Nature and Quantity of Fuels Consumed in Patients with Alcoholic Cirrhosis

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ABSTRACT Although alcoholism is a leading cause of morbidity and mortality of middle-aged Americans, there are no data available pertaining to the consequences of Laennec's cirrhosis on total body energy requirements or mechanisms for maintaining fuel homeostasis in this patient population. Therefore, we simultaneously used the techniques of indirect calorimetry and tracer analyses of [^{14}C]palmitate to measure the nature and quantity of fuels oxidized by patients with biopsy-proven alcoholic cirrhosis and compared the results with values obtained from healthy volunteers. Cirrhotic patients were studied after an overnight fast (10–12 h). Normal volunteers were studied after an overnight fast (12 h) or after a longer period of starvation (36–72 h).

Total basal metabolic requirements were similar in overnight fasted cirrhotic patients (1.05±0.06 kcal/min per 1.73 m^2), overnight fasted normal subjects (1.00±0.05 kcal/min per 1.73 m^2), and 36–72-h fasted normal volunteers (1.10±0.06 kcal/min per 1.73 m^2).

Indirect calorimetry revealed that in cirrhotic patients the percentages of total calories derived from fat (69±3%), carbohydrate (13±2%), and protein (17±4%) were comparable to those found in 36–72-h fasted subjects, but were clearly different from those of overnight fasted normal individuals who derived 40±6, 39±4, and 21±2% from fat, carbohydrate, and protein, respectively.

These data are strikingly similar to data obtained through tracer analyses of [^{14}C]palmitate, which showed that in overnight fasted patients with alcoholic cirrhosis, 63±4% of their total CO_2 production was derived from oxidation of 287±28 μmol free fatty acids (FFA)/min per 1.73 m^2. In contrast, normal overnight fasted humans derived 34±6% of their total CO_2 production from the oxidation of 147±25 μmol FFA/min per 1.73 m^2. On the other hand, values obtained from the normal volunteers fasted 36–72 h were similar to the overnight fasted cirrhotic patients.

These results show that after an overnight fast the caloric requirements of patients with alcoholic cirrhosis are normal, but the nature of fuels oxidized are similar to normal humans undergoing 2–3 d of total starvation. Thus, patients with alcoholic cirrhosis develop the catabolic state of starvation more rapidly than do normal humans. This disturbed but compensated pattern for maintaining fuel homeostasis may be partly responsible for the cachexia observed in some patients with alcoholic cirrhosis.

This study also showed remarkably good agreement between the results obtained with indirect calorimetry and those obtained with ^{14}C tracer analyses.

INTRODUCTION

Alcohol is the most commonly abused drug in America. Its devastating effects after chronic consumption, the most important of which is cirrhosis of the liver, are well recognized. Nonetheless, whereas there are a few studies published on the effects of alcoholism on individual organ systems (1, 2), there are no data available pertaining to the consequences of Laennec's cirrhosis on total body energy requirements and fuel homeostasis.

The human liver has a central role in regulating fuel homeostasis. In normal adults, after an overnight or a several-day fasting period, the liver contributes about one-half of the total body caloric requirements (2). This task is accomplished by the liver releasing

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both glucose and ketone bodies into the blood (2). In patients with alcoholic cirrhosis, however, the total number of caloric equivalents derived from ketone bodies plus glucose added to the bloodstream by their livers that can be terminally oxidized is less than the contributions made by normal livers, after both an overnight and a 3-d fast (2). Furthermore, since there is no renal glucose contribution to the bloodstream, the kidneys do not compensate for the observed deficiency in hepatic fuel delivery (2).

This diminished hepatic fuel delivery in alcoholic patients with cirrhosis may be related to decreased total body energy requirements. On the other hand, total body energy requirements may be normal, and the needs are supplied by heightened delivery of fuels other than glucose and ketone bodies to tissues. The well-recognized elevation of plasma FFA in patients with cirrhosis (3, 4) may reflect augmented mobilization and oxidation of these substrates. In addition, muscle wasting observed in patients with cirrhosis may be due in part to increased amino acid oxidation needed to meet caloric requirements. Data supporting or refuting these possibilities are not available.

The most practical method available for determining the total body caloric (energy) requirements and the quantities of carbohydrate (CHO),[1] protein, and fat oxidized is indirect calorimetry (5). Similar information, with respect to fuel production and utilization, can be obtained independently by ^{14}C-tracer analysis techniques (5).

We simultaneously used the techniques of indirect calorimetry and tracer analyses of [^{14}C]palmitate to measure the nature and quantity of fuels consumed in patients with biopsy-proven alcoholic cirrhosis and compared the results with values obtained from healthy humans.

METHODS

Patients. Nine patients with histories of ethanol abuse (6) and biopsy-proven cirrhosis of the liver were selected from the inpatient and outpatient populations of Temple University Hospital. 15 normal volunteers served as controls. All patients and normal volunteers were admitted either to the General Clinical Research Center of Temple University Hospital or to the Clinical Research Unit of Lankenau Hospital. All patients and volunteers were informed of the nature, purpose, and possible risks involved before obtaining their volunteered and signed consent to participate in this study.

The physical characteristics, hepatic histologies, and diagnoses for the patients and the controls are given in Table I. Individual data are given for the cirrhotic patients and mean±SEM data are given for the normal controls. To compare results, the values were standardized to 1.73 m^2 body surface area when applicable.

Several patients deserve special comments. E.B. and S.T. were cachectic. D.M., E.B., J.H., T.T., and G.D. had been previously hospitalized and treated for massive gastroesophageal variceal hemorrhage secondary to portal hypertension. J.H., T.T., and G.D. underwent surgical portacaval anastomoses 4 yr, 4wk, and 3 yr, respectively, before these studies. D.M. and T.T. had ascites. J.M. is presented separately because he consumed 4/5 of a quart of whiskey ~9 h before the study.

The liver biopsies taken before these studies revealed that most patients had micronodular (Laennec's) cirrhosis, fatty changes, and alcoholic hepatitis. J.H. had inactive, mixed nodular cirrhosis, rare fatty changes and no alcoholic hepatitis. J.M. had central hyaline sclerosis, moderate fatty metamorphoses, and alcoholic hepatitis.

At the time of these studies, none of these alcoholic patients had overt diabetes mellitus, hyperlipidemia, thyroid dysfunction, neoplasm, other chronic disease, or any acute illness. Except for J.M., they were all in stable clinical condition. Except for J.M., all the cirrhotic patients selected from the inpatient population had for several days been consuming mixed diets containing at least 1,800 kcal/d and 2,100 mixed kcal/d for females and males, respectively. The consumption of a diet adequate in caloric content to be anabolic for each cirrhotic patient was assured by direct dietary monitoring for at least 24 h before the overnight fast study. 10 healthy volunteers (nine males and one female) served as overnight fasted controls, and five completely healthy male volunteers as the 36–72-h fasted controls. They consumed mixed diets containing enough calories to maintain stable body weights before the studies were initiated.

Table II shows their clinical laboratory data obtained from peripheral sera on the morning of the studies. Mean±SEM total serum protein was 8.0±0.2 g/dl, being greater than the upper limits of normal in four of nine patients. On the other hand, mean±SEM serum albumin was 3.3±0.2 g/dl, being less than normal in six of nine patients. Mean±SEM total serum bilirubin was 2.8±0.9 mg/dl. Mean±SEM alkaline phosphatase was 190±60 IU/liter. Mean serum glutamic-oxalacetic transaminase activity was only mildly increased, while serum mean lactate dehydrogenase activity, urea nitrogen, and cholesterol concentrations were normal. The cirrhotic patients had slightly depressed hemoglobin and hematocrit values.

All patients with cirrhosis were studied after an overnight fast (10–12 h). Each had indirect calorimetric and [^{14}C]palmitate turnover and oxidation studies done simultaneously. The 10 normal volunteers were also studied after an overnight fast (12 h). Indirect calorimetric studies were done in all 10 control patients, but only four of these volunteers had simultaneous [^{14}C]palmitate studies done with the indirect calorimetric studies. The other five healthy controls, who were studied after a longer period of fasting (36–72 h), had simultaneous indirect calorimetric studies combined with the [^{14}C]palmitate turnover and oxidation studies. Part of the results obtained from these five fasted normal volunteers have been published (7).

Experimental procedure. Before selecting palmitate as a representative FFA for determining turnover and oxidation rates, we established that palmitic acid concentrations expressed as percentage of the total FFA concentrations were the same in cirrhotic patients and in normal controls (Table III).

[1] *Abbreviations used in this paper:* AcAc, acetoacetate; β-OHB, beta-hydroxybutyrate; CHO, carbohydrate; RQ, respiratory quotient.

TABLE I

Physical Characteristics and Diagnoses

Subjects	Sex	Age	Weight	Height	Body surface area	Histology and diagnoses	Concomitant disease	Comment
		yr	*kg*	*cm*	m^2			
Cirrhotic, overnight fast (n = 8)								
E.D.	M	26	73.5	175	1.88	Micronodular cirrhosis, moderate fatty changes, alcoholic hepatitis.	None apparent	—
D.M.	M	40	68.2	168	1.77	Advanced micronodular cirrhosis, moderate fatty changes, alcoholic hepatitis.	None apparent	Mild ascites
R.M.	M	40	64.8	170	1.75	Micronodular cirrhosis with central hyaline sclerosis, alcoholic hepatitis.	None apparent	—
E.B.	M	49	55.6	175	1.67	Advanced micronodular cirrhosis, mild fatty changes, alcoholic hepatitis.	None apparent	Generalized cachexia
J.H.	M	50	85.1	169	1.95	Mixed nodular cirrhosis, rare fatty changes.	Vein stripping 2 wk before; mild hyperglycemia.	Splenorenal shunt 4 yr before
T.T.	M	55	80.9	180	2.00	Advanced micronodular cirrhosis, moderate fatty changes, alcoholic hepatitis.	Mild hyperglycemia	Mesocaval shunt 4 wk before, mild ascites
G.D.	F	40	76.5	162	1.83	Micronodular cirrhosis, mild fatty changes, alcoholic hepatitis.	None apparent	Splenorenal shunt 3 yr before
S.T.	F	48	44.7	161	1.44	Acute micronodular cirrhosis, moderate fatty changes, acute alcoholic hepatitis.	Anxiety	Generalized cachexia
Mean		44	68.7	170	1.79			
±SEM		3	4.8	2	0.06			
J.M.	M	53	79.4	170	1.90	Central hyaline sclerosis, moderate fatty changes, alcoholic hepatitis.	Rosacea	4/5 quart of whisky consumed 9 h before study
Normal, overnight fast (n = 10; 9 M, 1 F)								
Mean		28	72.9	176	1.89			
±SEM		2	2.5	2	0.04			
Normal, 36–72-h fast (n = 5 M)								
Mean		21	75.2	177	1.94			
±SEM		1	5.1	3	0.08			

TABLE II
Clinical Laboratory Data°

	Total protein	Albumin	Bilirubin	Alkaline phosphatase	SGOT	LDH	Creatinine	BUN	Cholesterol	Hgb	Hct
	g/dl		*mg/dl*		*IU/liter*			*mg/dl*		*g/dl*	%
Cirrhotic, overnight fast (n = 8)											
Mean	8.0	3.3	2.8	190	65	208	0.7	11	165	12.4	37.9
±SEM	0.2	0.2	1.0	60	15	14	0.1	2	14	0.3	0.8
J.M.‡	7.0	3.9	0.8	176	134	194	0.7	12	217	13.5	40.8
Normal, overnight fast (n = 10)											
Mean	7.1	4.5	0.7	64	25	185	1.0	15	160	14.7	43.5
±SEM	0.2	0.1	0.1	4	1	16	0.0	1	8	0.5	1.4

° *Abbreviations used in this table:* SGOT, serum glutamic-oxalacetic transaminase; LDH, lactic dehydrogenase; BUN, blood urea nitrogen; Hgb, hemoglobin; Hct, hematocrit.
‡ J.M. was not included in mean values for cirrhotic patients.

Cirrhotic patients and healthy volunteers were studied in air-conditioned rooms equipped with efficient ventilation systems to exhaust exhaled $^{14}CO_2$ and to maintain normal room air content. The subjects rested on beds at least ½ h before and throughout the studies. They were allowed to drink water ad lib. Tobacco smoking was prohibited. The subjects voided urine before and at irregular intervals during the 6-h study period. The urine volume was measured and an aliquot stored at −20°C until analyzed. Catheters were inserted into antecubital veins of each arm. One catheter was used for obtaining blood samples and the other for infusing the isotope.

Tracer preparation. [1-^{14}C]palmitic acid (New England Nuclear, Boston, MA), bound to human serum albumin, was sterilized by passage through a 0.22-μm Swinnex filter unit (Millipore Corp., Bedford, MA), tested for pyrogenicity, and stored at 4°C until used. Immediately before each study, an aliquot of this solution containing 100 μCi of [1-^{14}C]palmitate was diluted with isotonic saline in a 100-ml glass syringe and a sample was removed for radiochemical analysis. At ~8:30 a.m., the subjects voided and base-line blood samples were taken. Then the tracer solution was administered by means of a constant infusion pump. A priming dose of 1.5 ml for 1 min (1,070–1,760 mμCi) was followed by a continuous infusion of 0.15 ml/min (107–176 mμCi/min) for 6 h. Cirrhotic patients received 39.6–65.1 μCi (0.8–1.2 μmol) and normal volunteers received 22.8–74.4 μCi (0.4–1.4 μmol) of [1-^{14}C]palmitate.

Respiratory gas measurements. To determine respiratory exchange of O_2 and CO_2 at 0, 1, 2, 3, 4, 5, and 6 h in cirrhotic patients and at an additional 7 or 8 h in normal volunteers, respiratory gas samples were obtained by an open collecting system previously described in detail (7, 8). Briefly, a plastic hood with a polyethylene curtain was placed over the head of the subject and an air flow through the hood of 50–60 liters/min, accurately measured by a flow meter, was maintained by a pump. At timed intervals (see above), samples of the diluted expired air were collected in Douglas bags and analyzed for O_2 and CO_2 content with a calibrated Noyons diaferometer (Kipp and Zonen, Delft, Holland).

Blood samples and preparations. Immediately after collecting respiratory gas samples, 20–30 ml of blood were drawn without stasis and injected into test tubes containing either no additives or heparin or EDTA and trasylol (500 kallikrein inhibitory units/ml blood). Plasma was obtained by centrifugation at 4°C for 15 min. Part of the plasma was used for determining glucose concentration. Another 6 ml of heparinized plasma were injected into 6 ml of ice-cold perchloric acid, mixed, and again centrifuged at 4°C. The protein-free supernate was rapidly analyzed for acetoacetate (AcAc), pyruvate, and beta-hydroxybutyrate (β-OHB). Plasma FFA were immediately double-extracted from 2 ml EDTA plasma. EDTA plasma for triglycerides and glycerol and serum for insulin were stored at −20°C until analyzed, usually within 1 wk. All analyses were done at least in duplicate.

Analytical technique. 2 ml plasma was repeatedly extracted and washed (9) and the isolated FFA methylated with boron trifluoride and methanol (Supelco Inc., Bellefonte, PA). Then the FFA methyl esters were injected into a gas-liquid chromatograph (Hewlett-Packard Co., Palo Alto, CA, model 5730A), fitted with a hydrogen flame ionization detector and a 6-ft-long coiled glass column packed with 15% (by weight) diethylene glycol succinate on an 80/100 Cromosorb, WA. Flow rate of the carrier nitrogen gas was 20 ml/min. Post-injection temperature was 200°C, detector temperature was 250°C, and oven temperature was 190°C. The plasma composition of these major FFA was computed, nine major individual FFA being used as external standards. The methods used and the analytical precision for determining the concentrations of circulating glucose, AcAc, β-OHB, lactate, pyruvate, glycerol, triglycerides, FFA, ethanol, acetate, insulin, and glucagon have been published (9–14). Urinary nitrogen was analyzed by the standard micro-Kjeldahl technique.

Radioactivity determinations. CO_2 specific activity in expired air was measured according to the method of Fredrickson and Ono (15). Radioactivity in plasma FFA and infusate was determined by a standard technique used in our laboratory (8).

Calculations. The individual FFA were calculated from their areas in percentage by weight of the integral of nine major FFA (Hewlett Packard 7130 recorder and 3380A in-

tegrator). The methods for calculating the respiratory quotient (RQ), nonprotein RQ, caloric expenditure of fat, CHO, and protein, total BMR and nonprotein BMR have been published (16). For convenience, however, we note that the caloric equivalent of protein is 26.4 kcal/g of excreted nitrogen.

The plasma FFA concentrations and specific activities were constant throughout the latter part of the study period in each subject, indicating that steady state conditions were present. Therefore, the FFA turnover rate was calculated by dividing the known infusion rate of the tracer by the average plasma FFA specific activity (7). Methods used in our laboratory to calculate the percentage of respiratory CO_2 derived from FFA oxidation and the rate of FFA oxidation have been published in detail (7).

Caloric expenditure of FFA was calculated by multiplying the caloric equivalent of 2.5 kcal/mmol of FFA (7, 8) with the quantity of FFA oxidized as determined by kinetic tracer analyses (7, 8).

Statistics. Values are expressed as mean±SEM. Statistically significant differences between values were determined with the *t* test for small samples (17) and the analysis of variance for repeated measurements (17).

The relationship between FFA turnover rates and plasma FFA concentrations were evaluated using the simple two-variable linear correlation analysis, and significance was tested by determining the correlation coefficients (*r*) (17).

RESULTS

Plasma FFA composition. Table III shows the nine major FFA found in peripheral venous plasma. Although the mean±SEM plasma FFA concentration was twofold greater in cirrhotic than in normal individuals, the percent composition of the three major FFA, oleic, stearic, and palmitic, as well as myristic, linoleic, linolenic, eicosatrienoic, and arachidonic acids were comparable in both groups after an overnight fast. Only one FFA, palmitoleic acid, was significantly different; it should be noted, however, that plasma palmitoleic acid concentrations in normal humans have varied. Dole et al. (18) and Havel et al. (19) reported that this $C_{16:1}$ FFA represented 2.4 and 4.4% of total FFA, respectively. Thus, despite the doubled total FFA concentration in cirrhotics, eight of the major individual FFA revealed percentage distribution patterns similar to those in normal subjects. This suggested that release and uptake (turnover) of most individual FFA are similar in our cirrhotics and normal subjects. Therefore, our selection of [1-^{14}C]palmitate as a representative FFA for determining total FFA turnover and oxidation rates in normal and cirrhotic patients seems valid.

Peripheral venous substrate and hormone concentrations. Table IV gives the initial basal peripheral venous plasma/serum substrate and hormone concentrations in overnight fasted cirrhotic patients and in overnight fasted and 36–72-h fasted normal volunteers. Plasma FFA concentrations are twofold greater in cirrhotic patients than in normal subjects after an overnight fast (2, 20). The concentrations of plasma FFA, however, were comparable in the overnight fasted cirrhotic patients and the 36–72-h normal volunteers. The base-line concentration of AcAc plus β-OHB was 411±122 μM in cirrhotic and 82±23 μM in normal subjects after the overnight fast (20). AcAc and β-OHB circulating concentrations were not measured in the 36–72-h fasted normal subjects. Data previously published from our laboratories would give AcAc plus β-OHB concentrations of 1,000–2,500 μM in normal humans starving for 36–72 h (10). Thus, overnight fasted cirrhotic patients had ketone-body concentrations that were about fivefold greater than overnight fasted normal subjects, but less than anticipated for 36–72-h fasted normal subjects. Plasma triglyceride,

TABLE III

FFA Composition of Peripheral Venous Plasma in Alcoholic Cirrhotic and Normal Subjects[*]

	$C_{14:0}$ Myristic	$C_{16:0}$ Palmitic	$C_{16:1}$ Palmitoleic	$C_{18:0}$ Stearic	$C_{18:1}$ Oleic	$C_{18:2}$ Linoleic	$C_{18:3}$ Linolenic	$C_{20:3}$ Eicosatrienoic	$C_{20:4}$ Arachidonic	Total FFA
										meq/liter
Cirrhotic, overnight fast (n = 8)										
Mean	1.8	19.8	4.2	11.2	38.7	11.9	0.1	0.2	9.0	880
±SEM	0.6	1.3	0.6	3.7	4.3	0.9	0.1	0.2	1.9	69
Normal, overnight fast (n = 10)										
Mean	1.0	19.4	2.1	13.8	36.1	13.5	0.7	0.6	12.9	410
±SEM	0.2	1.4	0.4	2.2	1.7	1.9	0.4	0.3	3.6	49
Statistical significance	NS	NS	$P < 0.005$	NS	NS	NS	NS	NS	NS	$P < 0.001$

[*] Data are expressed as weight percent, where the sum of nine selected major FFA is 100%.

TABLE IV
Peripheral Venous Substrate and Hormone Concentrations

	FFA	AcAc	β-OHB	Triglycerides	Glucose	Lactate	Pyruvate	Glucagon	Insulin
			μM		mM	μM		pg/ml	μU/ml
Base-line values									
Cirrhotic, overnight fast (n = 8)									
Mean	934	104	307	805	5.12	1,044	69	323	28
±SEM	106	33	90	101	0.45	59	9	80	9
Normal, overnight fast (n = 10)									
Mean	487	20	62	672	4.44	1,301	91	112	12
±SEM	38	6	17	91	0.16	72	5	10	1
Normal, 36–72-h fast (n = 5)									
Mean	905	—	—	—	4.34	—	—	—	—
±SEM	126	—	—	—	0.17	—	—	—	—
Study (6–8 h) values									
Cirrhotic, overnight fast (n = 8)									
E.D.	1,097	74	262	954	4.34	922	58	330	16
D.M.	978	9	71	721	4.34	1300	90	199	22
R.M.	1,178	355	792	1140	4.16	726	58	225	6
E.B.	896	47	106	616	4.26	1016	66	257	6
J.H.	741	75	204	602	5.75	740	98	286	42
T.T.	695	56	142	436	6.82	1024	94	810	54
G.D.	1,105	294	771	809	5.24	858	48	253	66
S.T.	878	294	671	1009	3.93	924	—	250	6
Mean	946	150	377	786	4.86	938	73	326	27
±SEM	62	49	110	84	0.35	65	8	70	8
J.M.	1,093	168	1,122	1,194	4.67	2,425	30	680	28
Normal, overnight fast (n = 10)									
Mean	604	40	133	605	4.30	1,102	—	110	9
±SEM	26	15	34	85	0.13	77	—	8	1
Normal, 36–72-h fast (n = 5)									
Mean	1,217	—	—	—	4.17	—	—	—	—
±SEM	148	—	—	—	0.22	—	—	—	—

glucose, lactate, and pyruvate concentrations in overnight fasted cirrhotic patients were indistinguishable from normal subjects. On the other hand, overnight fasted cirrhotic patients had plasma glucagon and serum insulin concentrations that were both about threefold greater than those observed in overnight fasted normal volunteers. These observations are in agreement with previously published results (2, 21–23).

Table IV also gives the average peripheral venous plasma/serum substrate and hormone values determined from the hourly samples taken over the 6-h (cirrhotics) and 6–8-h (normals) study periods. In the cirrhotic patients after an overnight fast during the 6-h study, plasma FFA concentrations remained constant, whereas plasma AcAc plus β-OHB concentrations increased slightly ($P < 0.05$). The decrease in plasma glucose was not significant. Plasma triglycerides, lactate, pyruvate, glucagon, and serum insulin concentrations remained steady in the cirrhotic patients. In the normal volunteers, there were significant increases in the plasma FFA concentration ($P < 0.05$) and plasma AcAc plus β-OHB concentrations ($P < 0.05$) during the 6–8-h study period of overnight fasted normal subjects.

The plasma FFA concentrations also increased ($P < 0.01$) during the 7–8-h study period of 36–72-h fasted normal individuals.

Indirect calorimetry. Total body energy expenditures in the resting state for overnight fasted cirrhotic patients and for overnight and 36–72-h fasted normal volunteers are shown in Table V.

The O_2 consumption for the overnight fasted cirrhotic patients was 225±13 ml/min per 1.73 m^2, and the CO_2 production was 170±11 ml/min per 1.73 m^2. J.M.'s values were 267 ml/min per 1.73 m^2 and 195 ml/min per 1.73 m^2, respectively. Although his values were greater than the mean values for the cirrhotic patients, they were within the ranges observed for the cirrhotic patients. The respiratory gaseous exchanges of O_2 and CO_2 in the cirrhotic patients were similar to normal volunteers fasted overnight and 36–72 h. Although nitrogen excretion in the cirrhotic patients (6.83±1.35 mg/min per 1.73 m^2) was less than that observed in the normal overnight fasted subjects (8.02±0.70 mg/min per 1.73 m^2) and in the normal 36–72-h fasted volunteers (9.50±1.11 mg/min per 1.73 m^2), the differences were not statistically significant. Nevertheless, when these particular values are collectively used to calculate RQ, nonprotein RQ, and percentage of calories derived from fat and CHO oxidations, differences among the groups emerge. Thus, in the cirrhotic patients, the RQ (0.75±0.01) and the nonprotein RQ (0.74±0.02) were lower ($P < 0.05$) than the RQ (0.82±0.01) and nonprotein RQ (0.85±0.02) observed in normal subjects after an overnight fast. The 36–72-h fasted normal volunteers had RQ (0.76±0.02) and nonprotein RQ (0.75±0.03) values clearly different from those observed in normal overnight fasted subjects ($P < 0.05$), but similar to the values observed in cirrhotic patients.

The total BMR were similar in the overnight fasted cirrhotic patients (1.05±0.06 kcal/min per 1.73 m^2), overnight fasted normal subjects (1.00±0.05 kcal/min per 1.73 m^2), and 36–72-h fasted normal volunteers (1.10±0.06 kcal/min per 1.73 m^2). These results show that overnight fasted cirrhotic patients have normal resting caloric requirement.

The percentages of total BMR derived from all three

TABLE V

Energy Expenditure of Major Fuels and Total Basal Metabolic Rate Determined by Indirect Calorimetry

Subjects	O_2 consumption	CO_2 output	RQ	N_2 excretion	Nonprotein RQ	Nonprotein BMR	Percentage of nonprotein calories Fat	Percentage of nonprotein calories CHO	Total BMR	Percentage of total BMR Fat	Percentage of total BMR CHO	Percentage of total BMR Protein
	ml/min/1.73 m²			*mg/min/ 1.73 m²*		*kcal/min/ 1.73 m²*	%		*kcal/min/ 1.73 m²*	%		
Cirrhotic, overnight fast (n = 8)												
E.D.	245	184	0.75	6.70	0.75	0.97	86	14	1.14	72	12	15
D.M.	227	173	0.76	7.99	0.76	0.85	83	17	1.06	66	14	20
R.M.	297	232	0.78	10.13	0.78	1.13	74	26	1.40	60	21	19
E.B.	172	134	0.78	3.67	0.78	0.72	75	25	0.82	66	22	12
J.H.	216	163	0.76	8.28	0.74	0.79	87	13	1.00	68	10	22
T.T.	197	138	0.70	13.06	0.64	0.92	100	0	0.90	62	0	38
G.D.	230	171	0.74	2.47	0.74	1.02	88	12	1.08	83	11	6
S.T.	218	165	0.76	2.31	0.75	0.97	83	17	1.03	78	16	6
Mean	225	170	0.75	6.83	0.74	0.92	84	16	1.05	69	13	17
±SEM	13	11	0.01	1.35	0.02	0.05	3	3	0.06	3	2	4
J.M.	267	195	0.73	5.62	0.72	1.11	94	6	1.25	84	6	11
Normal, overnight fast (n = 10)												
Mean	207	171	0.82	8.02	0.85	0.78	50	50	1.00	40	39	21
±SEM	9	8	0.01	0.70	0.02	0.05	6	6	0.05	6	4	2
Normal, 36–72-h fast (n = 5)												
Mean	234	179	0.76	9.50	0.75	0.83	84	16	1.10	64	13	23
±SEM	11	9	0.02	1.11	0.03	0.09	10	10	0.06	6	8	4

major fuels are also shown in Table V. The percentages of total calories derived from fat, CHO, and protein in the overnight fasted cirrhotic patients were 69±3, 13±2, and 17±4%, respectively. These values are comparable to those found in the 36–72-h fasted normal subjects (64±6, 13±8, and 23±4%, respectively). However, they are clearly different from overnight fasted normal individuals who derived 40±6, 39±4, and 21±2% from fat, CHO, and protein, respectively.

The nonprotein BMR were similar in overnight fasted cirrhotic patients (0.92±0.05 kcal/min per 1.73 m^2), overnight fasted volunteers (0.78±0.05 kcal/min per 1.73 m^2), and 36–72-h fasted normal volunteers (0.83±0.09 kcal/min per 1.73 m^2). In contrast, there were marked differences among the groups for the percentage of nonprotein calories derived from fat and CHO. Overnight fasted cirrhotic patients derived 84±3 and 16±3% of their nonprotein caloric requirements from fat and CHO, respectively. These values were similar to those observed in the 36–72-h fasted normal subjects of 84±10 and 16±10%, respectively, but are distinctively different from those observed in the overnight fasted normal subjects of 50±6 and 50±6%, respectively.

FFA turnover and oxidation rates. Table VI shows results obtained from kinetic analyses of [1-^{14}C]palmitate tracer studies. These tracer studies display the differences between the overnight fasted cirrhotic patients and the overnight fasted normal subjects, as well as the similarities between the overnight fasted cirrhotic patients and the normal individuals after prolonged fasting. In these three study groups, the concentrations of plasma FFA and specific activity of plasma FFA were constant, and the steady state conditions were used in all individuals to calculate FFA turnover and oxidation rates. In the cirrhotic patients, the steady state plasma FFA concentrations were 948±68 μM and 63±4% of their total CO_2 production was derived from the oxidation of 287±28 μmol FFA/min per 1.73 m^2, which represented 40±4% of their FFA turnover rates (721±59 μmol/min per 1.73 m^2). In contrast, the normal subjects studied after an overnight fast had plasma FFA concentrations of 578±81 μM and derived 34±6% of their total CO_2 production from the oxidation of 147±25 μmol FFA/min per 1.73 m^2, which represented 31±1% of their FFA turnover rate (469±65 μmol/min per 1.73 m^2). On the other hand, the values obtained from the nor-

TABLE VI
FFA Turnover and Oxidation Rates Determined by [1-^{14}C]Palmitic Acid Tracer Techniques

Subjects	FFA	Turnover	CO_2 from FFA	FFA oxidized		FFA oxidized in Percentage of		
						Total BMR	Nonprotein calories	Uptake
	μM	μmol/min/1.73 m^2	%	μmol/min/1.73 m^2	kcal/min/1.73 m^2	%		
Cirrhotic, overnight fast (n = 8)								
E.D.	1,146	835	62	311	0.77	68	79	38
D.M.	1,022	981	56	260	0.64	60	75	26
R.M.	1,132	731	64	396	0.99	71	88	54
E.B.	892	552	42	149	0.35	43	49	25
J.H.	726	764	68	294	0.74	74	94	33
T.T.	626	438	57	206	0.53	58	58	48
G.D.	1,092	760	72	325	0.82	76	81	43
S.T.	947	704	80	353	0.89	87	92	46
Mean	948	721	63	287	0.72	67	77	40
±SEM	68	59	4	28	0.07	5	6	4
J.M.	1,116	949	35	181	0.44	35	40	19
Normal, overnight fast (n = 4)								
Mean	578	469	34	147	0.37	36	42	31
±SEM	81	65	6	25	0.06	6	7	1
Normal, 36–72-h fast (n = 5)								
Mean	1,191	920	66	318	0.79	71	86	34
±SEM	134	96	6	27	0.07	8	9	2

mal volunteers studied after a 36–72-h fast were similar to the overnight fasted cirrhotic patients. Normal 36–72-h fasted volunteers had plasma FFA concentrations of 1,191±134 μM and 66±6% of their total CO_2 production was derived from the oxidation of 318±27 μmol FFA/min per 1.73 m^2, which represented 34±2% of their FFA turnover rates (920±96 μmol/min per 1.73 m^2).

Table VI also shows the calculated energy equivalents derived from the oxidation of FFA in the three groups. The quantity of FFA oxidized in overnight fasted cirrhotic patients was equivalent to 0.72±0.07 kcal/min or 67±5% of total BMR or 77±6% of nonprotein caloric requirements. These FFA values were approximately twice those observed for normal overnight fasted subjects but were comparable to those obtained from normal 36–72-h fasted volunteers.

Indirect calorimetry indicated that J.M. obtained 84% of his total BMR from the oxidation of fat (Table V), but [1-^{14}C]palmitic acid tracer analyses revealed that fat oxidation accounted for only 35% of his total BMR. This discrepancy could be explained by the preferential oxidation of alcohol.

DISCUSSION

Alcoholism, and its secondary disorder of hepatic cirrhosis, is a medical problem with an enormous influence on the health care cost in the United States. For the large patient population with Laennec's cirrhosis (24), the caloric requirements and fuel homeostatic mechanisms have previously remained unstudied. We determined the BMR and the caloric contributions of carbohydrate, fat, and protein to these requirements in alcoholic patients with biopsy-proven hepatic cirrhosis and compared their results with normal controls. The study showed that after an overnight fast the BMR of patients with alcoholic cirrhosis were normal, but the nature of the fuels oxidized were similar to those consumed in normal humans undergoing 2–3 d of total starvation.

Isselbacher (25) reviewed the indirect evidence suggesting that chronic alcohol ingestion is associated with a hypermetabolic state resembling the hyperthyroid state. Others have reported that chronic alcoholic patients have augmented energy requirements in response to acute ethanol consumption (25, 26). Chronic treatment with alcohol increased O_2 consumption in rat liver slices (25). These observations, however, do not necessarily imply that chronic alcoholic patients have increased total body energy requirements. Many chronic alcoholic patients are malnourished, and severe malnutrition is the classical situation that reduces metabolic requirements of the body to 60–70% of normal values (27). It is also possible that cirrhosis may selectively increase hepatic O_2 consumption independent of acute ethanol catabolism. This effect may be mediated through hepatic gluconeogenesis. After an overnight fast, the normal liver contributes about 0.86 mmol/min per 1.73 m^2 of glucose to the blood stream (28). About 80% of this glucose is derived from glycogenolysis and ~20% from gluconeogenesis (28). In patients with alcoholic cirrhosis, the liver contributes ~0.53 mmol/min per 1.73 m^2. About 33% of this is derived from glycogenolysis and ~67% from gluconeogenesis (2). Thus, although the total quantity of glucose delivered to the blood after an overnight fast is diminished, gluconeogenesis is increased twofold in patients with hepatic cirrhosis (2). Gluconeogenesis, unlike glycogenolysis, is an energy-requiring process (29). Although others have attributed the augmented hepatic O_2 requirement observed in chronic ethanol-fed rats to increased hepatic mitochondrial sodium-potassium-ATPase activity (25, 30) or to energy-wasting metabolic pathways, such as microsomal ethanol oxidizing system in the hepatic endoplasmic reticulum (31), it is reasonable to believe that part of the increased hepatic O_2 requirement in the alcoholic patient during sobriety is due to increased hepatic gluconeogenesis. This hypothesis is in agreement with the increase in hepatic ketogenesis (2), an O_2-consuming process (29) known to occur after an overnight fast in patients with hepatic cirrhosis (2). The net effect on total BMR of diminished O_2 consumption by peripheral tissue coupled with increased O_2 consumption by hepatic tissue may be minimal.

Our studies using indirect calorimetry showed no net effect of chronic alcoholism on total body energy requirements. Their BMR value was indistinguishable from the values obtained in normal humans after an overnight or 36–72-h fast (Table V).

The quantities of fat, CHO, and protein oxidized to meet the metabolic requirements in overnight fasted cirrhotic patients are unique for this brief starvation period (Table V). Specifically, the temporal relationships between duration of fasting and amounts of CHO and fat oxidized were markedly different. Cirrhotic patients fasted 10–12 h (overnight) have a metabolic profile that resembles normal humans fasted for 36–72 h in which fat furnishes the overwhelming majority of fuels oxidized. The time needed to develop the catabolic state of starvation is much shorter in patients with alcoholic cirrhosis than normal humans. This may be related to the diminished stores of glycogen in cirrhotic livers (2), resulting in its rapid depletion and a hastened catabolic state.

Although the energy yielded from protein oxidation was equal among the three groups (Table V), it should be recognized that some of the cirrhotic patients were cachectic (Table I). After prolonged starvation, when

lean body mass (predominantly muscle) is depleted, urinary nitrogen excretion is less than one-half of that observed in these cirrhotic patients after an overnight fast (32). Persistent mobilization of amino acids from lean tissues to aid in the maintenance of glucose or fuel homeostasis has profound effects on nitrogen stores. This results in extensive muscle wasting, and could be partly responsible for the frequently observed wasted muscle mass in alcoholic patients with hepatic cirrhosis and augmented gluconeogenesis.

The results obtained from indirect calorimetry are complimented by those obtained with the [1-^{14}C]palmitate turnover and oxidation studies (Table VI). In overnight fasted cirrhotics, FFA were oxidized at a rate that contributed 0.72±0.07 kcal/min per 1.73 m^2. This equates to 67±5% of total BMR or 77±6% of the nonprotein caloric requirements.

Elevated plasma FFA concentrations in patients with cirrhosis have been repeatedly documented (2–4). This could be due to enhanced mobilization of FFA from adipose tissue or decreased FFA oxidation by other tissues. Carnitine plays an essential role in FFA catabolism, because FFA must be converted into fatty acid acylcarnitine esters for translocation across the mitochondrial membranes before they can undergo β-oxidation (33). Rudman et al. (33) have reported carnitine deficiency in cachetic patients with cirrhosis. We did not measure carnitine in our patients, but we did confirm the observation that basal plasma FFA concentrations (934±106 μM) are elevated in cirrhotic patients after an overnight fast (Table IV). This increase in plasma FFA concentration was accompanied by heightened FFA turnover and oxidation rates (Table VI). Furthermore, there was a direct relationship between plasma FFA concentrations and turnover rates (Fig. 1). Our results from these tracer analyses studies reveal that increased lipolysis is the primary cause for elevated plasma FFA concentrations in cirrhotic patients. They also reveal that augmented lipolysis and FFA oxidation are the primary mechanism for maintaining fuel homeostasis when glucose delivery from cirrhotic livers is abnormally low (2).

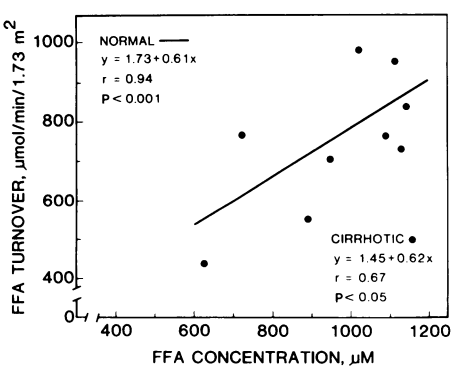

FIGURE 1 Relationships between FFA concentrations and FFA turnover rates. The solid line represents results obtained from normal humans undergoing various durations of starvation, and the individual dots represent the nine overnight fasted cirrhotic patients. The equation for the line was derived by the method of least squares (17).

Previous catherization studies revealed that after an overnight fast the livers from cirrhotic patients contribute 0.53±0.09 mmol/min per 1.73 m^2 of glucose to blood (2). After correcting for recycled lactate and pyruvate (2) and for gluconeogenesis from amino acids (2), only 0.22±0.06 mmol/min per 1.73 m^2 (39±11 mg) is added to the blood for terminal oxidation. This quantity of glucose is equivalent to 0.16±0.05 kcal/min per 1.73 m^2 and is in agreement with the value of 0.13±0.02 kcal/min per 1.73 m^2 obtained from indirect calorimetry (Table V).

Indirect calorimetry is rapidly being revitalized as a clinical investigational tool to determine the nature and quantity of fuels oxidized in a variety of states. Nonetheless, the validity of the results obtained with indirect calorimetry have never been confirmed. In Fig. 2, we integrated the results obtained from our previous catheterization study with our present tracer analyses and indirect calorimetry study in overnight fasted patients with Laennec's cirrhosis. Patients T.T. and G.D. in this study were also among the patients previously investigated by catheterization (2). These widely diverse techniques complement each other and show remarkable agreement for the nature of fuels produced and oxidized. Indirect calorimetry showed that these patients have normal overnight fasting BMR. In the absence of acute ethanol intake, fat oxidation furnished about two-thirds and CHO and protein each furnished about one-sixth of the total BMR. Tracer analyses of [1-^{14}C]palmitate also showed that fat oxidation contributed about two-thirds of the energy requirements. Catheterization results, corrected for recycled lactate and pyruvate and for glucose derived

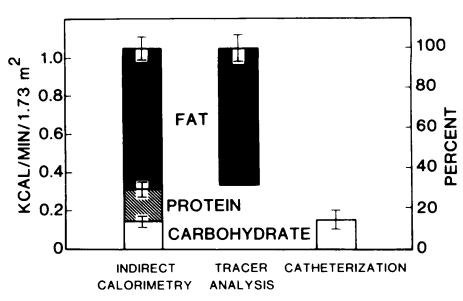

FIGURE 2 Comparison and integration of results obtained in this study by indirect calorimetry and tracer analyses and those in a previous study (2) by catheterization.

from amino acids, likewise showed that glucose delivered about one-sixth of the total BMR. It is now more evident that indirect calorimetry truly reflects the nature and quantity of fuels oxidized during resting and fasting states.

In addition to the chronic effects of hepatic cirrhosis on total body energy requirement, alcoholic patients may have a slightly greater thermic response (O_2 consumption) to oral ethanol than do nonalcoholic humans (26). One of our alcoholic patients (J.M.) had a moderate quantity of ethanol in his blood. While the ethanol was being catabolized, his total BMR was 1.25 kcal/min per 1.73 m^2. This value is within the range observed for overnight fasted patients with cirrhosis. Unlike the other patients, however, there was disagreement between the values obtained from fat oxidation determined by indirect calorimetry (84% of total BMR; Table V) and tracer analysis (35% of total BMR; Table VI) in patient J.M. This discrepancy could have been due to oxidation of ethanol, which has an RQ similar to that of fat.

From the data presented here and published elsewhere, the adaptations for maintenance of fuel homeostasis in patients with hepatic cirrhosis can at least be partially elucidated. The causes for the hyperglycemia, hyperinsulinemia, and hyperglucagonemia in patients with hepatic cirrhosis are multifactorial. Furthermore, differences exist in the fasting and fed states. Diminished peripheral glucose oxidation occurs in cirrhotic patients after an overnight fast. This is interrelated with increased FFA oxidation. In contrast, peripheral glucose uptake following a carbohydrate challenge is normal (34); the glucose intolerance after a glucose load is primarily due to the limited capacity of a fibrotic liver to remove and store glucose as glycogen (2). The resulting hyperglycemia promotes hyperinsulinemia (3, 4, 34–36). Chronic hyperinsulinemia induces a generalized decrease to the metabolic influences of insulin. The mechanism responsible for the observed insulin resistance is controversial (36–38). It could be due to down-regulation of insulin receptors or to postreceptor events (36–38). Nonetheless, insulin resistance is present in patients with cirrhosis, and this permits augmented gluconeogenesis, ketogenesis (2), and lipolysis during the postabsorptive period. Although there is no evidence for glucagon down-regulation (37–39), and the hyperglucagonemia accompanying cirrhosis may be needed to facilitate the mobilization of nutrients during fasting (40), it should be recognized that the elevated concentrations of immunoreactive glucagon observed in cirrhotic patients are due to three or four different molecular forms of glucagonlike materials (41). Therefore, it is difficult to be certain about the actual increase in circulating 3,500-D glucagon and the actual biological effects of hyperglucagonemia in cirrhotic patients. Other hormones, i.e., growth hormone (34, 36, 42) or catecholamines (43), may also influence the fuel mixture oxidized in patients with cirrhosis.

In summary, these studies show the unique nature and quantity of fuels oxidized by patients with biopsy-proven alcoholic cirrhosis. Their metabolic profiles are similar to those found in normal humans after 2–3 d of starvation. This abnormal but compensated pattern of metabolism reflects diminished hepatic glucose release secondary to decreased hepatic glycogen stores, and resembles the metabolic pattern associated with prolonged starvation. It may be partly responsible for the cachexia, particularly the muscle wasting, observed in these patients.

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