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Blood Ketone Bodies in Congestive Heart Failure

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Objectives. **The present study was designed to assess whether blood ketone bodies are elevated in congestive heart failure (CHF) and whether ketonemia is related to the hemodynamic and neurohumoral abnormalities of CHF.**

Background. **In CHF, consumption of the body's fat stores may become abnormally high, contributing to the development of cardiac cachexia. Increased mobilization of free fatty acids could, in theory, augment ketogenesis, but whether patients with CHF are prone to ketosis remains unknown.**

Methods. **Forty-five patients with chronic CHF (mean age [±SD] 57 ± 13 years) and 14 control subjects free of CHF (mean age 53 ± 13 years) underwent invasive and noninvasive cardiac studies and determination of blood ketone bodies (acetoacetate plus beta-hydroxybutyrate), circulating free fatty acids, glucose, lactate, insulin, glucagon, growth hormone, cortisol, norepinephrine, N-terminal proatrial natriuretic peptide, tumor necrosis factor-alpha and interleukin-6 after an overnight fast.**

Results. **Patients with CHF had elevated blood ketone bodies (median 267 μmol/liter, range 44 to 952) compared with control subjects (median 150 μmol/liter, range 31 to 299, $p < 0.05$). In the total study group, blood ketone bodies were related to pulmonary artery wedge pressure ($r_s = 0.45$, $p < 0.001$), left ventricular ejection fraction ($r_s = -0.37$, $p < 0.01$), right atrial pressure ($r_s = 0.36$, $p < 0.01$) and circulating concentrations of free fatty acids ($r_s = 0.52$, $p < 0.001$), glucose ($r_s = -0.39$, $p < 0.01$), norepinephrine ($r_s = 0.45$, $p < 0.001$), growth hormone ($r_s = 0.30$, $p < 0.05$) and interleukin-6 ($r_s = 0.27$, $p < 0.05$). In multivariate analysis, left ventricular ejection fraction, serum free fatty acids and serum glucose were independent predictors of ketonemia.**

Conclusions. **Blood ketone bodies are elevated in CHF in proportion to the severity of cardiac dysfunction and neurohormonal activation. This may be at least partly attributable to increased free fatty acid mobilization in response to augmented neurohormonal stimulation. Additional studies are needed to identify the detailed mechanisms and clinical implications of CHF ketosis.**

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Congestive heart failure (CHF) is a clinical syndrome that results from systolic or diastolic cardiac pump dysfunction and is accompanied by a number of neurohumoral and metabolic alterations in the body (1,2). In chronic CHF, wasting of subcutaneous fat and skeletal muscle is relatively common and suggests augmented consumption of noncarbohydrate substrates for energy production (1,3). Regarding the mechanisms leading to loss of the body's fat stores, elevated concentrations of stress hormones, including norepinephrine (4,5), may play a role by enhancing lipolysis, and increased basal metabolism (6) with insufficient food intake or absorption (1,7,8) may also contribute. It has also been shown recently that fat oxidation during exercise is increased in patients with CHF compared with healthy persons (9). These changes in lipid metabolism could boost hepatic ketone body production, and we have recently shown that fasting breath acetone concentrations are often elevated in patients with CHF (10). This study was designed to assess whether blood ketone bodies are elevated after an overnight fast in patients with clinical CHF and whether the degree of ketonemia depends on the hemodynamic abnormalities or the prevailing neurohumoral milieu, including circulating stress hormone and cytokine concentrations.

Methods

Patients. The study included 59 patients with cardiac disease admitted to Helsinki University Central Hospital between January and October 1994 for treatment or diagnostic evaluation. Of the patients, 45 (28 men; mean age [±SD] 57 ± 13 years) had definite clinical CHF and 14 (9 men; mean age 53 ± 13 years), constituting the control group, were free of CHF. The diagnosis of CHF required that the patient had a cardiovascular disease and at least three of the following four signs: 1) dyspnea or fatigue on ordinary effort; 2) audible third heart sound or heart rate >90 beats/min at rest; 3) enlarged heart volume per body area on chest radiograph (>500 ml/m^2 in women, >550 ml/m^2 in men) (11); or 4) pulmonary venous congestion on chest radiograph or abnormal neck vein disten-

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tion. Patients with diabetes or other endocrine, chronic infectious, hepatic, renal, gastrointestinal or connective tissue diseases or malignancy were excluded. Acute infectious or inflammatory diseases and recent myocardial infarction also led to exclusion, as did the use of drugs with a possible influence on the synthesis or metabolism of the ketone bodies (beta-adrenergic blocking agents, corticosteroids). Eventually, the most common reasons for exclusion were diabetes, recent myocardial infarction and use of beta-blockers.

In the CHF group, the underlying condition was valvular heart disease in 15 patients, coronary artery disease in 10, idiopathic dilated cardiomyopathy in 10, embolic or primary pulmonary hypertension in 6, constrictive pericarditis in 2 and congenital heart disease in 2. Twenty-eight patients were in sinus rhythm, 11 had chronic atrial fibrillation and 6 had pacemaker rhythm for most of the time. Functionally, 8 patients were in New York Heart Association functional class IV, 21 were in class III and 16 in class II. Forty-one patients were using furosemide (mean daily dose 135 mg, range 40 to 500), which was combined with spironolactone in 12 patients and metolazone in 4 patients. Three patients were taking hydrochlorothiazide. Thirty-six patients were taking digoxin, 26 were using angiotensin-converting enzyme inhibitors and 11 were using long-acting nitrates.

In the control group, eight patients had valvular disease (six aortic, two mitral), four had congenital heart disease (all septal defects; two atrial, two ventricular) and two had coronary artery disease. They underwent cardiac catheterization either for assessment of the hemodynamic significance of their structural heart disease or for preoperative evaluation. Twelve of them were in sinus rhythm and two had chronic atrial fibrillation. Functionally, eight control patients were in functional class II and six were in class I. None fulfilled our definition of CHF (presence of three or four of the four clinical signs specified previously), but two signs were identified in four patients and one sign in five patients. Two patients were taking angiotensin-converting enzyme inhibitors and diuretics; digoxin and nitrates were used by three patients each.

Study design. All studies were performed while the patients were in the hospital for treatment or examinations. Eligible patients with CHF who had been admitted for worsening congestion were studied after removal of fluid retention and restoration of earlier symptomatic status. Throughout their hospital stay, the patients were on a nonreducing hospital diet with an average total energy content of 2,030 kcal/day and with a minimum of 200 g/day of carbohydrates. The patients underwent clinical examination and echocardiography followed, within 1 to 2 days, by indirect calorimetry and blood sampling after a 12-h fast for the determination of circulating energy substrates, metabolites, hormones and cytokines. Cardiac catheterization was performed within 2 days after the blood tests. The patients continued their regular medication during the examinations. The study protocol was approved by the Institutional Ethics Committee. The nature and potential risks of the study were explained in detail to each patient before asking for their consent to participate.

Clinical examination. The patients were examined clinically, paying special attention to the history of exercise intolerance and to the signs of CHF specified in the diagnostic criteria (see previous discussion). The neck veins were studied by estimating the supraclavicular height of the blood column in the right internal jugular vein with the patient breathing quietly in the sitting position. Any venous bulging above the clavicle was considered abnormal. Brachial artery blood pressure was measured by the sphygmomanometric cuff method. Posteroanterior and lateral chest radiographs were obtained and the heart volume per body area was calculated (11). All participants, except one man with functional class IV symptoms, underwent a standardized 6-min walking test (12) supervised by one of the investigators (J.L.). Body height and weight were measured and body mass index was determined as weight (kg) divided by the square of height (m). The triceps, infracapular and suprailiac skinfold thicknesses were measured by a caliper, and the percent body fat was calculated using standard tables (13). Lean body mass was derived as body weight minus calculated fat mass.

Determination of circulating substrates, metabolites, hormones and cytokines. After a 12-h overnight fast (from 8 PM to 8 AM), while the patients were still in supine rest, blood was sampled from an antecubital vein cannulated 30 min in advance for the determination of glucose, free fatty acids, beta-hydroxybutyrate, acetoacetate, lactate, insulin, proinsulin C-peptide, glucagon, cortisol, growth hormone, norepinephrine, epinephrine, N-terminal proatrial natriuretic peptide (pro-ANP), tumor necrosis factor-alpha (TNF-alpha) soluble TNF-alpha receptor II and interleukin-6. The blood samples for ketone bodies, lactate, norepinephrine and epinephrine were frozen immediately and stored at −70°C until the assays. Other blood samples were collected on ice and centrifuged at 4°C; the serum was stored at −20°C until the determinations.

Blood acetoacetate, beta-hydroxybutyrate and lactate were determined in perchloric acid extracts by a Transcon 102 FN fluoronephelometer (Elomit, Transcon Instruments Ltd., Helsinki, Finland) using nicotinamide adenine dinucleotide–linked enzymatic methods (14,15). Acetoacetate and beta-hydroxybutyrate were summed to give the concentration of blood ketone bodies, which was used as an index of ketonemia in all analyses. Serum free fatty acids were measured by the microfluorometric technique described by Miles et al. (16). Plasma glucose was measured enzymatically using an Eppendorf EPOS 5060 analyzer (Eppendorf, Hamburg, Germany), and serum insulin was measured using a double-antibody radioimmunoassay kit (Pharmacia, Uppsala, Sweden); the interassay coefficient of variation for insulin was 8.0% at the concentration of 20 mU/liter. Serum proinsulin C-peptide was determined using a competitive radioimmunologic kit (Byk-Sangtec Diagnostica, Dietzenbach, Germany) with a coefficient of variation of 10.0% at the concentration of 0.11 nmol/liter and 4.5% at 1.8 nmol/liter. Serum glucagon was measured using a double-antibody radioimmunoassay kit (Diagnostic Products Corporation) from blood samples containing 1 mg of aprotinin; the interassay coefficient of variation was 15.7% at

the concentration of 10.6 pmol/liter and 57% at 153 pmol/liter. Serum growth hormone was measured using an immunoradiometric assay (CIS Bio International, Paris, France), with a coefficient of variation of 4.2% at the concentration of 3.3 μg/liter and 4.4% at 16.4 μg/liter. Serum cortisol was determined by a radioimmunoassay kit (Orion Diagnostica, Espoo, Finland), with a coefficient of variation of 5.2% at the concentration of 31.2 nmol/liter and 4.3% at 542 nmol/liter. Plasma norepinephrine was determined by high performance liquid chromatography with electrochemical detection after alumina adsorption and elution with 2% acetic acid (17); the interassay coefficient of variation was 5.6% at 2.01 nmol/liter. Plasma pro-ANP was determined using a radioimmunoassay kit (Biotop, Oulu and Medix Biochemica, Kauniainen, Finland), with an interassay coefficient <10%. Plasma TNF-alpha, soluble TNF-alpha receptor II and interleukin-6 were measured using quantitative enzyme immunoassay kits (Medgenix, Medgenix Diagnostics SA, Fleurus, Belgium; and Quantikine, Research and Diagnostic Systems). The detection limits for TNF-alpha, soluble TNF-alpha receptor II and interleukin-6 were 3, 5 and 0.7 ng/liter, respectively. All determinations were made in duplicate.

Indirect calorimetry. Indirect calorimetry was performed after a 12-h overnight fast with the patients in supine rest (18). Oxygen consumption and carbon dioxide production were measured over a minimum of 30 min using a computerized open-circuit system through a transparent plastic canopy (Deltatrac, Datex, Helsinki, Finland). Flow was measured by the air-dilution method, carbon dioxide concentration by an infrared detector and oxygen concentration by a fast differential paramagnetic oxygen sensor. No exact standardization of environmental temperature and humidity could be accomplished, but the patient-to-patient variation in environmental conditions was random across the study groups. The rates of basal metabolism and lipid oxidation were calculated according to validated formulas after estimating protein oxidation from concomitant urea nitrogen excretion in the urine (18).

Echocardiography. The ultrasound studies (pulsed and color Doppler) were obtained using a Toshiba SSH 140A echocardiograph equipped with a 2.5-MHz transducer for imaging. Left ventricular ejection fraction was determined by the two-dimensional area-length method (19) from an apical two- or four-chamber view using the cine loop memory and the built-in software of the equipment. The presence and severity of tricuspid regurgitation were assessed with color Doppler ultrasound. Several apical and parasternal views of the heart were examined, and the maximal regurgitant jet area in the right atrium was measured with a planimeter using the internal software of the echocardiograph. Both left ventricular ejection fraction and the jet area of tricuspid regurgitation were averaged over three determinations.

Cardiac catheterization. All patients underwent pulmonary artery cannulation with a balloon-tipped, flow-directed, 7F Swan-Ganz catheter introduced under fluoroscopy through the femoral, internal jugular or antecubital vein. Pressure waveforms were recorded in the right atrium, pulmonary artery trunk and pulmonary artery wedge positions using a Statham P23 transducer with the zero reference level set at the midaxillary line. Mean pressures were electronically integrated. Cardiac output was determined by the Fick principle; the Deltatrac monitor was used to measure oxygen consumption simultaneously with blood sampling for oxygen content in the pulmonary and femoral arteries. If clinically indicated, left heart catheterization with selective coronary angiography was performed thereafter.

Table 1. Anthropometric Measurements in Patients With Congestive Heart Failure and in Control Patients*

Measurement	Patients With CHF (n = 45) (mean ± SD)	Control Patients (n = 14) (mean ± SD)
Body height (cm)	169.5 ± 9.7	171.1 ± 12.0
Body weight (kg)	74.6 ± 16.5	79.1 ± 16.8
Body mass index (kg/m^2)	25.9 ± 4.9	27.0 ± 4.9
Lean body mass (kg)	52.6 ± 11.3	55.3 ± 13.3
Body fat mass (kg)	22.0 ± 8.7	23.7 ± 8.0
Body fat (%)	29.0 ± 7.8	30.1 ± 8.2

*Group differences were not statistically significant. CHF = congestive heart failure.

Statistical methods. The Kolmogorov-Smirnov one-sample test was used to assess the normality of data distribution. The concentrations of blood ketone bodies, free fatty acids, cytokines and most hormones were skewed toward high values. All differences between the CHF and control groups were then analyzed by the Mann-Whitney *U* test. Associations of blood ketone bodies with the clinical, hemodynamic and echocardiographic variables, and with the laboratory data, were analyzed by calculating the Spearman (distribution-free) rank correlation coefficients (r_s) or, after logarithmic data transformation, the Pearson product-moment coefficients. Statistically significant univariate correlates of blood ketone bodies were subjected to a stepwise, multiple linear regression analysis to identify the independent predictors of ketonemia. Ketone body concentration and the explanatory variables showing skewed data distribution were log transformed before regression analysis; $p < 0.05$ was considered statistically significant. The data are summarized as mean ± SD or as median and range. All analyses were made using a commercially available statistical package for microcomputers (Systat 5.03 for Windows, SYSTAT Inc.).

Results

Anthropometric and cardiovascular measurements and indirect calorimetry. On average, patients with CHF weighed somewhat less and had a slightly smaller body mass index and fat percentage than the control subjects, even though the differences were not statistically significant (Table 1). Men had a higher body weight and height and a higher lean body mass, but lower fat percentage, than women (data not shown);

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Table 2. Noninvasive and Invasive Characteristics of Cardiac and Circulatory Function in the Study Groups With and Without Congestive Heart Failure

Characteristic	Patients With CHF (n = 45) (mean ± SD)	Control Patients (n = 14) (mean ± SD)
Noninvasive data		
HR (beats/min)	84 ± 18*	67 ± 10
BA SBP (mm Hg)	115 ± 25†	135 ± 23
BA DBP (mm Hg)	73 ± 11	75 ± 8
LVEF‡	0.39 ± 0.21§	0.54 ± 0.12
Heart volume/body area, (ml/m^2)‖	839 ± 273*	505 ± 105
6-min walking distance (m)	309 ± 139*	464 ± 131
Invasive data		
CI (liters/min per m^2)	2.4 ± 0.6	2.5 ± 0.4
PAWP (mm Hg)	21 ± 9*	9 ± 3
PAP (mm Hg)	36 ± 13*	16 ± 4
RAP (mm Hg)	10 ± 6†	5 ± 3

*$p < 0.001$, †$p < 0.01$, §$p < 0.05$ versus control group. ‡Determined by two-dimensional echocardiography. ‖Measured from chest radiographs. BA = brachial artery; DBP = diastolic blood pressure; CHF = congestive heart failure; CI = cardiac index; HR = heart rate; LVEF = left ventricular ejection fraction; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; RAP = right atrial pressure; SBP = systolic blood pressure.

however, the proportion of male patients was similar in the CHF and control groups (62% and 64%, respectively).

Table 2 shows that patients with CHF had an increased mean rest heart rate, a decreased left ventricular ejection fraction, a shortened 6-min walking distance and elevated cardiac filling pressures compared with the control group. The overlap of the hemodynamic measurements was not negligible, however. Because of the heterogeneity of the underlying diseases, some patients with CHF had fully normal or even high left ventricular ejection fractions, whereas three control patients (two with valvular regurgitation and one with coronary artery disease) had an abnormally low ejection fraction despite the absence of definite clinical CHF (Fig. 1). Furthermore, as Figure 1 shows, even after exclusion of patients with precapillary pulmonary hypertension, a few patients with CHF had a normal pulmonary wedge pressure, although an elevated value was observed in one control patient with mitral valve disease.

Reliable evaluation of tricuspid regurgitation was possible in 48 patients. In the CHF group (n = 36), 6 patients had no regurgitation, 5 had jet areas <4 cm^2, 13 had jet areas between 4 and 10 cm^2 and 12 had jet areas >10 cm^2. In the control group (n = 12), 9 patients had no regurgitation, 2 had jet areas <4 cm^2 and 1 patient had a jet area >10 cm^2.

The basal metabolic rate could be determined in 38 patients with CHF and in 11 control subjects. Expressed per kilogram of lean body mass, basal metabolism averaged 77.9 ± 12.6 J·kg^{-1}·min^{-1} in the CHF group versus 75.7 ± 14.1 J·kg^{-1}·min^{-1} in the control group (p = NS). The rate of lipid oxidation averaged 49.1 ± 22.3 J·kg^{-1}·min^{-1} in patients with CHF and 42.1 ± 13.7 J·kg^{-1}·min^{-1} in the control subjects (p = NS).

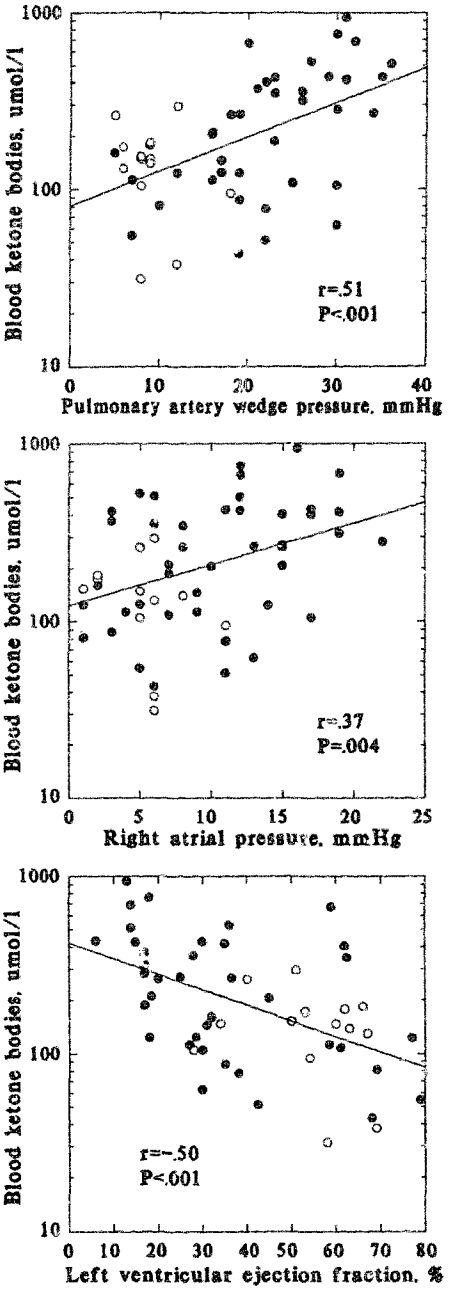

Figure 1. Relation of blood ketone bodies to pulmonary artery wedge pressure, right atrial pressure and left ventricular ejection fraction. **Solid** and **open circles** represent heart failure patients and control patients, respectively. Note that the scale of the **y axis** is logarithmic. The **regression lines** represent the least squares fits and the correlation coefficients are Pearson's. Six patients with pure right-sided heart failure (precapillary pulmonary hypertension) were omitted from plots of ketone bodies against pulmonary artery wedge pressure and left ventricular ejection fraction. When these patients were included, the correlation of log ketone bodies with pulmonary wedge pressure decreased to 0.44 (p = 0.001) and with ejection fraction to −0.35 (p = 0.007).

Table 3. Circulating Concentrations of Substrates, Metabolites, Hormones and Cytokines in the Study Groups With and Without Congestive Heart Failure

Variable	Patients With CHF (n = 45)	Control Patients (n = 14)
B-ketone bodies (μmol/liter)*	267 (44–952)†	150 (31–299)
B-lactate (mmol/liter)	0.74 ± 0.23	0.66 ± 0.18
P-glucose (mmol/liter)	5.2 ± 0.7	5.5 ± 0.3
S-free fatty acids (μmol/liter)	603 ± 284‡	469 ± 143
S-insulin (mU/liter)	6.1 (2.3–53)	6.7 (3.2–21)
S-glucagon (pmol/liter)	37.3 ± 5.7	34.5 ± 4.6
S-glucagon/insulin ratio (pmol/mU)	6.1 ± 3.2	5.7 ± 2.7
S-C-peptide (nmol/liter)	1.1 (0.27–4.8)†	0.72 (0.25–1.7)
S-growth hormone (μg/liter)	2.0 (0.1–15)‡	0.35 (0.1–2)
S-cortisol (nmol/liter)	462 ± 121‡	326 ± 84
P-norepinephrine (nmol/liter)§	1.9 (0.9–9.5)‡	1.2 (0.4–2.8)
P-epinephrine (nmol/liter)‖	0.31 (0.13–0.54)	0.23 (0.09–0.50)
P-pro-ANP (nmol/liter)	1.46 (0.12–4.43)¶	0.44 (0.14–2.75)
P-TNF-alpha (ng/liter)#	19 (0.8–68)	14 (5–63)
P-TNF-alpha receptor II (ng/liter)**	1890 (1,010–5,225)¶	1336 (878–1,596)
P-interleukin-6 (ng/liter)**	5.3 (0.2–39)	2.7 (0.3–41)

*Acetoacetate plus beta-hydroxybutyrate. †$p < 0.05$, ‡$p < 0.001$, ¶$p < 0.01$, versus control group. §n = 45 (34 + 11). ‖n = 37 (29 + 8). #n = 48 (37 + 11). **n = 54 (40 + 14). Data are mean ± SD or median (range). ANP = atrial natriuretic peptide; B = blood; CHF = congestive heart failure; P = plasma; S = serum; TNF = tumor necrosis factor.

Substrates, metabolites, hormones and cytokines. Table 3 compares the laboratory data between the two study groups. Blood ketone bodies were elevated in patients with CHF (Fig. 2), as were serum free fatty acids and C-peptide, but there were no statistically significant differences in the concentrations of glucose, lactate, insulin or glucagon or in the glucagon-to-insulin ratio. The stress hormones (cortisol, growth hormone and norepinephrine) and pro-ANP were also clearly higher in the patients with CHF than in the control group. The patients with CHF, likewise, had elevated concentrations of soluble TNF-alpha receptor II in the circulation, but the trends toward higher TNF-alpha and interleukin-6 were not statistically significant.

Figure 2. Blood ketone body concentration (acetoacetate plus beta-hydroxybutyrate) in 45 patients with congestive heart failure (CHF) and in 14 control subjects.

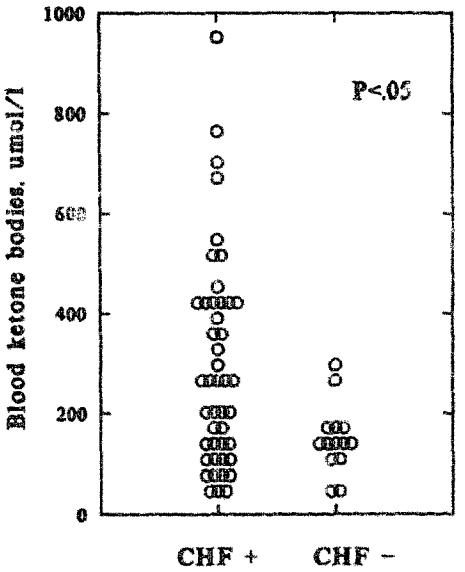

Table 4. Correlation of Blood Ketone Body Concentration With Cardiovascular Variables in the Total Study Group and in the Congestive Heart Failure Group

Variable	All Patients (n = 59) (r_s)	CHF Group (n = 45) (r_s)
NYHA functional class	0.35*	0.22
6-minute walking distance	−0.19	0.03
LVEF	−0.37†‡	−0.36*
PAWP	0.45§‖	0.45†
Mean PAP	0.46§	0.37*
Mean RAP	0.36†	0.34*
CI	−0.01	0.01
Tricuspid regurgitant jet area (n = 48)	0.38†	0.27

*$p < 0.05$, †$p < 0.01$, §$p < 0.001$. ‡Spearman rank correlation coefficient (r_s) was −0.51 ($p < 0.001$) when the six patients with precapillary pulmonary hypertension were excluded from the analysis. ‖Spearman rank correlation coefficient (r_s) was 0.56 ($p < 0.001$) when patients with precapillary pulmonary hypertension were excluded. NYHA = New York Heart Association; other abbreviations as in Tables 1 and 2.

Correlates of blood ketone body concentration. The concentration of ketone bodies was independent of age, gender, body weight, body mass index and lean body mass in the total study group, but correlated inversely with the calculated body fat mass ($r_s = -0.27$, $p < 0.05$). Correlations of ketone bodies with the rates of basal metabolism and lipid oxidation were not statistically significant.

The associations of blood ketone bodies with the cardiovascular and laboratory data are shown in Tables 4 and 5, respectively. In the total study group, blood ketone bodies rose with decreasing ejection fraction and with higher filling pressures and increasing tricuspid regurgitation (Table 4, Fig. 1). Ketone bodies correlated inversely with plasma glucose and directly with free fatty acids, norepinephrine, growth hormone, pro-ANP and interleukin-6 (Table 5, Fig. 3). Comparable analyses restricted to the patients with CHF gave basically similar findings, although some correlation coefficients were not statistically significant owing to the smaller number of subjects (Tables 4 and 5).

Multiple linear regression analysis in the total study group showed that log blood ketone bodies correlated independently with log serum free fatty acids (standardized beta coefficient 0.51, $p < 0.001$), plasma glucose (beta −0.29, $p < 0.01$) and left ventricular ejection fraction (beta −0.30, $p < 0.01$). The squared multiple correlation coefficient (R^2, the explanatory power of the model) was 0.51. The same three factors were the independent predictors of log ketone bodies, also in analysis restricted to the CHF group ($R^2 = 0.49$) and in analysis

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Table 5. Correlation of Blood Ketone Body Concentration With Circulating Substrates, Hormones and Cytokines in the Total Study Group and in the Congestive Heart Failure Group

Variable	All Patients (n = 59) (r_s)	CHF Group (n = 45) (r_s)
P-glucose	−0.39*	−0.34†
S-free fatty acids	0.52‡	0.49*
B-lactate	0.01	0.07
S-insulin	−0.15	−0.25
S-glucagon	0.15	0.05
S-glucagon/insulin ratio	0.18	0.25
S-cortisol	0.07	−0.13
S-growth hormone	0.30†	0.20
P-norepinephrine (n = 45)	0.45*	0.36†
P-pro-ANP	0.36*	0.30†
P-TNF-alpha (n = 48)	0.05	−0.13
P-soluble TNF-alpha receptor II (n = 54)	0.01	−0.21
P-interleukin-6 (n = 54)	0.27†	0.26

*$p < 0.01$, †$p < 0.05$, ‡$p < 0.001$. Data presented are Spearman rank correlation coefficients (r_s). Abbreviations as in Table 4.

involving the total study group less six patients with CHF due to pure right heart failure ($R^2 = 0.52$).

Discussion

We found that blood ketone bodies were elevated in patients with CHF in proportion to the severity of symptoms and to the degree of venous congestion, left ventricular dysfunction and neurohormonal as well as cytokine activation. Left ventricular systolic dysfunction, elevated circulating free fatty acids and low plasma glucose were independent predictors of high ketone body concentration. These findings suggest that CHF is a ketosis-prone state and that the susceptibility to ketosis increases with the severity of CHF.

Determinants of blood ketone bodies: the role of stress hormones and free fatty acids. In general, ketone bodies accumulate in blood if their synthesis in the liver is augmented or if their distribution volume, utilization or excretion is decreased (20). Augmented production, in turn, may result either from a rising supply of ketogenic substrates or from the activation of the hepatic ketogenic mechanism. In our work, circulating free fatty acids, the main ketogenic substrate, were elevated in the patients with CHF compared with control subjects, suggesting that increased production probably contributed to the higher level of blood ketone bodies in CHF. In the background, hormonally stimulated lipolysis may have been instrumental because norepinephrine, cortisol and growth hormone were all elevated in the patients with CHF, and these hormones can augment lipolysis and fatty acid supply, particularly if the antilipolytic effects of insulin are suppressed (20–25). In addition to boosting lipolysis, norepinephrine may have direct ketogenic action in the liver and can reduce the clearance of ketone bodies in the periphery (24). Norepinephrine and sympathetic stimulation also promote glycogen depletion (20), which favors fatty acid oxidation and ketogenesis (21,26,27).

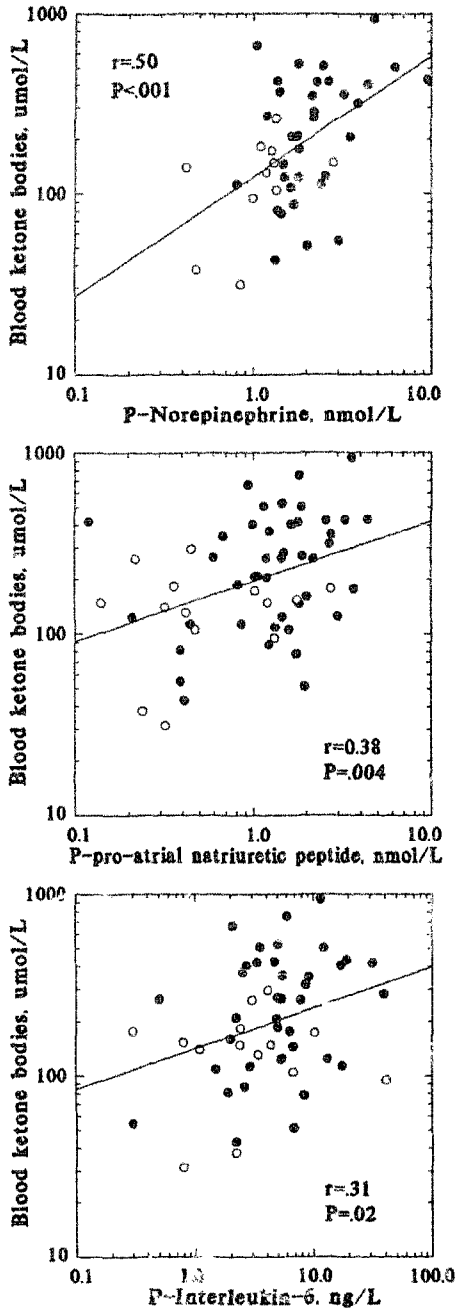

Figure 3. Relation of blood ketone bodies to the concentrations of norepinephrine, proatrial natriuretic peptide and interleukin-6 in the circulation. **Solid circles** represent patients with congestive heart failure, and **open circles** represent control patients. Both the **y** and **x axes** are in a logarithmic scale. The **regression lines** represent the least squares fits and the correlation coefficients are Pearson's.

Role of nutrition. Another factor that theoretically could potentiate ketogenesis in CHF is an imbalance between the supply of and need for calories. Malnutrition is not uncommon

in chronic CHF and is thought to reflect reduced food intake and absorption, in addition to increased basal metabolism and cellular hypoxia (1,7,8,28,29). Increased secretion of TNF-alpha may also contribute (30,31). Like simple fasting, malnutrition depletes the body of its glycogen stores, leading to fat utilization and ketogenesis. Our patients with CHF were not overtly malnourished, but many of them had markedly elevated right atrial pressure, which predicts nutritional problems in CHF (8). Although we found that blood ketone bodies were inversely related to the body's fat mass, supporting the role of nutrition, neither the other characteristics pertinent to the nutritional status nor the basal metabolic rate predicted the degree of ketonemia.

Role of glucagon and insulin. An increase in the glucagon-to-insulin ratio in serum has been raised as the key initiating factor in most ketotic states, including simple fasting (20,27). When glucagon increases relative to insulin, fatty acids taken up in the liver are rerouted from the synthesis of triglycerides and phospholipids to oxidation and ketogenesis—that is, the ketogenic machinery is switched to a higher activity. Surprisingly, the glucagon-to-insulin ratio was not elevated in our patients with CHF, nor was the degree of ketonemia associated with either serum glucagon or insulin concentration or their ratio. Therefore, these hormones seem unlikely to play a major role in the genesis of CHF ketosis. It is well known that increased free fatty acid supply can augment ketone body production, even if the activity of the hepatocytes' ketogenic mechanism is unaltered (27).

There are reports suggesting that CHF is accompanied by insulin resistance (32,33), and we initially thought that insulin resistance with impaired suppression of lipolysis could contribute to the development of CHF ketosis. However, our patients with CHF had no hyperinsulinemia suggestive of insulin resistance, compared with the control group, not even when the insulin concentrations were adjusted to plasma glucose (data not shown). Yet we admit that a precise assessment of the body's insulin sensitivity depends on the use of a euglycemic insulin clamp and that there was some discrepancy in our data because C-peptide levels were slightly but statistically significantly elevated in CHF. Earlier reports (32,33) associating insulin resistance with CHF included healthy control groups, whereas our control patients had a heart disease but no CHF. This is a crucial difference because insulin resistance may accompany such common conditions as atherosclerosis and hypertension, even in the absence of CHF (34).

Role of cytokines. Cytokines are low molecular weight proteins secreted by cells in response to stimuli varying from bacterial infections to myocardial injury (35). In addition to autocrine effects, cytokines have paracrine and endocrine actions on tissues as well as heart and blood vessels. We measured plasma cytokine concentrations in our patients primarily because increased concentrations of TNF-alpha and interleukins have been reported in CHF (30,31,36) and in particular because TNF-alpha has been linked with the development of malnutrition and cardiac cachexia (30,31). We found that blood ketone bodies were not associated with TNF-alpha but showed a direct relation to interleukin-6. However, there was also a linear relation between interleukin-6 and right atrial pressure ($r_s = 0.53$, $p < 0.001$), and the association of blood ketone bodies with interleukin-6 may simply have reflected the link between ketonemia and the severity of CHF. In multivariate analysis, interleukin-6 was not an independent predictor of ketonemia. The significance of interleukin-6 in CHF is still unknown, although experimentally it promotes cardiac dysfunction (37,38).

Possible clinical implications. Whether measuring the degree of ketonemia in patients with CHF has clinical relevance cannot be answered from our study. We believe, however, that the degree of ketosis proneness could give insight into the severity of CHF and that elevated blood ketone bodies after an overnight fast could be taken as a warning of incipient problems with the maintenance of the body's energy stores. Whether susceptibility to ketosis could have prognostic value, such as neurohormonal activation or serum sodium concentration convey (1), deserves attention in future studies.

Study limitations. Our CHF group may not represent the general CHF population well, because exclusion of patients taking beta-blockers led to underrepresentation of ischemic heart disease and hypertension. In the control group, several patients had one or two of the four diagnostic criteria of CHF, and some also had abnormal hemodynamic measurements (Fig. 2), even though none fulfilled our definition of clinical CHF. If we had included in the control group only patients with none of the four CHF criteria, the metabolic differences between the groups might have been more significant. Yet we have observed previously that cardiac patients free of clinical CHF by our criteria do not differ from healthy persons with regard to breath acetone concentration, which correlates linearly with blood acetone (10). The lack of a more detailed characterization of the patients' nutritional status and diet is another limitation. Although none of our patients with CHF was grossly edematous, some fluid retention was possible and may have biased the anthropometric measurements, apart from body height and percent body fat. Our study may also be criticized for not discontinuing drug therapy before the examinations. However, many of the patients with CHF were severely symptomatic, which made interruption of therapy for several drug half-lives an impractical alternative. Moreover, diuretics, angiotensin-converting enzyme inhibitors and digoxin have no known direct influence on the turnover of ketone bodies. Finally, we acknowledge that our inferences of altered ketogenesis are indirect because the production, utilization and excretion of ketone bodies were not separately quantified. It is fully possible that the clearance of ketone bodies (utilization and excretion) can be altered in patients with CHF having marked systemic congestion, low cardiac output and renal dysfunction. Future studies using isotope techniques with or without hepatic vein catheterization for the measurement of liver blood flow and net output of ketone bodies are needed to evaluate in detail how the elements of ketone body kinetics are altered in CHF.

Conclusions. Mild elevation of blood ketone bodies is common in patients with CHF. The degree of ketonemia is related to the severity of hemodynamic abnormalities and to the degree of neurohormonal and cytokine (interleukin-6) activation. Increased supply of free fatty acids from stress hormone–stimulated lipolysis is likely to be one of the mechanisms leading to ketonemia in CHF; insulin and glucagon appear to be relatively unimportant. Additional studies are needed, however, to detail the mechanisms of CHF ketosis and to assess its clinical significance.

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