Protein kinetics in stable heart failure patients

CHARLES W. CORTES,1,2 PAUL D. THOMPSON,1 NIALL M. MOYNA,1 MARGARET D. SCHLUTER,2 MARIA J. LESKIW,2 MELISSA R. DONALDSON,2 BRETT H. DUNCAN,1 AND T. PETER STEIN2

1Division of Preventive Cardiology, Hartford Hospital, Hartford, Connecticut 06102; and 2Department of Surgery Research, School of Osteopathic Medicine, University of Medicine and Dentistry of New Jersey, Stratford, New Jersey 07603

Received 26 June 2001; accepted in final form 20 June 2002

Protein kinetics in stable heart failure patients. J Appl Physiol 94: 295–300, 2003. First published July 5, 2002; 10.1152/japplphysiol.00654.2001.—Heart failure (HF) is a slow progressive syndrome characterized by low cardiac output and peripheral metabolic, biochemical, and histological alterations. Protein loss and reduced protein turnover occur with aging, but the consequences of congestive HF (CHF) superimposed on the normal aging response are unknown. This study has two objectives: 1) to determine whether there was a difference between older age-matched controls and those with stable HF (i.e., ischemic pathology) in whole body protein turnover and 2) to determine whether protein metabolism in liver and skeletal muscle protein turnover is impacted by CHF. We measured the whole body protein synthesis rate with a U-13N-labeled algal protein hydrolysate in 10 patients with CHF and in 10 age-matched controls. Muscle fractional synthesis rate of lateral vastus muscle was determined with [U-13C]alanine on muscle biopsies obtained by a standard percutaneous needle biopsy technique. Fractional synthesis rates of five plasma proteins of hepatic origin (fibrinogen, complement C-3, ceruloplasmin, transferrin, and very low-density lipoprotein apolipoprotein B-100) were determined by using 2H2-labeled t-phenylalanine as tracer. Results showed that whole body protein synthesis rate was reduced in CHF patients (3.09 ± 0.19 vs. 2.25 ± 0.71 g protein·kg−1·day−1, P < 0.05) as was muscle fractional synthesis rate (3.02 ± 0.58 vs. 1.33 ± 0.71%/day, P < 0.05) and very low-density lipoprotein apolipoprotein B-100 (265 ± 25 vs. 197 ± 16%/day, P < 0.05). CHF patients were hyperinsulinemic (9.6 ± 3.1 vs. 47.0 ± 7.8 μU/ml, P < 0.01). The results were compared with those found with bed rest patients. In conclusion, protein turnover is depressed in CHF patients, and both skeletal muscle and liver are impaired. These results are similar to those found with bed rest, which suggests that inactivity is a factor in depressed protein metabolism.

CONGESTIVE HEART FAILURE (CHF) is a progressive disease that causes chronic fatigue, muscle weakness, muscle atrophy, and exercise intolerance. The disease is characterized by low cardiac output and metabolic, biochemical, and histological alterations in the peripheral skeletal muscle (1, 7, 18). Peripheral factors, such as a selective loss of type 1 (slow, oxidative) fibers, decreased oxidative enzyme capacity (5, 23), and volume density of mitochondria (10), rather than central hemodynamic parameters seem to be of greater importance in the impaired response to exercise (6, 23, 25). There is a slow progressive loss of skeletal muscle (17, 25).

In other situations, decrements in the ability to make protein are associated with progressively increasing loss of strength and endurance together with decreased immune competence, poorer wound healing, and increased susceptibility to disease (4, 14, 21, 36). Protein turnover accounts for ~20% of the basal metabolic rate (35). The expenditure of such a high proportion of the metabolic rate on protein turnover attests to its physiological importance (29).

The present study had two objectives: first, to determine whether there was a difference between older age-matched controls and those with stable heart failure (i.e., ischemic pathology) in the total ability of the body to make protein, and second, to identify whether CHF impacted protein turnover in two noncardiac tissues (skeletal muscle and liver). The whole body protein and fractional protein synthesis rates of skeletal muscle and four plasma proteins of hepatic were measured in elderly patients with documented CHF and compared with age-matched controls. The four plasma proteins were transferrin, fibrinogen, ceruloplasmin, and complement C-3.

METHODS

Subjects

We obtained informed, written consent from 10 healthy elderly subjects and 10 patients with CHF, in accordance with the policies of the Institutional Review Board for the Protection of Human Subjects of Hartford Hospital and the University of Medicine and Dentistry of New Jersey School of Osteopathic Medicine. Patients with CHF were all New York Heart Association Class II to III, and all had ischemic heart disease as their primary diagnosis for an average of 42 ± 25
mo with a range of 24–92 mo. All patients were weight stable at the time of study. Control subjects had no prior history of cardiac disease and cardiovascular risk factors. All subjects were free living and ambulatory and did not participate in any formalized exercise program. Activity was not quantified.

Potential subjects were identified by review of their medical charts and were invited to participate in the study. A physical examination and medical history were taken on all subjects to confirm their suitability. CHF patients were required to be >65 yr of age and to have had a 2-D echocardiography or cardiac catheterization in the past 6 mo and a resting ejection fraction of <30%. Patients were excluded if they had any of the following: significant psychiatric disorders, neuromuscular disease or dystrophies, stroke, or alcoholism, or if they were residents in a nursing home.

Protein Kinetics

Subjects reported to the study site at 0700 for a 10-h period to determine the rate of whole body protein synthesis and muscle protein fractional synthesis rate. Body weight and height were measured to the nearest 0.5 kg and cm, respectively. Patients were instructed to report to the study center in a fasting state. Patients were instructed to take any required prescription medicines with water. Fasting serum, citrated plasma, and EDTA plasma were drawn before start of the stable isotope studies, centrifuged for 15 min at 3,000 revolutions/min, aliquoted in 1-ml samples, and stored at −70°C until analyzed.

The study lasted 10 h. The study was done in the fed state. During the 10-h period, subjects drank 25 kcal of Ensure (Ross Laboratories, Columbus, OH) every 0.5 h. Whole body protein synthesis and breakdown rates were determined with the single-pulse method by using a 99 atom% 15N Algal amino acid mixture (Isotec, Miamisburg, OH) (32, 34). Muscle and plasma protein synthesis rates were determined by primed constant dosing regimens of 99 atom% U-13C3-labeled alanine and 2H5-L-phenylalanine. The primes were followed by 0.050 and 0.200 g capsules of U-13C3-L-alanine and 2H5-L-phenylalanine. The primes were then eluted with 6 N NH₄OH and taken to dryness by aeration by N₂ at 60°C. The residue was then converted to the N-acetyl-N-propyl amino acid esters, as previously described (30), for analysis of the [U-13C]alanine and [2H5]phenylalanine enrichments by using a Hewlett-Packard 5973 quadrupole gas chromatograph mass spectrometer (VG Instruments, Cheshire, UK).

Plasma amino acid enrichments. One milliliter of 10% salicylic acid was added to 1.0 ml of plasma, and the precipitate was isolated by centrifugation at 5,000g for 20 min at 4°C. The supernatant was passed through a 2-cm Dowex 50 H⁺ column in a Pasteur pipette to remove sulfosalicylic acid. The amino acids were then eluted with 6 N NH₄OH and taken to dryness by aeration by N₂ at 60°C. The residue was then converted to the N-acetyl-N-propyl amino acid esters, as previously described (30), for analysis of the [U-13C]alanine and [2H5]phenylalanine enrichments by using a Hewlett-Packard 5973 quadrupole gas chromatograph mass spectrometer (VG Instruments, Cheshire, UK).

Plasma protein-bound amino acid enrichments. Fibrinogen plasma (0.75 ml, 0- and 10-h samples) was added to saline (20 ml) containing thrombin (20 U), and CaCl₂ (0.5 ml, 0.5 M) was added. The resultant clot was collected on a glass rod and washed with water as previously described (30).

Ceruloplasmin, transferrin, and complement C-3 were isolated by a combination of immunoprecipitation and subsequent purification by PAGE electrophoreses, as described by Jahoor et al. (20). Plasma (0.2 ml) was reacted with 0.1 ml of anti-sera (15 mg/ml) and allowed to stand at 4°C overnight. The protein antibody complexes were precipitated by centrifugation (5,000 g) at 4°C for 20 min. The precipitates were washed three times with 0.7 ml of 0.15 M NaCl and centrifuged. Thirty-five milliliters of buffer (0.187 M Tris, 0.104 M sodium dodecyl sulfate, 3.26 M glycerol, 0.85 M 2-mercaptoethanol, pH 6.8) containing 0.03% (wt/vol) bromophenol blue was added to the precipitate. The mixture was heated at 95°C for 5 min, cooled to 4°C, and centrifuged at 2,000 revolutions/min for 5 min. Aliquots of the immunoprecipitates together with the corresponding standards and antibodies were loaded onto 12% SDS-PAGE gel and electrophoresed in 25 mM Tris-192 mM glycine buffer (pH 8.3) at 20°C. After completion, the gels were stained with Coomassie blue R-250

**Analytical Methods**

**Blood chemistries.** Fasting serum and plasma glucose, cholesterol, and triglycerides were determined by using standard clinical techniques by the Clinical Chemistry Laboratories of the Hartford Hospital. Insulin resistance was derived by using the fasting insulin resistance index described by Duncan et al. (11). This method consists of taking the product of plasma insulin and glucose (normalized to an expected glucose of 5 mmol/l and insulin of 5 mU/l to give a reference range centered around unity). The index is equal to fasting glucose × fasting insulin/25.

**Whole body protein synthesis.** Blood urea nitrogen (BUN) was determined by the urease method by using Sigma diagnostic kit no. 640 (Sigma Chemical, St. Louis, MO). For determination of the isotopic enrichment of BUN, water (1 ml) and urease solution (1.0 ml, 60 μM units urease/ml in 0.1 M phosphate buffer, pH 6.5) were added to plasma (2.0 ml). After incubation for 30 min at 37°C, K₂CO₃ (2 ml) and 2-octanol (8 drops) were added. The resultant ammonia was removed by aeration and collected in 0.1 N H₂SO₄ (1 ml). Total urinary nitrogen was measured in 1 ml of urine by the Kjeldahl method (Thomas Scientific, Swedesboro, NJ). The 15Ν enrichment of BUN-derived ammonia and the Kjeldahl digests were converted to N₂ gas by the Rittenberg hypobromite method, as previously described (32), and the 15Ν enrichment of the resultant N₂ was determined by isotope ratio mass spectrometry with a VG-SIRA-II mass spectrometer (VG Instruments, Cheshire, UK).

**Plasma amino acid enrichments.** One milliliter of 10% salicylic acid was added to 1.0 ml of plasma, and the precipitate was isolated by centrifugation at 5,000g for 20 min at 4°C. The supernatant was passed through a 2-cm Dowex 50 H⁺ column in a Pasteur pipette to remove sulfosalicylic acid. The amino acids were then eluted with 6 N NH₄OH and taken to dryness by aeration by N₂ at 60°C. The residue was then converted to the N-acetyl-N-propyl amino acid esters, as previously described (30), for analysis of the [U-13C]alanine and [2H5]phenylalanine enrichments by using a Hewlett-Packard 5973 quadrupole gas chromatograph mass spectrometer (Hewlett-Packard, Palo Alto, CA). Ion pairs 132:135, 174:177, and 202:205 were monitored for alanine and leucine. The resultant mixture was then converted to the N-acetyl-N-propyl amino acid esters, as previously described (30), for analysis of the [U-13C]alanine and [2H5]phenylalanine enrichments by using a Hewlett-Packard 5973 quadrupole gas chromatograph mass spectrometer (Hewlett-Packard, Palo Alto, CA). Ion pairs 132:135, 174:177, and 202:205 were monitored for alanine and leucine. The resultant mixture was then converted to the N-acetyl-N-propyl amino acid esters, as previously described (30), for analysis of the [U-13C]alanine and [2H5]phenylalanine enrichments by using a Hewlett-Packard 5973 quadrupole gas chromatograph mass spectrometer (Hewlett-Packard, Palo Alto, CA). Ion pairs 132:135, 174:177, and 202:205 were monitored for alanine and leucine.
in 7% wt/vol acetic acid. After the bands corresponding to the respective protein standards were destained with two changes of 7% acetic acid, the bands were cut out and transferred to vessels for the acid hydrolysis of the protein.

The isolated proteins were hydrolyzed with HCl (6 N, 1 ml) at 110°C for 24 h, and the resultant amino acids were converted to their N-acetyl-N-propyl amino acid esters for gas chromatograph mass spectrometric analysis of the [3H2]-phenylalanine, as described in Plasma amino acid enrichments (25). Ion pairs at 91.96 and 145.153 were monitored.

Muscle. Muscle samples (~20 mg) were pulverized at −70°C and homogenized with 10% salicylic acid. The resultant mixture was centrifuged at 10,000 g for 15 min. The supernatant was removed, and the precipitate was washed once with water and then twice with ethanol. The supernatant was then treated as described in Plasma amino acid enrichments for the plasma supernatant to prepare the samples for [U-13C]alanine enrichment by using a Hewlett-Packard 5973 quadrupole gas chromatograph mass spectrometer. Ion pairs 132:135, 174:177, and 202:205 were monitored.

An aliquot of the precipitated protein was hydrolyzed with HCl (6 N, 1 ml) at 110°C for 24 h. HCl was removed, and the resultant amino acids were converted to their N-acetyl-N-propyl amino acid esters for analysis of the [13C]-alanine enrichment by gas chromatograph-to-combustion isotope ratio mass spectrometry by using a Europa-Orchid gas chromatograph-to-combustion isotope ratio mass spectrometer system (Europea). An Omegawax 320 (30 m × 0.32 mm ID, 0.25 μm thickness, Supelco Bellefonte, PA) was coupled to a Restek RTX 20 column (30 m × 0.32 mm ID, 0.5 μm thickness, Restek, Bellefonte, PA) and used to effect the separation of alanine under an initial temperature 70°C for 1 min, which was increased to 150°C at minute 1 and was maintained for 25 min. The combustion oven contained copper oxide granules at 825°C, and a helium flow rate of 2.0 ml/min.

Methods of Calculation

Whole body protein synthesis. The amount of the administered dose of [15N]glycine excreted was calculated by measuring the amount of 15N excreted in the 10-h period and the 15N remaining in the body urea pool at 10 h. The latter was calculated from the plasma obtained at the end of the experiment. Because urea is distributed uniformly throughout the body water pool, the amount of 15N remaining in the body urea pool can be calculated from the product of the BUN concentration, its 15N enrichment, and total body water expressed in liters. The body urea pool size was estimated from BUN by using an equation derived by Hume and Weyers (18a, 32)

\[ 15N \text{ in urea pool} = \text{TBW (in liters)} \times \text{BUN (in g/l)} \times 15N \text{ (APE} \times 0.01) \]

\[ \text{PSR} = E_t \left( \frac{d}{e} - 1 \right) \]

where \( d \) is 15N given in g N 10 h, \( e \) is 15N excreted (urea + BUN) in g N 10 h, \( E_t \) is N excretion in g N 10 h, and PSR is the rate of protein synthesis in g N 10 h.

The corresponding protein breakdown rate (PBR) was calculated from the relationship \( \text{PSR} = \text{PBR} = N_{\text{intake}} - N_{\text{excreted}} \).

Muscle fractional synthesis rate. The fractional muscle synthesis rate \( (k_s) \) was calculated from the relationship \( k_s = \frac{\Delta S_B}{S_1 \Delta t} \) where \( \Delta S_B \) is the difference in isotopic enrichment of alanine in protein-bound alanine between the 2.5- (t1) and 7-h (t2) samples, \( S_1 \) is the mean 13C enrichment of alanine in the muscle free amino acids pool for t1 and t2, and \( \Delta t \) is the difference in time between t1 and t2.

Plasma k_s. The \( k_s \) was calculated from the relationship \( k_s = \frac{\Delta S_B}{S_1 \Delta t} \) where \( \Delta S_B \) is the difference in isotopic enrichment of [3H2]phenylalanine in protein bound phenylalanine between the 2.5- (t1) and 7-h (t2) samples, \( S_1 \) is the mean 3H2 enrichment of phenylalanine in the plasma for times t1 and t2, and \( \Delta t \) is the difference in time between t1 and t2.

Statistical Analyses

Data were analyzed by using Student’s t-test or analysis of covariance as appropriate. Analysis of covariance was used to adjust the protein synthesis rate values for body weight and insulin. Significance was accepted at a P value of <0.05.

RESULTS

CHF patients weighed significantly more and had higher body mass indexes than control subjects (Table 1). BUN and plasma insulin levels were significantly higher in CHF patients (P < 0.05; Table 1). Whole body protein synthesis rate was significantly reduced in CHF patients when expressed either per total protein mass synthesized per subject or per kilogram of body weight (P < 0.01; Table 2). Analysis of covariance using weight as the covariate showed that this difference still applied with control for body weight. Because subjects were weight stable, it follows that synthesis is equal to breakdown.

The fractional rate of mixed muscle protein synthesis was reduced by ~55% in CHF patients compared with the normal age-matched controls (P < 0.03; Table 2). There was an inverse correlation between the elevation of the plasma insulin concentration and the whole body protein synthesis rate in CHF patients. Regression analysis showed a negative correlation between the elevated insulin levels and the whole body protein turnover in stable CHF patients (r² = −0.84; P = 0.002). There was one diabetic patient in the CHF group. If that subject was excluded from the regression analysis, the inverse relationship between plasma insulin and whole body protein synthesis rate was still statistically significant (P < 0.05). A similar inverse relationship of protein synthesis to plasma insulin level was found with the muscle fractional synthesis

<table>
<thead>
<tr>
<th>Table 1. Physical characteristics of subjects</th>
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<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Age, yr</td>
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<tr>
<td>Female, %</td>
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<tr>
<td>Male, %</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>Height, cm</td>
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<tr>
<td>BMI</td>
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<tr>
<td>NYHA Class (1–5)</td>
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<tr>
<td>S/P MI, %</td>
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<tr>
<td>S/P CABG, %</td>
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</tbody>
</table>

Values are means ± SE. CHF, congestive heart failure; BMI, body mass index; NYHA, New York Heart Association; S/P MI, status post myocardial infarction; S/P CABG, status post coronary bypass graph.

*Significant difference (P < 0.05).
rate in which the decline in muscle synthesis with increasing plasma insulin concentration approached statistical significance \( P = 0.063 \). Very low-density lipoprotein apolipoprotein B-100 synthesis was reduced by \( \sim 25\% \) in CHF subjects when compared against their age-matched controls \( P < 0.05; \) Table 3). There were no other differences between subjects for the other four plasma proteins studied.

**DISCUSSION**

The whole body protein synthesis rate was reduced with the CHF patients compared with age-matched controls. Because CHF patients were weight stable, it follows that protein breakdown was equally reduced, which results in an overall reduction in protein turnover. Interpretation of differences in the whole body protein turnover rate can be problematic if there are substantial differences in body composition between the two groups. Although we tried to recruit patients of similar age and build, we were only partially successful because CHF patients were heavier than the age-matched controls. Nevertheless, even after control for weight, the whole body protein turnover rate in these elderly patients with CHF was significantly reduced relative to age-matched controls \( P = 0.02 \).

Estimates of human fractional protein synthesis rates depend on what is used to estimate the precursor pool enrichment in lieu of measuring the enrichment of tRNA. Either the plasma amino acids or the tissue free amino acids can be used. The preference is for the tissue free amino acids because it is believed to be closer to the actual precursor site for protein synthesis; however, doing so does not necessarily provide an accurate value for the precursor pool because the intracellular amino acid pool is not homogeneous \( 2, 16, 27 \). The muscle fractional synthesis rates in this study may be a little high. The probable reason is that there is a large intracellular alanine pool due to alanine’s role in amino acid degradation. However, any underestimation of the true precursor pool for protein synthesis will be common to both groups. Although the values may not be the absolute numbers, any differences between the two closely related groups in this study are still valid. For plasma proteins, the tissue free amino acids cannot be used because liver biopsies were not taken.

Therefore, plasma \([\text{[H}_5\text{]}\)phenylalanine enrichment was used for estimating the isotopic enrichment of the liver protein synthesis precursor pool.

**Data Interpretation**

It is possible that some of the reduction in the whole body protein turnover rate could be due to the sarcopenia associated with CHF \( 23–25 \). If CHF patients have less skeletal muscle, total protein synthesis is likely to be lower. However, differences in body composition cannot account for the reduction found in the muscle fractional protein synthesis rate. The muscle fractional synthesis rate measurement is independent of body composition.

The muscle protein fractional synthesis rate was reduced by \( \sim 55\% \) in CHF patients compared with age-matched controls. Muscle accounts for between 20 and 50% of the total body protein synthesis rate \( 13, 26 \), so if the vastus lateralis muscle is representative of the entire skeletal muscle pool, the whole body protein should be reduced correspondingly, as the present study found (Table 2). Thus the disease is characterized by both a loss of skeletal muscle and a decreased rate of muscle protein turnover.

The reduction in protein turnover appears to be inversely related to the plasma insulin level. The insulin levels seen in CHF patients in this study are characteristic for insulin resistance. Hyperinsulinemia is common in heart failure patients \( 3, 8, 11 \) and after myocardial infarction \( 11, 19 \). A likely possibility is that CHF patients are less active than age-matched controls since impaired physical activity is one of the characteristics of the disease. Insulin resistance increases with decreased physical activity, e.g., bed rest \( 9, 22, 28, 33 \).

There are other parallels between the findings in this study and those found with bed rest studies. Bed rest studies are a common model for studying the effects of reduced activity or reduced gravity on skeletal muscle \( 15 \). The \( \sim 27\% \) decrease in the whole body protein synthesis rate found with CHF is similar to the \( \sim 19\% \) our laboratory found with bed rest \( [4.14 \pm 0.35 \text{ vs. } 3.36 \pm 0.30 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}, \) \( P < 0.05 \) \( 31 \) ] as well as to the findings of others \( 13, 26 \). Likewise, the \( \sim 55\% \) reduction in the skeletal muscle protein synthesis rate found with CHF pa-

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**Table 2. Summary of experimental results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>CHF Patients</th>
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<tbody>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>166 ± 11</td>
<td>152 ± 13</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>83 ± 9</td>
<td>69 ± 13</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>37 ± 4</td>
<td>33 ± 3</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>229 ± 59</td>
<td>249 ± 48</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>90 ± 4</td>
<td>113 ± 19</td>
</tr>
<tr>
<td>Lactate, mmol</td>
<td>1.5 ± 0.1</td>
<td>1.4 ± 0.6</td>
</tr>
<tr>
<td>Fasting insulin resistance index</td>
<td>0.65 ± 0.06</td>
<td>5.71 ± 1.10*</td>
</tr>
<tr>
<td>Insulin, µU/ml</td>
<td>9.6 ± 3.1</td>
<td>47.0 ± 7.8*</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dl</td>
<td>15.3 ± 1.1</td>
<td>22.0 ± 2.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n = 10 \); patients. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. *Significant difference \( P < 0.01 \).

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**Table 3. Effect of CHF on whole body, muscle, and selected plasma protein synthesis rates**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Elderly Control</th>
<th>CHF Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body PSR, g protein(-1) ( \cdot ) day ( ^{-1} )</td>
<td>3.09 ± 0.19(10)</td>
<td>2.25 ± 0.15(15)*</td>
</tr>
<tr>
<td>Mixed muscle FSR, %/day</td>
<td>5.02 ± 0.58(6)</td>
<td>1.33 ± 0.71(7)*</td>
</tr>
<tr>
<td>Fibrinogen FSR, %/day</td>
<td>19.2 ± 1.3(8)</td>
<td>21.9 ± 1.6(9)</td>
</tr>
<tr>
<td>Complement C-3 FSR, %/day</td>
<td>22.4 ± 2.7(8)</td>
<td>25.0 ± 1.4(9)</td>
</tr>
<tr>
<td>Ceruloplasmin FSR, %/day</td>
<td>14.9 ± 0.6(8)</td>
<td>13.7 ± 0.9(9)</td>
</tr>
<tr>
<td>Transferrin FSR, %/day</td>
<td>10.3 ± 0.8(8)</td>
<td>8.7 ± 0.7(9)</td>
</tr>
</tbody>
</table>

Values are means ± SE; no. of subjects in parentheses. PSR, protein synthesis rate; FSR, fractional synthesis rate. *Significant difference \( P < 0.05 \).
patients is similar to the ~50% reduction reported by Ferrando et al. (13) in their bed rest study. The large reduction in protein synthesis occurred although protein loss was <2% (13).

Measurement of plasma protein synthesis rates provides a minimally invasive way of assessing protein synthesis by a second major tissue, the liver. For this study, we selected four proteins, three acute-phase proteins involved in host defense processes (ceruloplasmin, complement C-3, and fibrinogen) and one protein sensitive to nutritional status (transferrin). The selection was predicated in part by a desire to examine proteins with different functions, the need for the turnover rate to be within the sensitivity range of our analytical equipment, and adequate presence in the plasma so that the isolation could be done on 0.3 ml of plasma or less.

There were no differences with any of the plasma protein synthesis rates between CHF patients and age-matched controls. We found a similar result in a bed rest study (Stein et al., unpublished observations). The reductions in protein synthesis in tissues other than muscle. Collectively, these observations suggest that a major factor in the reduction of protein turnover is the decreased activity that is characteristic of patients with CHF (6, 23, 25).

In conclusion, CHF is associated with decreased whole body and skeletal muscle protein synthesis. The reduction in protein turnover appears to be inversely related to the plasma insulin level. It is not clear what role insulin sensitivity played in regulating depressed protein synthesis in CHF patients relative to age-matched control subjects in this study. The similarities between the findings with CHF and with bed rest suggest that the reduced rate of muscle protein synthesis found with CHF may be a consequence of inactivity rather than of CHF per se.

We thank Michael J. Rewinski for technical assistance and the private cardiology groups affiliated with Hartford Hospital for allowing us to study their patients.

This work was supported by National Institute on Aging Grant AG-14098-01-A1 (to T. P. Stein) and American Heart Association Grant-In-Aid 9950255N (to C. W. Cortes).

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