Hypermetabolism in clinically stable patients with liver cirrhosis

Manfred J Müller, Joachim Böttcher, Oliver Selberg, Stefanie Weselmann, Klaus HW Böker, Mechthild Schwarze, Alexander von zur Mühlen, and Michael P Manns

ABSTRACT

Background: Hypermetabolism has a negative effect on prognosis in patients with liver cirrhosis. Its exact prevalence and associations with clinical data, the nutritional state, and β-adrenergic activity are unclear.

Objective: We investigated resting energy expenditure (REE) in 473 patients with biopsy-proven liver cirrhosis.

Design: This was a cross-sectional study with a controlled intervention (β-blockade) in a subgroup of patients.

Results: Mean REE was 7.12 ± 1.34 MJ/d and correlated closely with predicted values (r = 0.70, P < 0.0001). Hypermetabolism was seen in 160 patients with cirrhosis (33.8% of the study population). REE was > 30% above the predicted value in 41% of the hypermetabolic patients with cirrhosis. Hypermetabolism had no association with clinical or biochemical data on liver function. REE correlated with total body potassium content (TBP; P < 0.0001). Hypermetabolic patients had lower than normal body weight and TBP (P < 0.05). About 47% of the variance in REE could be explained by body composition whereas clinical state could maximally explain 3%. Plasma epinephrine and norepinephrine concentrations were elevated in hypermetabolic cirrhotic patients (by 56% and 41%, respectively; P < 0.001 and 0.01). Differences in REE from predicted values were positively correlated with epinephrine concentration (r = 0.462, P < 0.001). Propranolol infusion resulted in a decrease in energy expenditure (by 5 ± 3%; P < 0.05), heart rate (by 13 ± 4%; P < 0.01), and plasma lactate concentrations (by 32 ± 12%; P < 0.01); these effects were more pronounced in hypermetabolic patients (by 50%, 33%, and 68%, respectively; each P < 0.05).

Conclusions: Hypermetabolism has no association with clinical data and thus is an extrahepatic manifestation of liver disease. Increased β-adrenergic activity may explain ≈25% of hypermetabolism. Am J Clin Nutr 1999;69:1194–201.

KEY WORDS Liver cirrhosis, energy metabolism, energy expenditure, β-adrenergic activity, catecholamines, nutritional state, Child-Pugh score, humans, hypermetabolism, liver transplantation

INTRODUCTION

Hypermetabolism may occur in patients with liver cirrhosis. Its prevalence is unknown (1, 2). Hypermetabolic patients have a poor prognosis after liver transplantation and have been considered a high-risk group (3). In a previous study of 123 patients with cirrhosis (4), we found hypermetabolism in 15–20% of them. There was no association between metabolic and clinical data (4). When a subgroup of 26 patients was followed for a mean period of 432 d after liver transplantation, differences in resting energy expenditure (REE) from predicted values were found to be nearly unchanged despite normalization of liver function (5). There was a significant correlation between metabolic and nutritional data; hypermetabolism was associated with malnutrition (2, 4). Because standard techniques used for the assessment of nutritional state [e.g., body weight, anthropometry, and bioelectrical impedance analysis (BIA)] are of limited value in cirrhotic patients (2), the above-mentioned association has to be reassessed with more sophisticated methods.

We do not now understand the pathophysiology of hypermetabolism nor do we have treatment strategies for hypermetabolic patients. There is some evidence that hypermetabolism is associated with the hemodynamic alterations observed in cirrhotic patients (2, 5, 6). Preliminary data suggested that a fall in portal blood flow was associated with an increase in whole-body energy expenditure and concomitantly reduced hepatic oxygen consumption (2). It is tempting to speculate that increased sympathetic nervous system (SNS) activity and the concentrations of plasma catecholamines, which are frequently elevated with liver cirrhosis, contribute to systemic hypermetabolism (2). In fact, SNS and circulatory catecholamines play an important role in the circulatory and metabolic derangements, salt and water retention, and the development of the hepatorenal syndrome in patients with cirrhosis (7). However, the possible

1From the Medizinische Hochschule Hannover, Hannover, Germany; the Department of Gastroenterologie and Hepatologie, Klinische Chemie II and Klinische Endokrinologie, Hannover, Germany; and the Christian-Albrechts-Universität zu Kiel, Institut für Humanernährung und Lebensmittelkunde, Kiel, Germany.

2Supported by B Braun Melsungen, Melsungen, Germany.

3Reprints not available. Address correspondence to MJ Müller, Institut für Humanernährung und Lebensmittelkunde, Christian-Albrechts-Universität zu Kiel, Düsternbrooker Weg 17, D-24105 Kiel, Germany. E-mail: mmueller@nutrfoodsc.uni-kiel.de.

Received June 3, 1998.
Accepted for publication December 21, 1998.
association between hypermetabolism and measures of adrenergic activity or the effects of β-blockade on metabolic rate are unknown in cirrhotic patients.

The purpose of the present study was to assess the prevalence of hypermetabolism in a large group of cirrhotic patients \( n = 473 \). This gave us the opportunity to reassess possible associations between energy expenditure and clinical and nutritional data. In addition, the possible contribution of SNS activity to energy expenditure was investigated in a subgroup of patients.

SUBJECTS AND METHODS

This study was part of the liver transplantation program at the Medizinische Hochschule Hannover. Four hundred seventy-three patients with biopsy-proven liver cirrhosis were assessed between 1986 and 1993. The patients were admitted as potential candidates for liver transplantation; they had not been selected in any other way. The study protocol was approved by the ethical committee of the Medizinische Hochschule Hannover. Informed, written consent was obtained from each patient. All patients were in stable clinical condition, none had arterial hypoxemia, lung disease, renal dysfunction, or elevated body temperature. At admission, patients were consuming a weight-maintaining diet that included \( \geq 200 \) g carbohydrates (\( \approx 50\% \) of energy intake) and \( 0.8 \) g protein \( \cdot \) kg body wt \( ^{-1} \cdot \) d \( ^{-1} \). The sodium chloride content of the diets varied between 3 and 8 g/d. Seventy-one percent of the patients took diuretics (mostly potassium sparing). The clinical classification was based on the plasma concentrations of bilirubin and albumin, the prothrombin time, the occurrence of ascites, and clinical signs of encephalopathy (8).

Metabolic studies were performed after the patients had been on the ward for \( \geq 3 \) d. The details of the different clinical, physiologic (REE and nutritional state), and biochemical (including hormones and substrates) investigations were presented previously (3, 4, 9). Briefly, REE was measured with an open-circuit indirect calorimeter (Deltatrac Metabolic Monitor; Datex Instruments, Helsinki). Measurements were performed between 0700 and 0800 while the patient was still lying in bed. They had their last evening meal between 1800 and 1900 on the previous day. Gas-exchange measurements were done continuously for \( \geq 1 \) h. The first 20 min of data were omitted and data were integrated for 5-min intervals. The means of \( \geq 40 \) (1-min) measurements were calculated.

The gas analyzers were calibrated immediately before and after the measurements. Variation caused by the technique was calculated on the basis of 5 repeated measurements of propane and helium, and was found to be <4%. Daily variances between individuals, based on test-retest measurements in 10 clinically stable patients with liver cirrhosis performed on 3 different days within a 14-d period, were \( < 10\% \). REE was predicted according to Harris and Benedict (10). In addition, more recent formulas were used (11–14) to compare their predictive values. Hypermetabolism was defined as a measured REE exceeding the predicted value by \( \geq 20\% \). Normometabolic patients were within the range of \( \pm 20\% \) of the predicted value.

The effect of propranolol infusion on REE was investigated in a subgroup of 19 patients. After the assessment of REE, a nonselective β-blocker (propranolol, Dociton; Zeneca/Rhein Pharma, Schwetzingen, Germany) was given [120 \( \mu \)g/kg fat-free mass (FFM)] as a bolus, which was followed by a continuous infusion of 1.2 \( \mu \)g \( \cdot \) kg FFM \( ^{-1} \cdot \) min \( ^{-1} \) for 60 min and measurements of gas exchange were performed continuously. In addition, pulse rate and blood pressure were measured every 5 min with use of an automatic machine. In these experiments, venous blood samples (5 mL) were taken before and every 15 min after propranolol infusion for the immediate analysis of plasma substrate concentrations (ie, glucose, lactate, fatty acids, and ketone bodies).

Total body potassium (TBP) was measured by counting \(^{40}\text{K}\) with a whole body counter with a precision >97% (15, 16). The counter consists of 6 Nal (T1) detectors. Total scanning time was 45 min. The method relies on the detection of 1.46-MeV gamma rays from naturally occurring radioisotope \(^{40}\text{K}\). \(^{40}\text{K}\) is present as a constant fraction (0.012%) of total potassium. It is assumed that potassium is confined almost entirely to the FFM. In addition, creatinine measurements were used to estimate skeletal muscle mass (17). BIA was used as a measure of total body water at a standard frequency of 50 mA (BIA 101; RJL Systems, Detroit). Measurements and data analyses were done as described previously with normal ranges for epinephrine and norepinephrine of 0.3–2.8 and 0.2–0.5 \( \mu \)mol/L, respectively (4).

All data were recorded in a database by using a personal computer; statistical analyses were performed by using SPSS for WINDOWS (version 5.0.2; SPSS Inc, Chicago). Data are presented as means \( \pm \) SDs. The Mann-Whitney U test or Fisher’s exact test was used for comparisons between groups. Spearman’s correlation coefficient was calculated to test the relation between different quantities in a bivariate regression model. In addition, a multivariate stepwise regression analysis was performed with REE as the dependent variable.

RESULTS

Biological, physical, and clinical characteristics of the study population are given in Tables 1 and 2. Mean REE was 7.12 \( \pm 1.34 \) MJ/d (men: 7.73 \( \pm 1.36 \) MJ/d; women: 6.45 \( \pm 0.96 \) MJ/d; \( P < 0.01 \) for sex differences). REE was closely correlated with predicted REE \(( r = 0.70, P < 0.0001; \)(Figure 1)). The mean predicted values were 6.90 \( \pm 0.89 \) and 5.52 \( \pm 0.50 \) MJ/d for men and women, respectively.

The mean difference measured and predicted REE was 0.83 \( \pm 1.07 \) MJ/d (12.4 \( \pm 15.6\% \) in men and 0.93 \( \pm 0.81 \) MJ/d (17.1 \( \pm 14.9\% \) in women. Only 50% of the variance in REE could be predicted by the Harris-Benedict equation. Use of other equations, which considered estimates of body composition instead of body weight to predict REE (11–14), resulted in lower \( r \) values (<0.70) for the correlation between measured and predicted REE, and thus explained <50% of the variance in REE (data not shown).

Hypermetabolism was seen in 160 patients (33.8% of the study population). A small number, 3.2% of the patients, were considered hypometabolic (ie, measured REE was >20% below the predicted REE). Hypermetabolic patients had a mean REE of 7.56 \( \pm 1.38 \) MJ/d \( (P < 0.001) \); the REE of men was 8.32 \( \pm 1.45 \) MJ/d and of women was 6.89 \( \pm 1.02 \) MJ/d \( (P < 0.01 \) for sex differences). REE >30% above the predicted value in 41% of the hypermetabolic patients (ie, 14% of the study population). The prevalence of hypermetabolism was virtually unaffected by the formula used to estimate REE, but slightly higher values were obtained with use of more recent prediction formulas, ie, 32%, 36%, 33%, and 37% of cirrhotic patients being hypermetabolic (according to references 11–14, respectively). The mean respiratory quotient was 0.77 \( \pm 0.06 \) and there were no significant differences in respiratory quotient among the patients.

TBP was 2464 \( \pm 928 \) mmol in male and 1761 \( \pm 467 \) mmol in female patients (Table 1). There were no differences in TBP.
between Child A-, B-, and C-rated patients although there were significant sex differences (Child A: men, 2618 ± 910 mmol; women, 1780 ± 530 mmol; Child B: men, 2472 ± 1052 mmol; women, 1749 ± 467 mmol; Child C: men, 2308 ± 656 mmol; women, 1682 ± 377 mmol; \( P < 0.01 \) for sex differences). REE was closely correlated with TBP (\( r = 0.49, P < 0.0001; \) Figure 2). A similar correlation between REE and TBP was found in patients treated with diuretics (\( r = 0.53, P < 0.0001; n = 79 \)). There were no significant differences in the mean absolute TBP value or REE-TBP ratio between patients who 1) were or were not treated with diuretics, 2) were with or without significant ascites, and 3) had low or normal plasma sodium concentrations (data not shown). In cirrhotic patients, muscle mass (as assessed by urinary creatinine excretion) was 29% of body weight (data not shown). There were no significant differences in muscle mass among cirrhotic patients with respect to clinical state or biochemical measures of liver function (data not shown). Muscle mass correlated with TBP (\( r = 0.57, P < 0.001; n = 473 \)).

When compared with normometabolic patients, hypermetabolic patients with liver cirrhosis had reduced body weights as well as TBP (Table 1). No differences in percentage muscle mass and total body water (as assessed by BIA) were seen between hyper- and normometabolic patients. There were also no differences in clinical measures of liver disease between normo- and hypermetabolic patients.

### TABLE 1

Biological and physical characteristic of normo- and hypermetabolic patients with liver cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>All (n = 253 M, 220 F)</th>
<th>Normometabolic (n = 175 M, 138 F)</th>
<th>Hypermetabolic (n = 78 M, 82 F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>44.2 ± 12.6</td>
<td>43.5 ± 13.0</td>
<td>45.6 ± 11.8</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>66.0 ± 13.4</td>
<td>67.0 ± 13.8</td>
<td>64.1 ± 12.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 9.2</td>
<td>171 ± 8.9</td>
<td>169 ± 9.5</td>
</tr>
<tr>
<td>Creatinine-height index (%)</td>
<td>88.0 ± 37.8</td>
<td>87.5 ± 40.7</td>
<td>88.8 ± 31.6</td>
</tr>
<tr>
<td>Total body potassium (mmol)</td>
<td>2103 ± 805</td>
<td>2133 ± 795</td>
<td>2018 ± 831</td>
</tr>
<tr>
<td>Triceps skinfold thickness (mm)</td>
<td>10.5 ± 6.2</td>
<td>10.6 ± 6.5</td>
<td>10.5 ± 5.6</td>
</tr>
<tr>
<td>Sum of 4 skinfold thicknesses (mm)</td>
<td>34.1 ± 17.2</td>
<td>34.6 ± 18.7</td>
<td>33.0 ± 13.9</td>
</tr>
<tr>
<td>Midarm circumference (cm)</td>
<td>25.3 ± 3.7</td>
<td>25.6 ± 3.9</td>
<td>24.2 ± 3.2</td>
</tr>
<tr>
<td>Bioelectrical impedance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistance (( \Omega ))</td>
<td>596 ± 120</td>
<td>595 ± 123</td>
<td>598 ± 115</td>
</tr>
<tr>
<td>Reactance (( \Omega ))</td>
<td>56 ± 15</td>
<td>57 ± 16</td>
<td>54 ± 14</td>
</tr>
<tr>
<td>Total body water (L)</td>
<td>36.7 ± 7.7</td>
<td>37.2 ± 7.9</td>
<td>35.8 ± 7.4</td>
</tr>
<tr>
<td>Resting energy expenditure (MJ/d)</td>
<td>7.12 ± 1.34</td>
<td>6.69 ± 1.02</td>
<td>7.56 ± 1.38</td>
</tr>
</tbody>
</table>

\( ^1 \pm SD. \)

\( ^2, ^3 \) Significantly different from normometabolic: \( ^2 P < 0.05, ^3 P < 0.001 \)

### TABLE 2

Clinical variables in normo- and hypermetabolic patients with liver cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>All (n = 473)</th>
<th>Normometabolic (n = 313)</th>
<th>Hypermetabolic (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child A</td>
<td>33.9</td>
<td>71.9</td>
<td>28.1</td>
</tr>
<tr>
<td>Child B</td>
<td>52.1</td>
<td>63.5</td>
<td>36.5</td>
</tr>
<tr>
<td>Child C</td>
<td>14.0</td>
<td>65.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Etiology of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>40.1</td>
<td>66.1</td>
<td>33.9</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>16.7</td>
<td>65.9</td>
<td>34.1</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>10.1</td>
<td>58.8</td>
<td>41.2</td>
</tr>
<tr>
<td>Others</td>
<td>13.3</td>
<td>71.4</td>
<td>28.6</td>
</tr>
<tr>
<td>Toxic</td>
<td>16.1</td>
<td>74.7</td>
<td>25.3</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>15.5</td>
<td>75.3</td>
<td>24.7</td>
</tr>
<tr>
<td>Nonalcoholic</td>
<td>0.6</td>
<td>66.7</td>
<td>33.3</td>
</tr>
<tr>
<td>Biliary</td>
<td>18.0</td>
<td>54.7</td>
<td>45.3</td>
</tr>
<tr>
<td>Primary</td>
<td>14.6</td>
<td>53.4</td>
<td>46.4</td>
</tr>
<tr>
<td>Secondary</td>
<td>3.4</td>
<td>57.1</td>
<td>42.9</td>
</tr>
<tr>
<td>Cirrhosis plus carcinoma</td>
<td>3.2</td>
<td>70.6</td>
<td>29.4</td>
</tr>
<tr>
<td>Other</td>
<td>22.6</td>
<td>67.8</td>
<td>32.2</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>3.8</td>
<td>72.2</td>
<td>27.8</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>2.5</td>
<td>58.8</td>
<td>41.2</td>
</tr>
<tr>
<td>Metabolic</td>
<td>3.4</td>
<td>75.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>8.9</td>
<td>70.5</td>
<td>29.5</td>
</tr>
</tbody>
</table>
The trend of hypermetabolism was 28.1%, 36.5%, and 35.0% in Child A-, B-, and C-rated patients, respectively (NS). Most of our patients had liver disease because of viral infections. Comparing REE in subgroups with different etiologies of liver cirrhosis showed a higher prevalence of hypermetabolism in subgroups with hepatitis C infection, biliary cirrhosis, or autoimmune liver disease; for patients with biliary cirrhosis these differences were significant (P < 0.01). With use of stepwise multivariate regression analysis, ≈47% of the variance in REE could be explained by body-composition data; by contrast, clinical state could maximally explain only 3% of the variance.

Plasma epinephrine and norepinephrine concentrations were analyzed in a subgroup of 59 patients. Thirty-two percent of these patients were considered hypermetabolic (REE: 7.85 ± 0.79 compared with 6.75 ± 1.31 MJ/d; elevation of REE: 30.6 ± 13.1% compared with 1.9 ± 8.0%; P < 0.001 for both comparisons). The plasma concentrations of catecholamines were elevated in hypermetabolic patients (epinephrine: 1.53 ± 0.73 compared with 0.98 ± 0.33 nmol/L; P < 0.001; norepinephrine: 5.28 ± 2.74 compared with 3.75 ± 1.57 nmol/L; P = 0.01). Differences in REE from predicted values but not absolute values of REE were positively correlated with plasma epinephrine concentrations (r = 0.462, P < 0.001; Figure 3). No significant associations were found between plasma norepinephrine concentrations and REE or differences in REE from predicted values as dependent variables, neither plasma epinephrine nor plasma norepinephrine were significant contributors to the variance in REE. Propranolol infusion in 19 patients with cirrhosis (5 were hypermetabolic; REE: 8.20 ± 1.78 compared with 7.10 ± 1.20 MJ/d; elevation of REE: 30.0 ± 14.9% compared with 3.2 ± 8.4%; P < 0.01 for both comparisons) resulted in a decrease in energy expenditure (by 5 ± 3%; P < 0.05), heart rate (by 13 ± 4%; P < 0.01), and plasma lactate concentrations (by 32 ± 12%; P < 0.01) (Figure 4). Concomitantly, mean arterial blood pressure decreased by 7 mm Hg. When compared with normometabolic patients, the decreases in energy expenditure, heart rate, and plasma lactate concentrations were all more pronounced in hypermetabolic patients (by 50%, 33%, and 68%, respectively; P < 0.05) (Figure 4). Significant correlations were found between the propranolol-induced decrease in energy expenditure and the propranolol-induced decrease in heart rate (r = 0.58, P < 0.01; data not shown). β-Blockade also induced significant decreases in the plasma concentrations of fatty acids (20% below basal values, P < 0.05) and β-hydroxybutyrate (29% below basal values, P < 0.05). At the same time, no significant alterations in the plasma concentrations of glycerol or glucose were seen (data not shown). Similar changes in plasma concentrations of fatty acids and β-hydroxybutyrate and in blood pressure were seen in hypermetabolic and normometabolic patients (data not shown).

**DISCUSSION**

There is considerable variability of REE in liver disease. The scatter of results in cirrhotic patients is greater than that obtained in healthy subjects (18). Our data, so far the largest number of measurements performed in patients with liver cirrhosis, showed that 33.8% of clinically stable patients had an elevated REE (Table 1). By contrast, in our hands, hypermetabolism is found in only 10% of healthy subjects (MJ Müller et al, unpublished observations, 1999). Differences in the prevalences of hypermetabolism between healthy subjects and cirrhotic patients suggest that, besides constitutional factors, liver disease (or factors related to liver disease) has a profound influence on REE. Our definition of hypermetabolism was based on prediction of REE with the Harris-Benedict equation (10). A more recent reappraisal of energy requirements of men (19) and women (20) showed that the classic prediction equations overestimate REE in

---

**FIGURE 1.** Correlation between measured and predicted [according to the Harris-Benedict equation (10)] resting energy expenditure (REE) in 473 patients [○, men (n = 253); ●, women (n = 220)] with biopsy-proven liver cirrhosis (r = 0.70, P < 0.0001 for all patients; r = 0.619, P < 0.001 for men; r = 0.518, P < 0.001 for women).

**FIGURE 2.** Correlation between total body potassium (TBP) content and resting energy expenditure (REE) in 473 patients [○, men (n = 253); ●, women (n = 220)] with biopsy-proven liver cirrhosis (r = 0.49, P < 0.0001 for all patients; r = 0.393, P < 0.001 for men; r = 0.219, P < 0.05 for women).
both sexes. Use of the more recent prediction formulas would thus increase the magnitude and prevalence of hypermetabolism. This is also suggested by more recent prediction formulas based on metabolically active components of the body (11–14), which result in slightly higher prevalences of hypermetabolism.

Hypermetabolic patients cannot be identified by clinical or biochemical measures of liver disease (Table 2). This observation suggests that the variability of REE is an extrahepatic manifestation of liver cirrhosis. We showed previously that hypermetabolism persists over > 1 y after liver transplantation (5) and adversely affects survival (3). Although the pathophysiology of hypermetabolism is far from clear, these observational data suggest that metabolic characterization is mandatory in every patient with liver disease. Metabolically, even a clinically well-defined group of patients cannot be considered a homogeneous group. Thus, metabolic studies performed on small groups of patients should be evaluated very carefully and generalizations should be avoided (2).

REE was closely correlated with the nutritional state of the patients (Figure 2). Hypermetabolic patients had reduced body weights and TBP compared with normometabolic patients (Table 1). It is tempting to speculate that hypermetabolism contributes to malnutrition if energy intake is not increased adequately. However, this question cannot be answered by our data because energy intake was not assessed in our patients and we are not following them longitudinally. The association between hypermetabolism and the nutritional state of patients was examined in a longitudinal study of AIDS patients. In clinically stable patients, there was a positive correlation between increased energy expenditure and weight loss (21). Similar energy intakes were found in weight-stable and weight-losing patients, but the latter patients had increased REEs and lost 5.9 kg. This was close to the estimated weight loss based on the calculation of energy balance (ie, ~5.5 kg; 21). Weight loss was also associated with tumor necrosis factor receptor concentrations in HIV-infected patients (22). These data suggest that hypermetabolism contributes to malnutrition and may be related to activation of the immune system. Similar studies should be performed in cirrhotic patients. Interestingly, cirrhotic patients had higher serum concentrations of various cytokines regardless of the underlying disease (23). The percentage of patients with elevated circulating cytokines varied between 40% and almost 100%, depending on the individual cytokine measured. Preliminary data from our group, obtained in 19 cirrhotic patients (24), showed that arterial concentrations of tumor necrosis factor α were negatively associated with whole-body oxygen consumption. However, tumor necrosis factor concentrations also had a strong negative association with body cell mass and REE expressed per kg body cell mass increased with increasing tumor necrosis factor.
concentrations \( (r = 0.51, \ P < 0.03; 24) \). These data suggest that hypermetabolism is part of the systemic inflammatory response in cirrhosis that reduces skeletal protein mass while increasing splanchnic (ie, mainly liver) and systemic metabolism. It is tempting to speculate that 1) the cirrhotic liver cannot respond in a normal way, thus explaining the dissociation between hepatic and systemic energy expenditure that was seen in cirrhotic patients (2), and 2) at least part of the scenario is mediated by increased SNS activity, plasma catecholamines, or both.

A direct relation between circulating epinephrine and norepinephrine concentrations and the progression of liver disease has been described (25, 26). This finding was explained by decreased hepatic clearance of plasma catecholamines (7). Although significant differences in basal plasma catecholamines exist, stress- (eg, exercise) induced increases in plasma epinephrine and norepinephrine were found to be normal in cirrhotic patients at early stages of their disease (27). Catecholamines are determinants of daily energy expenditure. In this study we found no significant associations between REE and plasma concentrations of or urinary excretion of epinephrine and norepinephrine (Figure 3). The elevated plasma catecholamine concentrations of hypermetabolic cirrhotic patients suggest that they have increased adrenergic activity. In fact, there was a significant association between plasma epinephrine concentrations and the differences between measured and predicted REE.

Part of the metabolic response to increased adrenergic activity may be camouflaged by hyperinsulinemia. Cirrhotic patients are hyperinsulinemic (28) and the thermic effect of epinephrine is decreased by hyper- but increased by hypoinsulinemia (29–31). When compared with healthy control subjects, infusion of epinephrine into hyperinsulinemic cirrhotic patients produced a reduced metabolic response (9, 32).

In cirrhotic patients, infusion of propranolol significantly reduced REE (by 5%; Figure 4). However, the finding that \( - \)-blockade was able to reduce metabolic rate in cirrhotic patients suggests that \( - \)-adrenergic activity contributes significantly to REE. The effect of propranolol was most pronounced in patients with a high REE. These results were similar to data obtained in healthy subjects (33). Our short-term experiment suggested that \( - \)-adrenergic activity contributes to \( \approx 25\% \) of hypermetabolism in cirrhotic patients. As to the possible mechanisms, \( - \)-blockade decreases portal pressure (and also systemic hemodynamics) in cirrhotic patients (34–36). Because increased portal pressure and decreased portal blood flow were associated with increased REE (2, 37), alterations in portal hemodynamics may provide a key to our understanding of hypermetabolism in cirrhosis.

Malnutrition may lead to hypermetabolism. This idea is based on the different contributions of individual organs to REE. Because metabolic activity differs between individual organs, a preferential loss in muscle mass, which characterizes most clinical forms of malnutrition, increases the contribution of metabolically active organs and thus REE per kg body weight or per kg FFM (38). This may explain the inability of malnourished cirrhotic patients to “slow their internal fires” (39). Until now, detailed body-composition analyses have not been performed in patients with liver cirrhosis and few data on the contribution of different components of FFM to REE have been reported for healthy humans (40–42). The calculated ratio of muscle mass to body weight or to body cell mass showed no association between the deviations in REE and different proportions of muscle mass to body weight or body cell mass. However, our method to assess muscle mass is not sensitive enough to detect subtle changes within metabolically active components of FFM.

In healthy subjects, REE contributes \( \approx 65–75\% \) of 24-h energy expenditure. The contribution of REE to 24-h energy expenditure is nearly unknown in patients with cirrhosis because it has been determined only occasionally in these patients. Use of doubly labeled water (43), a factorial method (44), or measurements in a respiratory chamber (45, 46) in small groups of patients with cirrhosis all showed a low ratio of 24-h energy expenditure to REE. Thus, the contribution of REE to 24-h energy expenditure is likely to be elevated in patients with cirrhosis.

In conclusion, REE is highly variable but most cirrhotic patients have normal values. The prevalence of hypermetabolism in our study was 33.8%. Because REE cannot be predicted with accuracy, seems to be unrelated to clinical measures of liver disease, and has prognostic value, measurement of REE is mandatory in every patient with cirrhosis. Because hypermetabolism is associated with malnutrition, nutritional assessment and support are necessary in hypermetabolic patients (43, 47). In addition, treatment of hypermetabolic patients with \( - \)-blockade seems to be justified in controlled studies.

FIGURE 4. Decreases in energy expenditure, heart rate, and plasma lactate concentrations after \( - \)-blockade in 19 patients with biopsy-proven liver cirrhosis. Data are presented for all patients as well as for subgroups of patients with normal (normometabolic) and elevated (hypermetabolic) resting energy expenditure. *Significantly different from normometabolic, \( P < 0.05 \).
REFERENCES

44. Nielsen K, Kondrup J, Martinsen L, Stilling B, Wikman B. Nutri-