Influence of the degree of liver failure on systemic and splanchnic haemodynamics and on response to propranolol in patients with cirrhosis

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SUMMARY Systemic and splanchnic haemodynamics were studied in patients with cirrhosis who had been classified in three groups (A, B, and C) according to the degree of liver failure (modified Pugh's classification). In patients of group A, cardiac index was significantly lower than that of group C and systemic vascular resistance was higher, but not significantly so, than that of patients with liver failure. Wedged hepatic venous pressure was significantly lower in the former group than in the latter. In patients in group B, corresponding values fell between those of groups A and C. Azygos blood flow averaged 0.477±0.242 l/min (mean±SD) in group A and it was significantly lower than in groups B and C (0.642±0.224 and 1.061±0.476 l/min, respectively). In the three groups, acute administration of propranolol induced statistically significant changes in systemic and splanchnic haemodynamics. In patients of group C but not of group B, the mean value of azygos blood flow after propranolol remained significantly higher than in group A. Moreover, the fraction of azygos blood flow to cardiac output decreased in groups A and B while slightly increased in group C. This study shows that in patients with cirrhosis, the degree of liver failure may be a determinant for the haemodynamic responses to drugs acting on portal hypertension.

In patients with cirrhosis, the changes in systemic circulation have been well characterised, and there are indications that the magnitude of systemic haemodynamic changes is related both to development of portal hypertension and to impairment of liver function. The relationship between alterations in splanchnic circulation and degree of liver failure, however, has received less attention. Such a relationship would have therapeutic implications. For example, it has been reported that the effects of propranolol on hepatic venous pressure gradient would be less marked in patients with end stage liver disease, with the consequence that propranolol might be less efficient in the prevention of recurrent gastrointestinal bleeding in patients with advanced liver failure than in patients in good condition.

This study is intended first to determine whether changes in systemic and splanchnic haemodynamics are related with the stage of liver disease and second, to evaluate the haemodynamic effects of propranolol according to the degree of liver failure in patients with cirrhosis.

Methods

PATIENTS

Fifty patients with histologically proven cirrhosis admitted for hepatomegaly and/or ruptured oesophageal varices and/or ascites, and/or jaundice were investigated (Table 1). According to a modified Pugh's classification – not including prolongation of the prothrombin time – those patients whose score totalled four or five were considered to be in good condition (class A), six to eight moderate (class B), and patients with 9–12 were considered to be in poor condition (class C). Accordingly, there were 16 class A (seven had four points and nine had five), 18 class B (three had six points, seven had seven and eight had eight) and 16 class C patients (nine had nine points and seven had 10). Causes of cirrhosis, clinical characteristics and laboratory data are summarised in Table 1. All patients gave oral informed consent...
to the investigation described below which was done at the same time as a transvenous liver biopsy, or as a part of the evaluation of portal hypertension. (This investigation is routinely carried out in this Liver Unit.) In patients admitted for ruptured oesophageal varices, this haemodynamic investigation was done eight to 15 days after haemorrhage when the circulatory condition returned to a steady state. They did not receive any drugs, particularly no β-blocking agent. Patients admitted for ascites received diuretics for one to two weeks. Paracentesis was not undertaken in these patients. Moreover, in all patients heart rate and mean arterial pressure were stable during the week preceding the haemodynamic investigation. In patients with alcoholic cirrhosis, no clinical, electrocardiographic or radiologic manifestations of alcoholic cardiomyopathy were observed. The results of this haemodynamic assessment are thereafter referred to as baseline haemodynamic values. In 24 of these 50 patients, the haemodynamic study was done before and 15 minutes after intravenous administration of 15 mg propranolol. The dose of 15 mg, a large dose, slowly and carefully injected, was used in order to saturate β-adrenoceptors in all patients. A part of the results has been previously reported.

The haemodynamic studies were carried out in patients lying in the supine position after an overnight fast; they were sedated with meperidine hydrochloride, 50 mg, intramuscularly. Mean arterial pressure was measured with an external sphygmomanometer (Dinamap, Critikon, Tampa, FL, USA), using electronic pressure integration. After local anaesthesia, a vessel dilatator with a polypropylene sheath (Desilets, Vygon, Ecouen, France) was inserted percutaneously into the lumen of the right internal jugular vein for successive introduction of different catheters. Cardiac output was determined in triplicate by the thermodilution technique with a Swan-Ganz thermodilution catheter (Edwards Lab, Santa Ana, CA, USA) advanced into a pulmonary artery. The mean value was used. The variability of the measurements was less than 5%. The gradient between wedged and free hepatic venous pressures (hepatic venous pressure gradient) was then measured with a 7F catheter (Cordis SA, Miami, FL, USA) introduced into the right hepatic vein under fluoroscopic control. The wedged position of the catheter was checked by the absence of reflux after injection of 2 ml contrast medium into the catheter. The free hepatic venous pressure was measured in the right hepatic vein just before its junction with the inferior vena cava. Right atrial pressure was measured before withdrawing the catheter. The zero reference level was arbitrarily positioned at the midaxillary line level. Systemic vascular resistance (dynes s cm⁻⁵) was calculated according to the following formula: (mean arterial pressure (mmHg) – right atrial pressure (mmHg)) • 80/cardiac output (l/min). Azysgos blood flow was measured by the local continuous thermodilution method using a digital electronic computer (Calculateur de débit, AHS/France, Saint Ouen-l’Aumône, France), as previously described.

In brief, a continuous-thermodilution catheter (Webster Lab, Altadena, CA, USA) with a curved tip was introduced into the arch of the azygos vein up to 5 cm from its junction with the superior vena cava, under fluoroscopic control; its position was checked by injection of contrast medium into the catheter. The continuous-thermodilution catheter was then fixed to the polypropylene sheath (so as to be able to repeat azygos blood flow measurements with the catheter tip being at the same level in the lumen of the azygos vein). The mean of six determinations of azygos blood flow was used (variability less than 7%).

The results are expressed as mean±SD. Analysis
of variance and the Bonferroni method for multiple statistical comparison were used. Accordingly, results were considered significant only at p<0.02. Student's t test for unpaired and paired data was used to compare the results among the different groups of patients and, within a group, the results before and after propranolol administration.

Results

BASELINE HAEMODYNAMICS ACCORDING TO THE DEGREE OF LIVER FAILURE
The results are presented in Table 2. There was no significant difference between the three groups of patients with regard to mean arterial pressure, free hepatic venous pressure, and systemic vascular resistance. There were, however, significant differences between the three groups with regard to heart rate, cardiac index, wedged hepatic venous pressure, azygos blood flow, and fractional distribution of cardiac index to azygos venous bed. Changes from normal were more marked in group C patients than in groups A and B patients; statistically significant differences were only found between group A and group C.

HAEMODYNAMIC EFFECTS OF PROPRANOLOL ACCORDING TO THE DEGREE OF LIVER FAILURE
The effects of propranolol according to the degree of liver failure were evaluated in 24 patients. The results are presented in Table 3. Propranolol significantly altered heart rate, cardiac output, and systemic vascular resistance in all three groups of patients. After propranolol, cardiac outputs were not significantly different between the three groups. Changes were proportionally greater in group C than in group A; the differences between group A and group B responses and between group B and group C responses were not statistically significant. Propranolol significantly decreased hepatic venous pressure gradient with similar proportional change in the three groups of patients. After propranolol administration, one patient in group A, one patient in group B, and two patients in group C showed no change in hepatic venous pressure gradient. Azygos blood flow was decreased in all patients except one in group C; the magnitude of the decrease, however, was highly variable in group C patients while it was consistent in group A and B patients. After propranolol administration in group C, mean azygos blood flow remained higher than baseline mean azygos blood flow in groups A and B. The fractional distribution of cardiac output to azygos blood flow decreased after propranolol administration in groups A and B and increased in group C. A significant change was, however, observed only in group B.

Discussion
In agreement with several previous reports, this study documents a relationship between liver failure and the hyperkinetic circulatory state that is associated to cirrhosis. This study also shows a less well documented relationship between the degree of liver failure and the magnitude of the circulatory alterations in the splanchnic vascular bed. Portal pressure and portal tributary blood flow are two major factors characterising splanchnic haemodynamics. The present findings indicate a weak relationship between liver function and wedged hepatic venous pressure – a reliable estimate of portal venous pressure in patients with cirrhosis.11 12 Similarly, other workers have reported a correlation between hepatic venous pressure gradient and bilirubin or albumin serum level.13 Such a relationship is not surprising as deteriorating liver function may be expected to follow the progressive structural alterations that are
Table 3  Acute effects of propranolol on haemodynamic values in patients with cirrhosis according to the degree of liver failure*

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=7)</th>
<th></th>
<th>Group B (n=9)</th>
<th></th>
<th>Group C (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal values</td>
<td>15 min after 15 mg (% change)</td>
<td>Basal values</td>
<td>15 min after 15 mg (% change)</td>
<td>Basal values</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>85.6±12.8†</td>
<td>89.4±11.3‡</td>
<td>(5.0±6.1)</td>
<td>85.9±7.8</td>
<td>85.9±10.7§</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74.7±9.4</td>
<td>63.1±5.8§</td>
<td>(15.1±3.9)</td>
<td>88.4±10.8</td>
<td>65.3±7.1§</td>
</tr>
<tr>
<td>Cardiac index (l·min⁻¹·m⁻²)</td>
<td>3.66±0.45</td>
<td>2.90±0.38§</td>
<td>(20.8±4.2)</td>
<td>4.15±0.98</td>
<td>3.33±0.50</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne·s·cm⁻²)</td>
<td>1032±295</td>
<td>1329±393§</td>
<td>(28.9±6.7)</td>
<td>1002±254</td>
<td>1162±241‡</td>
</tr>
<tr>
<td>Hepatic venous pressure gradient (mmHg)</td>
<td>20.9±5.7</td>
<td>17.7±5.6§</td>
<td>(15.7±8.7)</td>
<td>24.2±7.8</td>
<td>20.8±6.7§</td>
</tr>
<tr>
<td>Wedged hepatic venous pressure (mmHg)</td>
<td>27.9±5.8</td>
<td>25.7±6.1§§</td>
<td>(8.0±6.7)</td>
<td>31.3±8.4</td>
<td>29.2±7.3‡</td>
</tr>
<tr>
<td>Free hepatic venous pressure (mmHg)</td>
<td>7.0±1.6</td>
<td>8.0±1.4‡‡</td>
<td>(19.0±30.0)</td>
<td>7.1±3.9</td>
<td>8.4±3.2</td>
</tr>
<tr>
<td>Azygos blood flow (l/min)</td>
<td>0.57±0.24</td>
<td>0.39±0.17‡</td>
<td>(30.6±10.5)</td>
<td>0.62±0.16</td>
<td>0.40±0.11§</td>
</tr>
<tr>
<td>Azygos blood flow/cardiac output (%)</td>
<td>8.5±2.7</td>
<td>7.4±2.2‡‡</td>
<td>9.6±3.5</td>
<td>7.5±2.4§§</td>
<td></td>
</tr>
</tbody>
</table>

* According to a modified Pugh's classification (see Method section). † Mean±SD. ‡ Non-significantly different from the basal values. § Significantly different from the basal values (p<0.01). §§ Significantly different from % change of group A (p<0.01). †† Significantly different from % change of group A (p<0.01). ‡‡ Significantly different from per cent change of group B (p<0.01). ‡‡‡ Significantly different from % change of group B (p<0.01).
known to be related to portal venous pressure. The presence of ascites in patients of group C might also influence the interpretation of the results obtained. This mechanism is, however, unlikely because it has previously been shown that the effect of increased intraabdominal pressure has no effect on portal pressure (hepatic venous pressure gradient) in patients with cirrhosis.

At the present time, portal tributary blood flow cannot be easily measured in patients with cirrhosis. A part of portal tributary blood flow is shunted towards the systemic circulation through collateral veins, among which the superior ones are of utmost clinical importance because they include oesophageal varices. Most of the superior portosystemic collateral channels drain into the azygos vein; thus, azygos blood flow represents the sum of blood flow in the superior portosystemic collaterals and of blood flow in the lumbar, intercostal, and mediastinal veins. This latter part of the azygos blood flow amounts to approximately 100 ml/min in patients without portal hypertension and with normal cardiac output. It may reasonably be assumed that in patients with cirrhosis, owing to a 20–50% increase in cardiac output, this part of azygos blood flow should be increased to approximately 120–150 ml/min. The increase in azygos blood flow observed in patients with cirrhosis does not directly depend on the increase in cardiac output as in patients with distal splenorenal shunt, azygos blood flow decreased whereas cardiac output, in general, increases. Accordingly, in this study, the part of azygos blood flow corresponding to the portosystemic collateral circulation was increased on average by 300 ml/min in group A but by 800 ml/min in group C patients. Thus, the high grade hyperkinetic state that characterises the systemic circulation in patients with advanced liver failure also affects the portosystemic collateral circulation. The increase in portosystemic collateral blood flow could be a mere consequence of the hyperdynamic circulatory state affecting equally portal venous tributary blood flow and other regional blood flows. Alternatively, it could result from a particular increase in portal tributary blood flow as compared with other regional blood flows. The latter hypothesis would be supported by the observations that (a) fractional distribution of cardiac output to the azygos venous bed was significantly increased in patients with advanced liver failure as compared with patients with no or moderate impairment in liver function and (b) rats with portal hypertension due to portal vein stenosis showed a disproportionately marked increase in portal tributary blood flow when compared to the simultaneous moderate increase in cardiac output. Significant differences in azygos blood flow according to the degree of liver failure have not recently been found in cirrhotic patients.

The cause of the increasing changes in portal and systemic haemodynamics that are associated with progressively more severe impairment in liver function is not clearly known. Alterations in the metabolism of endogenous substances with circulatory actions are likely. The main substances which have been implicated include catecholamines, false neurotransmitters, substance P, vasoactive intestinal peptide. That adrenergic activation is an important determinant of the hyperdynamic state is indicated by the significant reduction obtained after β-adrenergic blockade with propranolol in all the groups of patients in this study. This observation is at variance with the results of a study in which hepatic venous pressure gradient was little reduced by propranolol in patients with advanced liver failure; in that study, though, azygos blood flow was measured. A recent paper, however, has shown similar results to our study. On the other hand, the hyperdynamic syndrome affecting both the systemic circulation and the portosystemic collateral circulation might also be determined by factors unrelated to adrenergic activation because β-adrenergic blockade did not return haemodynamic values to normal especially in patients with advanced liver failure. Incidentally, it must be noted that the significant decreases in hepatic venous pressure gradient, azygos blood flow and cardiac output after intravenous administration of 15 mg propranolol are similar to those recently reported in a group of unselected patients with cirrhosis but the decrease in hepatic venous pressure gradient and in cardiac output slightly differs from other previously reported investigations where 40 mg or more of propranolol were administered per os; the reason for this discrepancy is unclear but may be attributed, at least in part, to the route of administration of this β-blocker.

The respective importance of adrenergic and non-adrenergic factors in mediating the circulatory changes associated with cirrhosis might vary according to the degree of impairment in liver function. For example, the fractional distribution of cardiac output to the azygos venous bed was significantly decreased after propranolol only in patients with good or moderately impaired liver function. In other words, in spite of a marked decrease in azygos blood flow in patients of group C, the value of azygos blood in this group remained higher than in groups A and B whereas the values for cardiac output in patients of the three groups became similar after propranolol administration. Thus, in view of the present findings, careful stratification according to
the degree of liver failure, is warranted in any study on drugs acting on the circulation in cirrhosis.

Drs A Braillon and D Valla hold fellowships from the Fondation pour la Recherche Médicale. This work was presented in part (poster) at the 35th Annual Meeting of the American Association for the Study of Liver Diseases in Chicago on 10–11 November 1984 and published in abstract form (Hepatology 1984; 4: 1026). The authors thank Ms C Bertin and M Naudet for assistance and Dr C Dupont from ICI Pharma-France for her help.

References
1 Kowalski HJ, Abelman WH. The cardiac output at rest in Laennec's cirrhosis. J Clin Invest 1953; 32: 1025–33.