concentrations.

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Methods

Patients

Thirteen patients with histologically proven alcoholic cirrhosis and five healthy volunteers were studied. The subjects had no sign or history of cardiovascular or lung disease and were normotensive. Alcohol intake had ceased for at least 2 weeks; accordingly, they had no symptoms of alcohol withdrawal. Only two patients were heavy smokers. No subject received drugs known to interfere with the sympathetic nervous activity, in particular adrenoceptor antagonists. The plasma creatinine level was below 100 μmol l^{-1} in all patients. In nine of these patients a haemodynamic study was performed during transvenous liver biopsy (a technique which is routinely performed in this department when percutaneous liver biopsy is not feasible because of coagulation defects (Lebrec *et al.*, 1982a)). Cardiac output and wedged hepatic venous pressure—a reflection of portal venous pressure (Valla *et al.*, 1984b)—were measured as previously described (Lebrec *et al.*, 1982b). The isoprenaline test was done during the same admission. All subjects gave verbal informed consent to the investigation described below.

Isoprenaline dose-response curve

The procedure was performed as previously described (George *et al.*, 1972; Cleaveland *et al.*, 1972; Vestal *et al.*, 1979; Bercoff *et al.*, 1984). All tests were carried out in the same room, at the same time of the day (11.00–13.00 h) with the same nurse and practitioner. The procedure and possible side effects were explained to each subject; thereafter, conversation was reduced to a minimum. After 10 min of supine rest, a small catheter was inserted in a brachial vein and after 10–15 min, a blood sample was obtained for determination of plasma catecholamine concentration. An intravenous infusion of 5% dextrose was then begun. The desired concentrations of isoprenaline hydrochloride were made from sterile stock ampoules of 0.2 mg in 1 ml. Convenient dilutions of isoprenaline hydrochloride were made by adding the appropriate amount to a 250 ml bag of 5% dextrose with 0.5 mg ml^{-1} of ascorbic acid added as an antioxidant. Isoprenaline was given as a rapid injection and flushed with 5% dextrose. The initial dose was 0.1 μg, then the doses were progressively increased (0.2, 0.4, 0.6, 0.8, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11 μg) until an increase in heart rate of 20 to 35 beats min^{-1}. The total amount of 5% dextrose infused during the test never exceeded 150 ml. Heart rate was allowed to return to baseline before each injection which usually required 5–10 min. The baseline heart rate was measured from the three shortest R–R intervals of the electrocardiogram at rest; the heart rate after each injection of isoprenaline was similarly measured. The increase in heart rate as a function of the isoprenaline dose was plotted on a semilog scale. The log dose-response curve was linear and determined by the maximum number of points significantly aligned; this number ranged from four to eight for cirrhotic patients and from three to six for controls. The chronotropic dose 25 (CD_{25}) i.e. the dose which increases the resting heart rate by 25 beats min^{-1}, was calculated from the straight line.

Determination of plasma catecholamine concentration

Blood samples obtained for catecholamine concentration estimation were immediately centrifuged at 4°C. The plasma was then frozen and kept at −80°C. A radio-enzymatic method was used to determine noradrenaline and adrenaline concentrations (Da Prada & Zürcher, 1976). Normal values of noradrenaline are less than 450 pg ml^{-1} and of adrenaline less than 100 pg ml^{-1} in this laboratory.

Statistical analysis

Comparisons were made by the Wilcoxon-rank test and the Spearman-rank correlation coefficient was used.

Results

The 13 patients with alcoholic cirrhosis were aged from 32–69 (median: 53 years). All but three had ascites. According to Pugh's classification (Pugh *et al.*, 1973) two were in good condition (grade A), seven in poor condition (grade C), and the four others were intermediate (grade B) (see Table 1).

In patients with cirrhosis, CD_{25} values ranged from 2.50 to 34.73 μg with a median of 4.47 μg (Figure 1 and Table 2). In controls, CD_{25} ranged from 0.66 to 2.76 μg with a median of 1.34 μg (Table 2). A statistically significant difference in CD_{25} was found between the two groups ($P < 0.01$). CD_{25} was not significantly correlated with age either in cirrhotic patients ($r = -0.22$) or in control subjects ($r = 0.50$). In patients with cirrhosis, CD_{25} was not significantly correlated with plasma bilirubin level ($r = 0.30$), plasma proaccelerin concentration ($r = -0.47$), nor

Table 1 Clinical characteristics and laboratory values of patients with cirrhosis

Number	*Age (years)*	*Basal heart rate (beats min^{-1})*	*Plasma albumin concentration (g l^{-1})*	*Plasma bilirubin concentration (μmol l^{-1})*	*Plasma proaccelerin concentration (%)*	*Ascites*	*Pugh's score (Pugh et al., 1973)*
1	69	81	34.3	47.9	70	present	9
2	50	96	30.0	97.9	37	present	10
3*	56	79	29.0	29.0	57	present	8
4	66	76	31.1	70.0	70	present	10
5*	47	80	34.0	51.3	59	absent	7
6	52	68	40.8	17.9	57	absent	5
7	61	88	28.0	97.9	44	present	10
8	45	110	32.0	128.0	48	present	11
9	59	85	29.0	58.0	40	present	10
10	32	110	30.0	148.0	28	present	11
11†	53	93	29.0	33.0	67	absent	6
12	52	95	22.4	300.0	32	present	11
13	59	115	25.9	47.9	47	present	9

* heavy smoker; † alcoholic polyneuropathy.

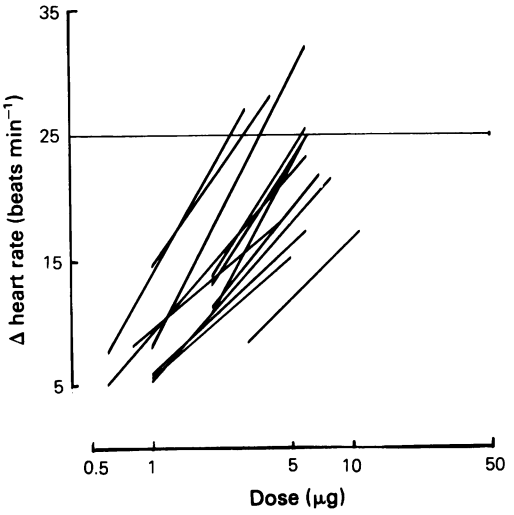

Figure 1 Log dose-response curves to intravenous injections of isoprenaline in 13 patients with cirrhosis. Response is calculated as the increase in heart rate.

score on Pugh's classification ($r = 0.13$). Significant correlations were found between CD_{25} values and plasma albumin concentration ($r = -0.58$, $P < 0.05$) and with baseline heart rate ($r = 0.59$, $P < 0.05$). The haemodynamic results obtained in nine cirrhotic patients are set out in Table 3. CD_{25} was significantly correlated with wedged hepatic venous pressure ($r = 0.72$, $P < 0.05$) and with the gradient between wedged and free hepatic venous pressures (hepatic venous pressure gradient) ($r = 0.78$, $P < 0.02$). No correlation was found between CD_{25} and cardiac index and systemic vascular resistance.

In cirrhotic patients, plasma noradrenaline concentrations ranged from 192 to 978 pg ml^{-1} (median: 444 pg ml^{-1}); plasma adrenaline concentrations ranged from 5 to 183 pg ml^{-1} (median: 47 pg ml^{-1}) (Table 3). Plasma catecholamine measurements were obtained for only three controls (Table 2). In patients with cirrhosis, noradrenaline and adrenaline concentrations were not significantly correlated with CD_{25}, age, plasma albumin or bilirubin concentration, wedged hepatic venous pressure or hepatic venous pressure gradient.

Discussion

Although the reactivity to rapid isoprenaline infusion varied from patient to patient, CD_{25} values were higher in patients with cirrhosis than in our healthy subjects and in those previously

Table 2 Age, basal heart rate, chronotropic dose 25 (CD_{25}) and plasma catecholamine concentration in healthy subjects

Number	Age (years)	Basal heart rate (beats min^{-1})	CD_{25} (μg)	Plasma concentration (pg ml^{-1}) Noradrenaline	Adrenaline
1	41	64	0.66	159	23
2	24	69	0.90		
3	45	62	1.34	196	50
4	38	70	1.50		
5	53	75	2.76	343	64

Table 3 Chronotropic dose 25 (CD_{25}), plasma catecholamine concentration, wedged hepatic venous pressure, cardiac index and systemic vascular resistance of patients with cirrhosis

Number	CD_{25} (μg)	Plasma concentration Noradrenaline (pg ml^{-1})	Adrenaline (pg ml^{-1})	Wedged hepatic venous pressure (mm Hg)	Cardiac index (l min^{-1} m^{-2})	Systemic vascular resistance (dyn s cm^{-5})
1	2.50	578	24			
2	2.58	531	92	22		
3	3.52	403	183	29	4.37	951
4	5.68	494	< 5			
5	5.96	491	108			
6	6.03	444	46	19	3.48	751
7	7.47	288	47	32	3.33	1365
8	9.92	965	153	29	5.67	832
9	11.74	192	< 5	37	4.63	923
10	14.71	617	66	31	5.67	548
11	19.74	251	< 5			
12	25.59	308	< 5	37		
13	34.73	978	163	36	3.13	1481

reported (Cleaveland *et al.*, 1972; London *et al.*, 1976; Vestal *et al.*, 1979). The other causes which could explain a high CD_{25} value in these cirrhotic patients may be excluded. An alteration of isoprenaline metabolism can be excluded because, after rapid injection of this substance, the decline of heart rate mirrors the decline of free serum isoprenaline (Conolly *et al.*, 1972); moreover, the activity of the liver catecholamine-*O*-methyl-transferase is not altered in patients with cirrhosis (Keller *et al.*, 1984). Reported causes of decreased reactivity to isoprenaline injections or elevated plasma catecholamine values were ruled out: none of our patients suffered from asthma (Cookson & Reed, 1963), arterial hypertension (Vestal *et al.*, 1979), diabetes mellitus (Cryer, 1980), thyroid disorder (Christensen, 1973), duodenal ulcer (Christensen *et al.*, 1979) or pulmonary insufficiency Henriksen *et al.*, 1980). There was no stress, no hypoglycaemia and only two patients were heavy smokers. Significant sympathetic nervous abnormalities have not been found in chronic alcoholics with polyneuropathy (Low *et al.*, 1975) and only one of our patients had signs of polyneuropathy (see Table 1). Alcohol intake had ceased for at least 2 weeks and there was no withdrawal symptom.

A decreased reactivity to isoprenaline has been demonstrated in the elderly with a significant positive correlation between age and CD_{25} (Cookson & Reed, 1963; Cryer, 1980; Fitzgerald *et al.*, 1984). In our five healthy subjects, the absence of correlation between CD_{25} and age is probably due to the small number of subjects. In our patients with cirrhosis, there was a striking lack of correlation between age and CD_{25}. The relative small number of patients should not explain this absence of relationship since a significant correlation has been found in normals with only 11 subjects (Fitzgerald *et al.*, 1984).

In patients with cirrhosis, alterations of isoprenaline sensitivity or CD_{25} could be linked to the severity of the liver disease and, in fact, our patients had higher CD_{25} and more severe liver disease than those studied by Bercoff *et al.* (1984). In our cirrhotic patients, CD_{25} was negatively correlated with plasma albumin level, tended to be positively correlated with plasma proaccelerin, and was positively correlated with

wedged hepatic venous pressure. This finding is in agreement with previous observations suggesting a relationship between portal hypertension and sympathetic abnormalities. A hyperdynamic circulatory state has been found in patients with portal venous obstruction and normal liver (Lebrec *et al.*, 1983), and in rats with portal vein stenosis (Blanchet & Lebrec, 1982; Vorobioff *et al.*, 1983). In these animals, impairment of the chronotropic response to isoprenaline has also been found but was less marked than in rats with cirrhosis due to bile duct ligation, thus indicating that liver disease also plays a role (Geoffroy *et al.*, 1984).

In this study, no comparison of plasma catecholamine concentrations has been made between cirrhotic patients and controls because of the inadequate number of normal subjects. However, the elevation of basal plasma catecholamine concentration is well established in patients with cirrhosis and the mean value of noradrenaline in our patients was similar to the other series (Ring-Larsen *et al.*, 1982; Keller *et al.*, 1984). Catecholamine concentrations were not correlated with CD_{25} suggesting that the decreased responsiveness to isoprenaline is not simply a desensitization of β-adrenoceptors by high plasma catecholamine levels (Lefkowitz *et al.*, 1984) and that basal plasma catecholamine determination may be inadequate to detect sympathetic nervous abnormalities in some cirrhotic patients.

In conclusion, alteration of β-adrenoceptor responsiveness is reported in patients with cirrhosis. Further studies are needed to determine if this alteration is part of, the cause or consequence of the hyperkinetic syndrome in these patients.

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