Effect of meal and propranolol on whole body and splanchnic oxygen consumption in patients with cirrhosis

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Krag, Alesander, Lene Simonsen, Jens H. Henriksen, Lone Ottesen, and Flemming Bendtsen. Effect of meal and propranolol on whole body and splanchnic oxygen consumption in patients with cirrhosis. Am J Physiol Gastrointest Liver Physiol 291: G8–G15, 2006.—Our aim was to measure whole body energy expenditure after a mixed liquid meal, with and without simultaneous propranolol infusion, in patients with cirrhosis. We also wanted to investigate the effect of propranolol on substrate fluxes and oxygen uptake in the tissues drained by the hepatic vein and ayzygos vein in the postprandial period in these patients. Whole-body oxygen uptake, hepatic blood flow, hepatic blood flow, hepatic venous pressure gradient and net-hepatic fluxes of oxygen, lactate, glucose, glycerol, and free fatty acids (FFA) were measured in 12 patients with alcoholic cirrhosis before and for 2 h after ingestion of a mixed liquid meal (700 kcal). Half of the patients (n = 6) were randomized to a treatment group receiving intravenous infusion of propranolol in combination with the meal. The meal-induced energy expenditure was significantly lower in patients given propranolol (15.0 ± 18.9 vs. 67.0 ± 26.1 kJ/120 min (means ± SD), P < 0.01). Meal-induced whole body oxygen uptake was lower in patients receiving propranolol (19.2 ± 38 vs. 135.7 ± 61 mmol/120 min, P < 0.01), and the meal-induced increase in splanchnic oxygen uptake was nonexistent when propranolol was administered in combination (−13.2 ± 34.8 vs. 110.4 ± 34.8 mmol/120 min, P = 0.04). Postprandially, the propranolol group had a tendency toward a reduced splanchnic glucose output, and the FFA uptake was significantly reduced. Propranolol reduces meal-induced whole body oxygen uptake and energy expenditure as well as splanchnic oxygen uptake. The splanchnic reduction in oxygen consumption can explain almost the entire reduction in whole body oxygen consumption.

collateral circulation and thereby reduces portal venous pressure and collateral blood flow (13, 30, 39). Infusion of propranolol obliterates the meal-induced increases in hepatic blood flow (HBF), ayzygos blood flow, and hepatic venous pressure gradient in patients suffering from cirrhosis (7, 9). Apart from the hemodynamic changes (33), patients with cirrhosis are characterized by a number of metabolic defects: hypermetabolism, increased lipid utilization, and insulin resistance (21). In fasting cirrhotic patients, propranolol decreases energy expenditure (EE), splanchnic oxygen uptake (7), and lactate concentration in both normo- and hypermetabolic patients (36). Studies evaluating the effect of propranolol on postprandial EE show divergent results. In healthy subjects, infusion of glucose indicates that a component of the glucose-induced thermogenesis is most likely mediated by the sympathetic nervous system, because the administration of β-blockers is accompanied by a significant reduction in EE (36). Similarly, acute administration of the nonselective β-blocker propranolol decreased the thermogenic response after an oral glucose load (4), but the increase was not initiated before 120 min after the glucose load. However, the thermogenic response to a mixed meal in healthy persons does not seem to be influenced significantly by β-adrenergic blockade (42). Only a few studies have dealt with the meal-induced increase in whole body and splanchnic oxygen uptake in cirrhosis. The diet-induced thermogenesis is normal in cirrhosis (19), but the effect of acute β-adrenergic inhibition in cirrhotic patients is unknown.

The aims of the present study were 1) to measure whole body EE in patients suffering from cirrhosis after a mixed liquid meal and with and without simultaneous propranolol infusion and 2) to investigate the effect of propranolol on substrate fluxes and oxygen uptake in the tissues drained by the hepatic vein and ayzygos vein during the postprandial period in these patients.

MATERIALS AND METHODS

Patients. Twelve patients with biopsy-proven alcoholic cirrhosis and portal hypertension were studied. All patients had endoscopically verified esophageal varices without previous bleeding. All had abstained from alcohol for at least 3 wk before the study. After measurements of basal hemodynamic variables in the fasting patient, the patients were randomized to treatment groups receiving either a
liquid meal alone or in combination with intravenous infusion of propranolol. Six patients ingested the meal alone, and six received propranolol in addition. Patient’s characteristics of the two study groups are listed in Table 1. Nine patients received diuretic treatment: five in the propranolol group [5 received spironolacton (100–200 mg/day), and 5 were given furosemide (40–160 mg/day)] and four in the control group [4 received spironolacton (100–200 mg/day), and 4 furosemide (40–160 mg/day)]. The diuretic treatment was withheld 24 h before the study. The patients had not previously been treated with propranolol or any other drug, with a potential influence on portal pressure. All gave written informed consent, and the ethics committee approved medical research in Copenhagen approved the study (V100.770/87) as being in accordance with the Helsinki II declaration.

The volume of test meal (designed and prepared by the nutrition unit, Hvidovre Hospital, Copenhagen, Denmark) was 450 ml, consisting of 58 g (233 kcal) protein, 26 g lipid (234 kcal), and 58 g (233 kcal) carbohydrate, a total of 700 kcal. The meal was ingested over a period of up to 10 min by all patients. The patients were subsequently studied in the supine position after an overnight fast. The patients were randomized after baseline measurements by drawing a sealed envelope.

**Propranolol infusion.** Patients randomized to a meal in combination with propranolol received a bolus intravenous injection of 0.1 mg/kg propranolol immediately after the termination of the meal. Subsequently, a constant infusion of 1 μg·min⁻¹·kg⁻¹ propranolol was administered until cessation of the measurements 2 h after ingestion of the meal. To ensure that the propranolol did not influence the absorption of the meal, plasma glucose was measured at baseline and in 30-min intervals for the whole period. All patients had an increase in plasma glucose of >20%, and no difference was observed between the two treatment groups. Maximal plasma glucose occurred 60–90 min after the meal, irrespective of treatment.

**Whole body oxygen uptake.** Whole body oxygen uptake (VO₂), carbon dioxide output, and respiratory exchange ratio (RER) were measured continuously by indirect calorimetry using an open-circuit ventilated hood system before and for 2 h after the meal. For calculations, mean values for every half hour were used. Oxygen was measured with an electrochemical oxygen sensor (Amtec Thermox, Pittsburg, PA), and carbon dioxide was measured by an infrared carbon dioxide sensor (Amtec Thermox). Airflow through the system, relative air humidity, and air temperature were measured, and all the parameters were monitored online by computer. A detailed description of this system and the calibration procedure has been given in previous studies (41).

EO was calculated as EE = (15.48 + 5.55 × RER) × VO₂ (kJ) (18).

The meal-induced thermogenesis was calculated as the difference between resting EE and the integrated postprandial EE, as area under curves by the trapezoid method. Meal-induced thermogenesis is also expressed as the postprandial increase in EE as percentage of the energy content of the meal in the control group.

**Catheterization.** After an overnight fast, hepatic venous catherization was performed. In brief, a Courmand catheter, size 7-Fr, was inserted through the right femoral vein under local analgesia and guided to a hepatic vein under fluoroscopy. In addition, a venous introducer, size 8-Fr, was placed in the right femoral vein to permit passage of an azygos catheter. A short indwelling catheter (5-Fr) was introduced in the right femoral artery by the Seldinger technique. Azygous-venous catherization was performed by a dedicated terminisor coronary sinus catheter (Webster Laboratories, Altadena, CA), and blood flow was measured by thermodilution (11). At each observation, at least three measurements were performed, and the mean value was applied.

**Assessment of splanchnic hemodynamics.** HBF was measured by the indocyanine green (ICG) technique (24). Proceeded by a priming dose (2 mg), a constant intravenous infusion of ICG (0.2 mg/min; calibrated pump, O Dich, Copenhagen, Denmark) in a 5% human albumin was given until termination of the catheterization. An equilibrium period of 20 min was required before blood samples were simultaneously drawn from the hepatic vein and artery for analyses of ICG. ICG clearance was determined as infusion rate of ICG (ICG_C; corrected for unsteady plasma concentration) divided by arterial plasma concentrations of ICG. A hepatic extraction of ICG >10%, required for the assessment of HBF, was present in all patients. HBF = ICG/(ICG_A – ICG_H) × (1 – Hct), where ICG_A represents arterial ICG concentration, and ICG_H represents hepatic venous ICG concentration. The hepatic blood flow was not measured at 90 min. The 90-min value was extrapolated from values at 60 and 120 min.

**Blood sampling and analyses.** Blood samples were simultaneously drawn from all three catheters after discharge of catheter dead space. Blood was collected for analyses of hemoglobin, glucose, pyruvate, glycerol, and free fatty acids (FFA). Glycerol and FFA were determined as described by Laurell and Tibbling (28, 29). Lactate and pyruvate were determined after precipitation of protein by perchloric acid as described by Bergmeyer (10). Blood gas analyses were performed electrometrically (Radiometer ABL, OSM, Copenhagen) on simultaneously drawn samples from femoral artery, hepatic vein, and azygos vein. Oxygen uptake (VO₂) was determined as HBF × Hb × 22.4 × (SO₂,H × SO₂,A), where Hb is the concentration of hemoglobin in blood and SO₂,H and SO₂,A are oxygen saturation in the artery and vein, respectively. The oxygen content of the blood was adjusted for physically dissolved oxygen by determination of oxygen tension. Meal-induced increases in oxygen uptake, in tissues drained by the hepatic vein (splanchnicus), and the azygos vein were calculated as the integrated increase in oxygen uptake above the baseline fasting level during the 2 h after the meal. Fluxes of lactate, glucose, pyruvate, glycerol, and FFA across the tissues drained by the hepatic vein and the azygos vein were calculated by Fick’s principle (arteriovenous concentration differences multiplied by the appropriate blood flow/plasma flow). Plasma flow was used in FFA and blood flow in oxygen, lactate, pyruvate, glucose, and glycerol. Glucose and lipid oxidation rates were calculated by a protein oxidation rate (0.35 mg·kg⁻¹·min⁻¹) from a previous study in cirrhotic patients by Shmueli et al. (40).

**Statistics.** All results are presented as means ± SD. Comparisons within each group were performed with Student’s t-test for paired
Table 2. Systemic and splanchnic hemodynamics in patients with cirrhosis before and after a meal alone, or in combination with i.v. propranolol infusion

<table>
<thead>
<tr>
<th></th>
<th>Minutes After Meal Ingestion</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Heart rate/min</td>
<td></td>
</tr>
<tr>
<td>Meal</td>
<td>86±4</td>
</tr>
<tr>
<td>Meal + propranolol</td>
<td>88±5</td>
</tr>
<tr>
<td>HVPG, mmHg</td>
<td></td>
</tr>
<tr>
<td>Meal</td>
<td>17.5±6.4</td>
</tr>
<tr>
<td>Meal + propranolol</td>
<td>16.5±5.0</td>
</tr>
<tr>
<td>HBF, l/min</td>
<td></td>
</tr>
<tr>
<td>Meal</td>
<td>1.39±0.58</td>
</tr>
<tr>
<td>Meal + propranolol</td>
<td>1.33±0.36</td>
</tr>
<tr>
<td>Azygos blood flow, ml/min</td>
<td>343±71</td>
</tr>
<tr>
<td>Meal + propranolol</td>
<td>388±159</td>
</tr>
</tbody>
</table>

Values are means ± SD. HVPG, hepatic venous pressure gradient; HBF, hepatic blood flow. *P < 0.05 compared with baseline. †P < 0.05 compared with meal without propranolol.

data. ANOVA was used for comparison between groups. Analyses of effect of time between groups were done in SAS statistical software package using the method of “repeated measurements.” Fixed factors were group and time and random factor person. P < 0.05 is considered statistically significant.

RESULTS

Clinical data and biochemical test values of the study groups are given in Table 1. No significant differences between the two groups were observed regarding age, sex, and severity of the disease (Child-Pugh score). As earlier reported (9), we observed the well-known effects of B-adrenergic blockade on systemic and splanchnic hemodynamics (Table 2): postprandial rise in hepatic venous pressure gradient and HBF were both reduced by propranolol. Heart rate also decreased after the meal in combination with propranolol. The HBF increased in the control group. However, in the propranolol group, it did not change significantly after the meal and remained significantly lower compared with the control group.

Oxygen consumption and EE. Whole body oxygen consumption, EE, RER, and oxygen consumption across the tissues drained by the hepatic and the azygos veins are shown in Table 3. Figures 1 and 2 show the individual values of whole body oxygen uptake and the integrated increase in oxygen uptake after meal; the difference was statistically significant (Table 3). Individual values of whole body oxygen uptake showed the same pattern, with an increase for all patients receiving meal alone, whereas no increase was observed for patients given propranolol together with the meal (Fig. 1). The hepatic oxygen uptake was unchanged after the meal in the propranolol group (Fig. 2). The integrated meal-induced EE was significantly lower in patients who received propranolol compared with those who did not [15.0 ± 18.9 vs. 67.0 ± 26.1 kJ/120 min (means ± SD), P < 0.01]. In the control group, the meal-induced thermogenesis as percentage of energy content of the meal was 2.3%. The integrated meal-induced whole body oxygen uptake was reduced using propranolol (19.2 ± 38 vs. 13.5 ± 61 mmol/120 min, P < 0.01); see Fig. 2. The splanchnic oxygen consumption was measured in both the hepatic vein and azygos vein (Table 3); the integrated meal-induced increase in hepatic vein oxygen uptake was nonexistent when propranolol was administered in combination (−13.2 ± 34.8 vs. 110.4 ± 34.8 mmol/120 min, P = 0.04; see Fig. 2). There was a significant postprandial increase in VO2 in the tissues drained by the azygos vein but no significant difference between the groups.

Arterial concentrations and arteriohepatic venous differences of metabolites as well as the hepatic lactate-to-pyruvate ratios are shown in Table 4. The time curves of arterial glucose were similar in the two groups, indicating that the absorption of nutrients was not affected by propranolol. The arterial concentration of FFA after the meal was significantly decreased in both groups, but among patients receiving propranolol, the level was significantly reduced (both compared with baseline and with controls). The arterial lactate and glycerol did not change in the two groups after the meal intake. The effect of propranolol on hepatic blood flow and the azygos blood flow are shown in Table 2.

Table 3. Whole body oxygen uptake energy expenditure, respiratory exchange ratio, splanchnic oxygen uptake, and glucose and lipid oxidation rates

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen uptake, mmol/min, mmol/min + kg^-1</td>
<td>Meal alone</td>
<td>9.3 ± 1.8</td>
<td>10.1 ± 1.6</td>
<td>10.3 ± 1.7</td>
<td>10.5 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>Meal + propranolol</td>
<td>8.6 ± 1.9</td>
<td>8.9 ± 1.9</td>
<td>8.9 ± 1.8</td>
<td>8.7 ± 2.1</td>
</tr>
<tr>
<td>Energy expenditure, kJ/min</td>
<td>Meal alone</td>
<td>4.1 ± 0.8</td>
<td>4.5 ± 0.7</td>
<td>4.6 ± 0.8</td>
<td>4.7 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Meal + propranolol</td>
<td>3.9 ± 0.8</td>
<td>4.0 ± 0.8</td>
<td>4.0 ± 1.0</td>
<td>4.0 ± 1.0</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>Meal alone</td>
<td>0.76 ± 0.03</td>
<td>0.78 ± 0.03</td>
<td>0.79 ± 0.04</td>
<td>0.83 ± 0.05*</td>
</tr>
<tr>
<td></td>
<td>Meal + propranolol</td>
<td>0.81 ± 0.06</td>
<td>0.82 ± 0.07</td>
<td>0.85 ± 0.06</td>
<td>0.90 ± 0.06*</td>
</tr>
<tr>
<td>Hepatic vein oxygen uptake, mmol/min; % whole body uptake</td>
<td>Meal alone</td>
<td>2.96 ± 0.69; 32%</td>
<td>3.74 ± 1.60; 37%</td>
<td>3.93 ± 1.63; 38%</td>
<td>3.76 ± 1.55; 35%</td>
</tr>
<tr>
<td></td>
<td>Meal + propranolol</td>
<td>2.58 ± 0.18; 30%</td>
<td>2.64 ± 0.54; 30%</td>
<td>2.57 ± 0.29; 29%</td>
<td>2.63 ± 0.59; 30%</td>
</tr>
<tr>
<td>Azygos vein oxygen uptake, mmol/min; % whole body uptake</td>
<td>Meal alone</td>
<td>0.53 ± 0.11; 5.7%</td>
<td>0.90 ± 0.23*; 8.7%</td>
<td>0.65 ± 0.21; 6%</td>
<td>1.15 ± 0.59; 8.1%</td>
</tr>
<tr>
<td></td>
<td>Meal + propranolol</td>
<td>0.55 ± 0.33; 6.1%</td>
<td>1.01 ± 0.56*; 9.6%</td>
<td>0.65 ± 0.21; 6%</td>
<td>1.15 ± 0.59; 8.1%</td>
</tr>
<tr>
<td>Glucose oxidation rate, g/min</td>
<td>Meal alone</td>
<td>0.04 ± 0.04</td>
<td>0.06 ± 0.03</td>
<td>0.08 ± 0.05</td>
<td>0.12 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Meal + propranolol</td>
<td>0.08 ± 0.03</td>
<td>0.09 ± 0.06</td>
<td>0.12 ± 0.05</td>
<td>0.16 ± 0.06</td>
</tr>
<tr>
<td>Lipid oxidation rate, g/min</td>
<td>Meal alone</td>
<td>0.08 ± 0.01</td>
<td>0.08 ± 0.02</td>
<td>0.07 ± 0.02</td>
<td>0.06 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>Meal + propranolol</td>
<td>0.05 ± 0.03</td>
<td>0.05 ± 0.03</td>
<td>0.04 ± 0.02</td>
<td>0.03 ± 0.02</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 compared with baseline. †P < 0.05 compared with meal without propranolol.

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Splanchnic metabolic fluxes. Hepatic net fluxes of metabolites are shown in Table 5 and Fig. 3. Net hepatic output of glucose tended to increase in the control group, but the difference did not reach statistical significance, whereas in patients treated with propranolol, it did not change. The hepatic uptake of lactate and FFA decreased after the meal, but this was only significant in the group receiving propranolol. The net glycerol uptake was significantly decreased after the meal in the control group. No difference between the two groups was found regarding the fluxes of metabolites in the tissues drained by the azygos vein. The glucose oxidation rate increased significantly after meal in both groups, and the lipid oxidation rate decreased (Table 3).

DISCUSSION

The present study showed that meal-induced whole body oxygen uptake and splanchnic oxygen uptake are reduced by propranolol in patients with cirrhosis. The splanchnic reduction in oxygen consumption can explain almost the entire reduction in whole body oxygen consumption (Table 3, Fig. 2). Our results are in contrast to findings in healthy persons, where β-blockade has no effect on the postprandial thermogenic response after a mixed meal (42). The meal-induced thermogenesis consists of two components: the obligatory thermogenesis refers to the EE for digestion, absorption, conversion, and storage of nutrients, and the facultative thermogenesis is the energy spend in excess of the obligatory requirements. The facultative thermogenesis has been shown by Acheson et al. (1) to be mediated by the sympathico-adrenal system.

The patients were followed 2 h after meal ingestion, a period that does not cover the total postprandial metabolism. In a study by Jensen et al. (26), normal subjects were investigated 6 h postprandially after a mixed meal and diet-induced increase in whole body and splanchnic oxygen uptake was not back to baseline after the end of the study. On the other hand, despite the elevated plasma glucose at 120 min, splanchnic substrate exchange may be completed because splanchnic glucose output was back to normal (Fig. 3), which has previously been observed in patients with cirrhosis (19). The elevated plasma glucose at 120 min more likely reflects peripheral insulin resistance, which is well known in patients with cirrhosis (37, 40).

Crossover design was not done, although it could have adjusted for baseline heterogeneity. However, we could not ethically justify performing two long-lasting catheterizations within a short interval, and the numerous blood samples may cause anemia. Furthermore the patients had significant portal hypertension and esophageal varices, a clinical condition that should be treated with propranolol to prevent bleeding from...
esophageal varices. The patients are in this randomized setup and are matched regarding child class, decompensation, and splanchnic and systemic hemodynamics.

**β-Adrenergic blockade.** To obtain a stable β-adrenergic blockade and to avoid interference between intestinal food absorption and propranolol absorption, we infused propranolol. With respect to duration of catheterization, we could not wait 90 min for an oral dose of propranolol to be absorbed (4, 32). Mean dose of propranolol was 14.2 mg during the 2 h. This dose correspond to a plasma level of 50–60 ng/ml in normal controls (42) and a blockade of 60–70% of exercise-induced tachycardia (15).

To shorten the catheterization period, a baseline period during β-adrenergic blockade without the meal was omitted. This would have been preferred, but with these types of patients, the studies have to be of limited duration and with limited blood sampling. In a similar setup, MacMathuna et al. (32) found unaltered systemic and hepatic oxygen consumption following intravenous propranolol. However, we have shown earlier that splanchnic oxygen consumption decreases ~18% after an oral dose of 80 mg propranolol (7). In the present study, the splanchnic oxygen consumption in the control group increased by 30% after the meal, whereas no response was observed in the propranolol group. This indicates that the difference in response represents a combined effect of propranolol on both the hemodynamics and the meal-induced thermogenesis.

In patients with cirrhosis, 16–34% are hypermetabolic, which is partly explained by increased sympathetic activity (36). In the present study, the level of catecholamine was not measured, but is well known that the level of circulating catecholamine is increased in patients with cirrhosis and portal hypertension (5, 8). Muller et al. (36) has observed that propranolol infusion reduces whole body oxygen uptake, maximum 6%, even in hypermetabolic persons. When comparing the resting EE (REE) of the patients in the present study with resting EE in healthy humans, our patients were without signs of significant hypermetabolism, when hypermetabolism is defined as REE exceeding the predicted value by 20% (20, 36). This minor effect does not explain our findings, because we observed a postprandial reduction of ~25% (90 min after the meal). On the other hand, Jensen et al. (26) found a significant increase in plasma norepinephrine concentrations after ingres-

### Table 4. Arterial values of metabolites and A–V differences

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial lactate, mM (A–V lactate)</td>
<td>0.91±0.33</td>
<td>1.05±0.35</td>
<td>1.12±0.27</td>
<td>1.11±0.20</td>
<td>1.10±0.31</td>
</tr>
<tr>
<td>Mean + propranolol</td>
<td>0.91±0.18</td>
<td>1.09±0.31</td>
<td>1.11±0.31</td>
<td>1.11±0.29</td>
<td>1.14±0.27</td>
</tr>
<tr>
<td>Arterial pyruvate, µM (A–V pyruvate)</td>
<td>24.1±8.3</td>
<td>26.9±9.2</td>
<td>55.5±9.6</td>
<td>75.5±21.7</td>
<td>78.8±23.0</td>
</tr>
<tr>
<td>Mean + propranolol</td>
<td>30.7±10.4</td>
<td>57.5±23.9</td>
<td>56.6±26.8</td>
<td>62.6±11.9</td>
<td>59.7±15.0</td>
</tr>
<tr>
<td>Arterial glucose, µM (A–V glucose)</td>
<td>4.9±0.3</td>
<td>5.9±0.3</td>
<td>6.1±0.4</td>
<td>6.6±0.5</td>
<td>6.4±0.5</td>
</tr>
<tr>
<td>Mean + propranolol</td>
<td>4.7±0.3</td>
<td>5.8±0.5</td>
<td>6.1±0.5</td>
<td>6.4±0.5</td>
<td>6.5±0.5</td>
</tr>
<tr>
<td>Arterial FFA, µM (A–V FFA)</td>
<td>1003±206</td>
<td>679±321</td>
<td>608±310</td>
<td>526±116</td>
<td>508±285</td>
</tr>
<tr>
<td>Mean + propranolol</td>
<td>812±231</td>
<td>563±200</td>
<td>369±166</td>
<td>263±188</td>
<td>189±124</td>
</tr>
<tr>
<td>Arterial glycerol, µM (A–V glycerol)</td>
<td>322±64</td>
<td>255±76</td>
<td>295±181</td>
<td>326±209</td>
<td>315±187</td>
</tr>
<tr>
<td>Mean + propranolol</td>
<td>59±117</td>
<td>53±42</td>
<td>71±116</td>
<td>100±129</td>
<td>101±145</td>
</tr>
<tr>
<td>Lactate/pyruvate ratio hepatic vein</td>
<td>53±31</td>
<td>28±30</td>
<td>19±7</td>
<td>12±4</td>
<td>12±5</td>
</tr>
<tr>
<td>Mean + propranolol</td>
<td>37±12</td>
<td>18±7</td>
<td>24±13</td>
<td>16±6</td>
<td>17±7</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 compared with baseline. †P < 0.05 compared with meal without propranolol. A–V differences are given in parentheses.

### Table 5. Hepatic net flux of metabolites

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After Meal</th>
</tr>
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<tbody>
<tr>
<td>Lactate uptake, mmol/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meal alone</td>
<td>0.14±0.13</td>
<td>0.07±0.31</td>
</tr>
<tr>
<td>Meal + propranolol</td>
<td>0.26±0.11</td>
<td>0.08±0.15</td>
</tr>
<tr>
<td>Glucose output, mmol/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meal alone</td>
<td>0.38±0.22</td>
<td>0.83±0.88</td>
</tr>
<tr>
<td>Meal + propranolol</td>
<td>0.41±0.23</td>
<td>0.47±0.41</td>
</tr>
<tr>
<td>Free Fatty Acids uptake (µmol/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meal alone</td>
<td>89.4±81.8</td>
<td>47.9±28.8</td>
</tr>
<tr>
<td>Meal + propranolol</td>
<td>138.0±102.2</td>
<td>22.3±18.3</td>
</tr>
<tr>
<td>Glycerol uptake, µmol/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meal alone</td>
<td>99.2±33.13</td>
<td>−18.0±63.14</td>
</tr>
<tr>
<td>Meal + propranolol</td>
<td>80.6±94.24</td>
<td>75.7±36.83</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 compared with baseline. †P < 0.05 compared with meal without propranolol. The hepatic blood flow was not measured at 90 min. The 90 min value was extrapolated from values at 60 and 120 min.
tion of a mixed meal (but no increase in epinephrine), indicating a meal-induced increase in sympathetic activation, which can be involved in mediating the meal-induced increase in oxygen consumption and can be inhibited by the infusion of propranolol.

In healthy subjects, an increased hepatic oxygen demand can be met by increasing the oxygen extraction from the blood. In cirrhosis, hepatic and splanchnic oxygen uptake is decreased and the splanchnic oxygen demand is dependent on the splanchnic blood flow (27, 43). In the present experiment, we observed a postprandial increase in HBF and oxygen extraction across the splanchnic tissue in the control group, whereas the propranolol group did not experience postprandial change in oxygen extraction despite a significant decrease in HBF compared with the control group. Therefore, it could be speculated that propranolol may reduce hepatic metabolic functions by decreasing splanchnic blood flow and thereby splanchnic oxygen uptake (7). Apart from the reduction in splanchnic oxygen consumption, the extrasplanchnic effects include reduced cardiac oxygen uptake parallel to reduction in heart rate and mean arterial pressure.

In the baseline fasting period, it can be calculated that gluconeogenesis may contribute to 30–40% of the splanchnic glucose output assuming that all the splanchnic uptake of lactate and glycerol is used for gluconeogenesis. This is probably a minimum estimate because alanine, which was not measured, also contributes to gluconeogenesis. Postprandially, uptake of gluconeogenic precursors decreases in both groups, which probably represents a decrease in hepatic glucose production. If we assume that all glucose (58 g) is absorbed at 120 min (see Fig. 3; splanchnic substrate exchange seems to be completed) and that hepatic glucose production is reaching zero, we can assume that most of the absorbed glucose is taken up in the liver. The splanchnic glucose output was ~5 mmol/min (Table 5), which is equivalent to ~11 g/120 min of glucose. This corresponds to the integrated increase in peripheral glucose oxidation after the meal, which is ~7 g/120 min (see Table 3) in both groups. Gluconeogenesis is an energy-consuming process, and because there is a tendency of lower postprandial glucose output in the propranolol group (Table 5), this may explain some of the difference in postprandial splanchnic thermogenesis. Gluconeogenesis decreases due to reduced precursor uptake; however, the increase in glucose output may partly be due to glycogenolysis, which is an energy-consuming process via cAMP-dependent protein kinase, although not as energy consuming as gluconeogenesis. The postprandial arterial FFA concentration decreased as expected, most likely due to an increase in circulating insulin. However, the decrease was more pronounced in the propranolol group, indicating that propranolol may also have peripheral antilipolytic effects in cirrhotic patients. The pronounced decrease in FFA gives rise to a decreased delivery of FFA to the liver. This is in accordance with the present results where the postprandial splanchnic FFA uptake was significantly lower in the propranolol group compared with the control group. Ketone body production from fatty acid metabolism is an energy-consuming process, and in the propranolol group, it could explain some of the decreased postprandial splanchnic oxygen consumption. However, postprandial oxygen consumption is substrate specific, and amino acids have the strongest thermic effect on hepatic metabolism, due to protein synthesis, ureagenesis, and gluconeogenesis from amino acids (35). In the present study, we did not measure the protein metabolism, but it has been shown that β-blockade reverses muscle protein catabolism in severely burned patients and thereby decreases the amino acid delivery to the liver (25).

Decreased splanchnic oxygen uptake in cirrhosis has been shown to be associated with a decrease in metabolic liver functions, because a decrease in splanchnic VO2 correlates
significantly with decreased splanchnic glucose production as well as a decrease in splanchnic FFA extraction (43). Therefore, hepatic blood flow can become limiting for the metabolic capacity of the liver, and in the postprandial period, there may be a risk of severe hypoxemia and local injury in the liver. We found no significant difference in oxygen concentrations between patients who received propranolol and those who did not (data not shown). The oxygen concentration decreased after the meal in both groups in the azgos and hepatic veins. Only one patient had a severe drop in oxygen concentration in the hepatic vein (from 3.46 to 1.16 mM). However, this did not lead to anaerobic metabolism reflected by pyruvate and lactate.

The postprandial lactate-to-pyruvate ratio (Table 4) in the hepatic vein decreased in both groups, which indicates improved energy balance. This is in accordance with a study by MacMathuna et al. (32), who measured what the ratio between the ketone bodies acetoacetate and β-hydroxybutyrate was in the hepatic vein as an indirect measurement of the hepatic mitochondrial state. They found that β-blockade did not alter the hepatic redox state in the total group of patients with cirrhosis but found an improvement in the patients with the most advanced disease.

The main energy-requiring processes in the liver are ureagenesis, futile cycling of substrates, gluconeogenesis, protein synthesis, Na⁺ K⁺-ATPase activity, and ketogenesis (34, 35). It has been reported that the cirrhotic liver seems to have reduced glycogen stores and limited gluconeogenetic capacity (35, 44). The present study indicates that ketogenesis and gluconeogenesis may be impaired by propranolol infusion, although we did not measure ketogenesis or gluconeogenesis. On the other hand, the postprandial increases in RER in both groups, together with the increased glucose concentration, indicate that the extrahepatic carbohydrate metabolism is unaltered during β-blockade.

Azgos vein in cirrhosis. In healthy persons, the azgos vein is mainly draining the interscapular region of the thoracic wall. However, in patients with portal hypertension, portosystemic collaterals develop; these are mainly drained by the azgos vein, and the azgos blood flow is often markedly increased compared with controls (~500 vs. 115 ml/min) (13, 14, 23). The magnitude of collateral flow seems to influence the course of variceal bleeding (12, 13). The blood flow in other portosystemic collaterals is very difficult to quantify and thereby the oxygen consumption and flux of metabolites is in these (6, 22). Therefore, the calculations regarding collaterals are minimum values and probably an underestimate. In the patients studied, the VO₂ in the azgos is ~6% of whole body VO₂ at rest and increases after the meal (Table 3). This is in accordance with the concept that the azgos vein is partly derived from the splanchnic area, because in normal subjects, the VO₂ in the tissues drained by the azgos vein amounts to 2% of whole body VO₂ and does not increase after a meal (14). Furthermore propranolol prevented a significant increase in azgos flow after the meal (Table 2).

In conclusion, propranolol reduces meal-induced whole body oxygen uptake and EE as well as splanchnic oxygen uptake in patients with cirrhosis. The splanchnic reduction in oxygen consumption can explain almost the entire reduction in whole body oxygen consumption. Postprandially, in the propranolol group, a tendency toward a reduced splanchnic glucose output and a significant reduction in FFA uptake was observed.

REFERENCES