Whole-Body Protein Metabolism in Chronic Heart Failure: Relationship to Anabolic and Catabolic Hormones

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ABSTRACT. Background: Patients with chronic heart failure frequently experience profound wasting during the course of the disease, a syndrome termed cardiac cachexia. Although protein is the primary structural and functional component of most tissues, few studies have examined the effect of heart failure on protein metabolism. Moreover, no study has assessed the relationship of protein turnover to hormonal alterations thought to promote cachexia. Thus, our goal was to determine if whole-body protein metabolism is altered in heart failure patients and to assess the relationship of protein kinetics to circulating levels of anabolic and catabolic hormones. Methods: We measured whole-body protein metabolism using \(^{13}\)C-leucine, body composition, and circulating anabolic and catabolic hormone levels in 10 patients with chronic heart failure and 11 elderly controls. Results: No differences in leucine rate of appearance, oxidation, or nonoxidative disposal were noted between heart failure patients and controls. However, in a subgroup of patients characterized by increased resting energy expenditure for their metabolic body size (n = 4; \(\geq20\%) above that predicted from fat-free mass), leucine rate of appearance (mean \(\pm\) SE; \(146 \pm 6\) \(\mu\)mol/min), an index of protein breakdown, tended to be higher compared with patients with normal resting energy expenditure (n = 5; \(120 \pm 8\) \(\mu\)mol/min) and controls (\(127 \pm 4\) \(\mu\)mol/min; \(p = .06\)). Alterations in anabolic/catabolic hormone balance did not explain increased protein breakdown in this subgroup, and no correlations were found between hormone levels and protein breakdown in the heart failure group as a whole. In contrast, increased circulating interleukin-6 soluble receptor (\(r = 0.829\); \(p < .01\)) and reduced insulin-like growth factor-I (\(r = -0.751\); \(p < .05\)) levels were related to greater rates of leucine oxidation in heart failure patients. Conclusion: Our results demonstrate that, although increased protein turnover is not a generalized feature of heart failure, there is a subgroup of patients characterized by resting hypermetabolism and increased protein breakdown. Moreover, hormonal alterations related to the heart failure syndrome were related to increased protein oxidation. (Journal of Parenteral and Enteral Nutrition 30:194–201, 2006)
METHODS

Subjects

Ten male volunteers with chronic HF due to left ventricular systolic dysfunction were recruited from the Heart Failure Clinic of the Cardiology Unit of the University of Vermont (ejection fraction: 32% ± 4% by echocardiography). New York Heart Association (NYHA) functional class averaged 2.5 ± 0.2 with 6 patients in class II, 3 in class III, and 1 in class IV. HF was due to coronary artery disease in 7 patients, defined by a history of myocardial infarction or multivessel coronary obstructions at cardiac catheterization, idiopathic dilated cardiomyopathy in 2 patients, and dilated cardiomyopathy secondary to severe hypertension in 1 patient. HF patients were taking the following medications: diuretics (n = 10; 100%), digoxin (n = 7; 70%), angiotensin-converting enzyme inhibitors/receptor blockers (n = 9; 90%) and β-adrenergic blocking agents (n = 8; 80%). Three of the 9 patients had diabetes mellitus, 1 patient had insulin-dependent diabetes mellitus, and 2 patients had non–insulin-dependent diabetes mellitus (NIDDM). Patients were tested at least 6 months after inpatient management of their HF and were clinically stable and free of peripheral edema.

Eleven male volunteers were recruited to serve as controls. Nine of these volunteers were healthy and free of disease, had no signs or symptoms of heart disease, and had normal rest and exercise electrocardiograms. The control group also included 2 individuals with known coronary artery disease but normal left ventricular contraction patterns and no exertional ischemia, as demonstrated by a normal electrocardiographic stress test to exhaustion without angina. Both of these volunteers were treated with aspirin: 1 with a Ca2+ channel blocker and the other with an HMG-CoA reductase inhibitor. Because inclusion of these 2 controls did not affect group differences (see Results section), they were retained in the control group. Other medications in the control group were antiepileptic (n = 1), antianxiety (n = 1), 5a-reductase inhibitor (n = 1) and nonsteroidal antiinflammatory (n = 1). Controls had no history of diabetes mellitus, normal fasting blood glucose (<6.22 mmol/L), and normal glucose tolerance (glucose <7.77 mmol/L 2 hours after 75-g oral glucose load). The nature, purpose, and possible risks of the study were explained to each subject before they gave written consent to participate. The experimental protocol was approved by the Committee on Human Research at the University of Vermont. Data from these volunteers describing the effect of HF on skeletal muscle myofibrillar protein metabolism have been presented elsewhere.20

Protocol

Volunteers were tested during outpatient and inpatient visits to the University of Vermont General Clinical Research Center. Body composition and exercise capacity were measured on an outpatient basis at least 1 week prior to protein metabolism measurements. For 3 days prior to the inpatient admission, all subjects were provided a standardized, weight-maintenance diet (approximately 55% carbohydrate, 25% fat, 20% protein). Protein intake was standardized and was similar between HF patients and controls as a percentage of the total caloric content of the diet (HF: 19.3 ± 0.3 vs control [C]: 19.7 ± 0.4%). All food was provided by the research center. The last meal of the standardized diet was consumed by 7 PM the evening of admission, and subjects were fasted until completion of testing the following day. Volunteers were asked to refrain from exercise the day before admission to prevent any residual effect of physical exercise on protein metabolism or circulating hormone levels. Medications were maintained for all volunteers per normal dosing regimens throughout testing.

On the morning of study, catheters were placed in an antecubital vein for infusion and retrograde in a dorsal hand vein of the contralateral arm. The hand was placed in a warming box to obtain arterialized venous blood. Blood and breath samples were drawn just before the start of infusion for the measurement of baseline 13C enrichments. At approximately 6:30 AM, a primed (4.8 μmol/kg), continuous (5.6 μmol/kg/min) infusion of [1,2-13C2]leucine was started (time 0 minutes). The bicarbonate pool was primed (3.1 μmol/kg) with sodium [13C]bicarbonate. Blood and breath samples were drawn at 165, 180, 195, and 210 minutes for measurement of whole-body leucine metabolism. Oxygen consumption and carbon dioxide production rates were determined at 60 and 195 minutes for 15 minutes using the ventilated hood technique (DeltaTrac, Yorba Linda, CA).

Whole-Body Leucine Metabolism

Analytical methods. Plasma leucine and ketoisocaprate (KIC) enrichments were measured by gas chromatography mass spectrometry (GCMS), as described previously.21,22 The amino and keto acids were isolated from plasma and derivatized to the N-heptafluorobutyryl, n-propyl (HFBP) amino acid esters and t-butyldimethylsilyl-quinoxalinol ketoacid derivatives, respectively.21,22 HFBP amino acid derivatives were measured by GCMS (model 5973, Agilent, Palo Alto, CA) by negative chemical ionization and selected monitoring of ions at m/z = 349 and 351 for unlabeled and [1,2,13C2]leucine, respectively. KIC was measured by electron impact ionization GCMS (model 5971A, Hewlett-Packard, Palo Alto, CA) with selected monitoring of ions at m/z = 259 and 260 for unlabeled and [1,2,13C2]KIC, respectively. For each measurement, the background corrected enrichment was calculated. The 13C enrichment of expired CO2 was measured from breath samples by isotope ratio mass spectrometry (VG SIRA II, Middlewich, Cheshire, United Kingdom).

Calculations. Plasma KIC and breath CO2 enrichments from 165, 180, 195, and 210 minutes were used to calculate whole-body leucine kinetics, as described previously.23 The rate of appearance (Ra) of leucine into plasma (μmol/min), an index of protein breakdown, was calculated as: Ra = I (Ei/Ei−1), where I is the infusion rate (μmol/min) of the tracer, and Ei and Ei−1 are the enrichment (mpe) of tracer in the infusate and plasma, respectively. Plasma KIC enrichment, a
proxy of intracellular leucine enrichment, was used for \( E_p \). Leucine oxidation (C), an index of protein oxidation, was calculated as: \( C = F_{\text{13C}} \times (1/E_p - 1/E_i) \times 100 \), where \( F_{\text{13C}} \) is the rate of \(^{13}\text{CO}_2\) excretion into expired air (\( \mu\text{mol}\) \(^{13}\text{C}/\text{h} \)) and the constant 2 accounts for the 2 \(^{13}\text{C}\) labels in the leucine molecule. \( F_{\text{13C}} \) was calculated as: \( F_{\text{13C}} = F_{\text{CO}_2} \times E_{\text{CO}_2}\), where \( F_{\text{CO}_2} \) is the \( \text{CO}_2 \) production rate \((\text{cm}^3/\text{min})\) and \( E_{\text{CO}_2} \) is the enrichment of expired \( \text{CO}_2 \) (mpe \( \times\) 1000). The constants 60 (min/h) and 44.6 \((\mu\text{mol}/\text{H} \times 262\)) convert \( F_{\text{CO}_2} \) to \( \mu\text{mol}/\text{h} \), the factor 100 changes atom percent excess to a fraction, 0.81 accounts for the retention of \(^{13}\text{CO}_2\) in the bicarbonate pool, and 0.79 for the loss of the 2 \(^{13}\text{C}\) label of leucine in tricarboxylic acid cycle exchange reactions.\(^{23}\) Nonoxidative leucine disposal, an index of protein synthesis, was calculated from the difference between leucine rate of appearance and oxidation. Indirect calorimetry was not performed on one HF patient because of abnormal breathing patterns related to claustrophobia caused by the ventilated hood. Thus, oxidative and nonoxidative leucine disposal data were not calculated on this patient.

### Body Composition

Body mass was measured on a digital scale (Scale-Tronix, Inc, Wheaton, IL). Fat mass and fat-free mass were measured by dual energy x-ray absorptiometry, using a Lunar DPX-L densitometer (Lunar Co, Madison, WI).

### Hormones and Cytokines

Norepinephrine and epinephrine levels were measured using a radioenzymatic assay, as described previously,\(^{24}\) with an interassay coefficient of variability (CV) of 10% for norepinephrine and 16% for epinephrine. Norepinephrine data for one HF patient were omitted as an outlier (10.2 pg/mL). Insulin levels were determined by radioimmunoassay (Linco Research Inc, St. Charles, MO), with an interassay CV of 7.4%. Insulin-like growth factor-1 (IGF-1) was measured by radioimmunoassay (ALPCO, Windham, NH) with an interassay CV of 5%. C-reactive protein (CRP) was measured by enzyme-linked immunosorbent assay (ELISA), with an interassay CV ranging from 2% to 4%. TNF-\(\alpha\) and IL-6 plasma concentrations and soluble receptors levels (TNF-\(\alpha\), sRII and IL-6 sR, respectively) were measured by ultra-sensitive ELISA assays (R&D Systems, Minneapolis, MN) with interassay CVs of 16% and 6% for TNF-\(\alpha\) and IL-6 concentration and 9% and 10% for their respective receptors. Cortisol was determined by radioimmunoassay (Diagnostic Products Co, Los Angeles, CA), with an interassay CV of 8.7%.

### Resting Energy Expenditure (REE)

REE and substrate use were measured using the ventilated hood technique (DeltaTrac). The average of measurements taken at 60 and 195 minutes during the infusion was calculated. Leucine oxidation data were used to estimate protein oxidation, and rates of carbohydrate and fat oxidation (mg/min) were calculated according to standard equations, as described previously.\(^{25}\) In addition to direct measurements, we predicted REE from fat-free mass (kg) in all volunteers using the equation: \( \text{REE (kcal/d)} = (14 \times \text{fat-free mass}) + 804. \)\(^{26}\) HF patients were then divided into groups with normal or elevated (high) REE for their metabolic body size. High REE was defined as \( \geq20\% \) above predicted values. The basis for using 20% as a cutoff was derived from previous studies that have shown elevations in REE in HF patients on the order of 15%.\(^{27}\) Thus, a cutoff of \( \geq20\% \) should be sufficient to identify those patients with resting hypermetabolism. Indirect calorimetry was not performed on one HF patient, because of abnormal breathing patterns related to claustrophobia caused by the ventilated hood.

### Statistical Analysis

Differences between groups were determined by unpaired, Student’s \( t \)-tests or Mann-Whitney \( U \)-tests, depending on the distributional characteristics of the variable. For subgroup analyses, parametric or nonparametric (Kruskal-Wallis H statistic) analysis of variance models were used. Individual leucine metabolism and REE data were statistically adjusted for fat-free mass using a regression-based approach, as described previously.\(^{28}\) Relationships between variables were assessed using Pearson correlation coefficients. Variables that were not normally distributed (eg, cytokines) were log\(_{10}\) transformed before correlation analysis. Distributional assumptions of log\(_{10}\)-transformed variables were verified using the Shapiro-Wilk test. All analyses were conducted with SPSS software 9.0 (SPSS Inc, Chicago, IL). All values are mean \( \pm \) SE.

### RESULTS

Physical characteristics are shown in Table I. No differences in age, body size, or body composition were noted between groups. Similar results were observed when 2 controls with coronary artery disease were excluded from the analyses. Peak aerobic capacity (\( \text{VO}_3 \)) was lower \(( p < .01) \) in HF patients \((26.9 \pm 2.5 \text{ mL/kg FFM/min})\) compared with controls \((43.3 \pm 2.0 \text{ mL/kg FFM/min})\).

Leucine metabolism data, statistically adjusted for differences in fat-free mass, are shown in Figure 1. No differences in leucine rate of appearance (HF: 132 \( \pm 8 \text{ vs \ control (C): 127 \pm 4 \mu\text{mol/min}} \), nonoxidative leucine disposal (HF: 111 \( \pm 8 \text{ vs \ C: 106 \pm 4 \mu\text{mol/min}} \), or

<table>
<thead>
<tr>
<th>Physical characteristics*</th>
<th>Heart Failure</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63 ( \pm 3 )</td>
<td>70 ( \pm 3 )</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175 ( \pm 1 )</td>
<td>174 ( \pm 2 )</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>80 ( \pm 4 )</td>
<td>80 ( \pm 5 )</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>18 ( \pm 2 )</td>
<td>18 ( \pm 3 )</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>59 ( \pm 2 )</td>
<td>58 ( \pm 3 )</td>
</tr>
</tbody>
</table>

\*Data are mean \( \pm \) SE.
Leucine oxidation (HF: 20 ± 2 vs C: 21 ± 2 μmol/min) were found between groups. Similar results were observed when 2 controls with coronary artery disease were excluded from the analyses. No differences were found between groups in plasma leucine concentration (HF: 120 ± 7 vs C: 131 ± 6 μmol/L).

Although REE was slightly elevated in HF patients compared with controls (HF: 1887 ± 80 vs C: 1664 ± 82), this difference did not reach statistical significance (p = .12). The magnitude elevation in REE, however, is similar to what we have reported previously in a group of HF patients with similar body size and composition.29 No differences in respiratory quotient (HF: 0.791 ± 0.021 vs C: 0.783 ± 0.011), carbohydrate (HF: 87 ± 21 vs C: 75 ± 10 mg/min), or fat oxidation (HF: 97 ± 11 vs C: 91 ± 7 mg/min) were noted.

We divided HF patients into groups with normal and high REE for their metabolic body size (i.e., fat-free mass) in an attempt to identify patients with elevated rates of protein turnover. Criteria for these group designations are provided in the REE portion of the Methods section. We identified 4 patients with high and 5 with normal REE (Table II). REE was greater (p < .05) in high-REE patients compared with normal-REE patients and controls. The average relative increase above predicted REE was greater in the high-REE group compared with the normal-REE group and controls (p < .01). After statistical adjustment for differences in fat-free mass, REE remained greater (p < .01) in high-REE vs normal-REE patients and controls. No differences in respiratory quotient or substrate oxidation were found.

Leucine metabolic data in patients with high REE and normal REE and controls are shown in Figure 2. All measures were statistically adjusted for fat-free mass. Leucine rate of appearance showed a strong trend (p = .06) toward being greater in high REE (146 ± 6) compared with normal REE (120 ± 8) and controls (127 ± 4 μmol/min). No differences in leucine oxidation (high REE: 23 ± 2 vs normal REE: 19 ± 2 vs C: 21 ± 2 μmol/min; p = .49) or nonoxidative disposal (high REE: 123 ± 5 vs normal REE: 101 ± 12 vs C: 106 ± 4 μmol/min; p = .16) were found.

Differences in circulating anabolic and catabolic hormones and cytokines among HF patients with high REE, normal REE, and controls are shown in Table III. No differences were found in norepinephrine, epinephrine, insulin, CRP, tumor necrosis factor (TNF)-α, or cortisol levels among groups. IGF-1 was greater in

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**Table II**

Resting energy expenditure (REE) and substrate oxidation in heart failure patients with high and normal REE and controls*  

<table>
<thead>
<tr>
<th></th>
<th>Normal REE</th>
<th>High REE</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>5</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Measured REE (kcal/d)</td>
<td>1664 ± 72</td>
<td>2030 ± 73†</td>
<td>1664 ± 82</td>
</tr>
<tr>
<td>Predicted REE (kcal/d)</td>
<td>1654 ± 51</td>
<td>1592 ± 35</td>
<td>1623 ± 37</td>
</tr>
<tr>
<td>Difference between measured and predicted REE (%)</td>
<td>1 ± 3</td>
<td>27 ± 3‡</td>
<td>2 ± 3</td>
</tr>
<tr>
<td>Adjusted REE (kcal/d)</td>
<td>1614 ± 61</td>
<td>2083 ± 68‡</td>
<td>1667 ± 41</td>
</tr>
<tr>
<td>Respiratory quotient</td>
<td>0.804 ± 0.036</td>
<td>0.775 ± 0.018</td>
<td>0.783 ± 0.011</td>
</tr>
<tr>
<td>Carbohydrate oxidation (mg/min)</td>
<td>93 ± 37</td>
<td>79 ± 19</td>
<td>75 ± 10</td>
</tr>
<tr>
<td>Fat oxidation (mg/min)</td>
<td>83 ± 14</td>
<td>116 ± 13</td>
<td>91 ± 7</td>
</tr>
</tbody>
</table>

*Values are mean ± SE. Heart failure patients were divided into groups with normal and high REE relative to their predicted REE for their metabolic body size, as described in the Methods section. Adjusted REE represents measured REE after statistical adjustment for fat-free mass; †p < .05 and ‡p < .01, high REE greater than normal REE and controls.
normal-REE patients compared with high-REE patients and controls (p = .02). Both TNF-α RII and IL-6sR were greater in normal- and high-REE patients compared with controls (both p < .05). When HF patients were considered as a single group (n = 10), as expected, there were higher levels of CRP (p = .05), TNF-α RII (p < .05), IL-6 (p < .01) and IL-6sR (p < .01). No differences in circulating norepinephrine, epinephrine, insulin, IGF-I, TNF-α, or cortisol were found.

Correlations between leucine metabolism variables and hormones in HF patients are shown in Table IV. IGF-1 levels were negatively related to leucine oxidation (p < .01). In addition, leucine oxidation was positively related to IL-6sR (p < .01). Scatterplots for these relationships are shown in Figure 3.

**DISCUSSION**

Increased rates of protein turnover were not evident when HF patients were considered as a single homogeneous group, suggesting that HF, per se, does not alter protein metabolism. Despite the absence of group differences, there was considerable variability in protein metabolism in HF patients (eg, variance of protein breakdown and synthesis was twice that of controls). To explore the nature of this variability and to identify patients that might exhibit elevated rates of protein turnover, we divided patients into groups with normal and elevated REE for their metabolic body size. The rationale behind this approach is that increased REE often accompanies increased protein turnover in disease states characterized by cachexia.30,31 This may be due to the fact that catabolic hormones thought to induce cardiac cachexia increase both thermogenesis and protein turnover.18,19 After patients were divided into groups with normal and high REE, a strong trend (p = .06) toward increased (15%–22%) protein breakdown was found in those patients with resting hypermetabolism. Although these group differences did not reach statistical significance, the magnitude increase in protein breakdown was similar to findings in other cachectic conditions.17,32 This type of heterogeneity in protein metabolism among HF patients is consistent with variability in protein turnover observed in other disease states characterized by cachexia.33 More importantly, the fact that increased REE and protein breakdown segregate in this subgroup of patients suggests that they could be at greater risk for developing cachexia.

Our findings differ from other studies that have found reduced whole-body protein turnover in HF.34,35 Divergent results among studies are likely due to the different conditions under which protein metabolism was measured. Morrison et al34 found reduced rates of protein turnover in HF patients studied after inpatient clinical management. Because hospitalization is accompanied by bedrest and malnutrition,36 2 factors

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### Table III

Catabolic and anabolic hormones and cytokines in heart failure patients with high and normal REE and controls*

<table>
<thead>
<tr>
<th></th>
<th>Normal REE</th>
<th>High REE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (µg/mL)</td>
<td>302 ± 78</td>
<td>372 ± 95</td>
</tr>
<tr>
<td>Epinephrine (µg/mL)</td>
<td>50 ± 16</td>
<td>23 ± 6</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>14.0 ± 2.0</td>
<td>12.0 ± 2.3</td>
</tr>
<tr>
<td>Insulin-like growth factor-1 (ng/mL)</td>
<td>179 ± 28</td>
<td>120 ± 27</td>
</tr>
<tr>
<td>CRP (µg/mL)</td>
<td>5.14 ± 2.12</td>
<td>5.12 ± 2.11</td>
</tr>
<tr>
<td>TNF-α (ng/mL)</td>
<td>1.75 ± 0.17</td>
<td>2.20 ± 0.76</td>
</tr>
<tr>
<td>IL-6 (ng/mL)</td>
<td>3758 ± 414</td>
<td>3730 ± 636</td>
</tr>
<tr>
<td>IL-6sR (ng/mL)</td>
<td>3.20 ± 0.90</td>
<td>5.17 ± 1.47</td>
</tr>
<tr>
<td>Cortisol (µg/dL)</td>
<td>20.4 ± 1.5</td>
<td>18.8 ± 2.9</td>
</tr>
</tbody>
</table>

*Data are mean ± SE. For norepinephrine data, n = 3 for high REE group. ‡p = .02, Normal REE greater than high REE and controls; ‡p < .05, high REE and normal REE greater than controls; ‡p < .02, high REE greater than control.

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### Table IV

Correlations of leucine metabolism variables to anabolic and catabolic hormones in heart failure patients*

<table>
<thead>
<tr>
<th></th>
<th>Rate of Appearance of Leucine</th>
<th>Nonoxidative Leucine Disposal</th>
<th>Leucine Oxidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>0.293</td>
<td>0.520</td>
<td>−0.553</td>
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<tr>
<td>Epinephrine</td>
<td>−0.193</td>
<td>0.072</td>
<td>0.377</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.333</td>
<td>0.429</td>
<td>−0.512</td>
</tr>
<tr>
<td>Insulin-like growth factor-1</td>
<td>−0.254</td>
<td>−0.111</td>
<td>−0.751†</td>
</tr>
<tr>
<td>CRP</td>
<td>0.362</td>
<td>0.409</td>
<td>−0.266</td>
</tr>
<tr>
<td>TNF-α</td>
<td>−0.036</td>
<td>0.061</td>
<td>0.063</td>
</tr>
<tr>
<td>TNF-α RII</td>
<td>−0.143</td>
<td>−0.147</td>
<td>−0.167</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.095</td>
<td>0.096</td>
<td>−0.988</td>
</tr>
<tr>
<td>IL-6 sR</td>
<td>−0.085</td>
<td>−0.266</td>
<td>0.829‡</td>
</tr>
<tr>
<td>Cortisol</td>
<td>0.249</td>
<td>0.305</td>
<td>−0.221</td>
</tr>
</tbody>
</table>

*Values are Pearson correlation coefficients. CRP, IL-6, and TNF-α data were log10 transformed before correlation analysis. For leucine oxidation, n = 9 patients, and for norepinephrine, n = 9. 
†p < .03; ‡p < .01.
known to decrease protein turnover, their results may relate to factors associated with hospitalization, rather than HF. Cortes et al found a lower rate of whole-body protein synthesis in HF patients compared with controls during 10 hours of oral feeding. These findings are not directly comparable to our study or the work of Morrison et al, however, because these studies examined postabsorptive protein metabolism. Thus, variability in the conditions under which measurements have been conducted prevents conclusions from being drawn regarding the effect of HF on protein metabolism.

We further explored the role of circulating hormones and cytokines on the regulation of whole-body protein metabolism. No differences in hormone levels were found between high-REE and normal-REE groups to explain elevated protein breakdown in the high REE group. Furthermore, in the HF group as a whole, correlations between hormone levels and leucine rate of appearance were not found. Thus, our results argue against the notion that changes in circulating anabolic or catabolic hormones contribute to altered whole-body protein turnover or hypermetabolism.

In contrast to leucine appearance data, leucine oxidation was negatively related to circulating IGF-1 levels. This relationship is in keeping with the effect of IGF-1 to reduce leucine oxidation and suggests that reductions in plasma IGF-1 within the HF population could promote the irreversible loss of protein substrates (ie, increased amino acid oxidation). Such a role for IGF-1 in the regulation of protein metabolism may be relevant to the development of cardiac cachexia in HF patients, considering that some patients exhibit reduced circulating IGF-1 and a diminished IGF-1 response to GH administration. Indeed, these patients are characterized by reduced protein reserves and other features of cardiac cachexia.

We also found a positive relationship between circulating IL-6sR levels and leucine oxidation in HF patients. The role of the IL-6 system in the development of cachexia has been demonstrated repeatedly. The reason why IL-6sR, rather than IL-6, correlated with leucine oxidation, however, is not readily apparent. Recent studies suggest that IL-6sR may facilitate some of the effects of IL-6 at the cellular level. Moreover, because a portion of circulating IL-6sR is generated from proteolytic cleavage of the membrane-bound receptor, it may more closely reflect the action of IL-6 at the level of target tissues. Assuming that circulating IL-6sR levels are, at minimum, an indicator of immune activation in HF patients, the nature of their association to leucine oxidation agrees with studies showing that cytokines increase protein oxidation. Increasing IL-6 and its soluble receptor with increasing disease severity in HF could stimulate protein oxidation.

What do our results reveal about the effect of HF on protein metabolism and their implications for nutrition management? An answer to this question requires that we consider the population from which the data were gathered. Our HF patients had relatively mild to moderate disease and were not characterized by cachexia. Although some might consider it a limitation that we did not study cachectic patients, we view this as a strength of our study because we are certain that alterations in protein metabolism are not a consequence of the cachectic state. In this context, we have identified a subgroup of patients relatively early in the course of the disease that are characterized by resting hypermetabolism and increased protein turnover. Studies are needed to determine whether this phenotype predicts which HF patients develop cachexia over time. Importantly, alterations in anabolic and catabolic hormone levels widely believed to be a cause of cardiac cachexia were not present in those patients with resting hypermetabolism and increased protein turnover. This finding would challenge the notion that endocrine abnormalities associated with the HF syndrome predispose to metabolic abnormalities associated with cachexia, namely, hypermetabolism and excessive protein breakdown. We should point out, however, that endocrine alterations would favor the irreversible disposal of protein substrates (ie, amino acid oxidation) in HF patients (Figure 3). Thus, there may indeed be some role for hormonal abnormalities in the development of cardiac cachexia. The alterations in energy and

**Figure 3.** Relationship of leucine oxidation to insulin-like growth factor-1 (IGF-1; $r = -0.751; p < .03$) and interleukin-6 soluble receptor (IL-6sR; $r = 0.829; p < .01$) in heart failure patients ($n = 9$).
protein metabolism observed in the present study may reflect a constellation of metabolic adaptations to the HF syndrome that predispose to cachexia as the disease progresses, although this hypothesis requires careful longitudinal study for confirmation. Identification of such patients may be advantageous because early nutrition intervention may mitigate the loss of body mass and protein reserves and, in turn, reduce mortality associated with cachexia.7

In summary, our results suggest that altered whole-body protein metabolism is not a generalized feature of the HF syndrome. In a subgroup of patients characterized by resting hypermetabolism, however, there is a trend toward elevated rates of protein turnover. Although we were unable to identify any circulating hormones that were related to increased protein turnover in HF patients, we found correlations between leucine oxidation and both circulating IGF-1 and IL-6sR. Future studies that examine protein metabolism and hormone levels in HF patients over time or under catabolic conditions are needed to clarify whether these metabolic alterations predispose to the development of cardiac cachexia.

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