Altered interorgan response to feeding in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background: Previously, we reported increased values for whole-body protein turnover in patients with chronic obstructive pulmonary disease (COPD) in the postabsorptive state.

Objective: The objective was to investigate whether intake of a carbohydrate-protein meal influences whole-body protein turnover differently in COPD patients and control subjects.

Design: Eight normal-weight patients with moderate COPD and 8 healthy control subjects were examined in the postabsorptive state and after 2 h of repeatedly ingesting a maltodextrin casein-based protein meal (0.02 g · kg body wt \(^{-1}\) · 20 min \(^{-1}\)). Combined simultaneous, continuous, intravenous infusion of \(\lbrack\text{ring-2H}_5\rbrack\)-phenylalanine and \(\lbrack\text{ring-2H}_2\rbrack\)-tyrosine tracer and oral repeated ingestion of \(\text{L-1}^\text{13C}\)-phenylalanine were performed to measure whole-body protein synthesis (WbPS) and first-pass splanchnic extraction of phenylalanine. Endogenous rate of appearance of phenylalanine as the measure of whole-body protein breakdown (WbPB) and net-WbPS was calculated as WbPS − WbPB. Arterialized venous blood was sampled for amino acid enrichment and concentration analyses.

Results: Feeding induced an increase in WbPS and a reduction in WbPB. The reduction in WbPB was larger in the COPD group than in the control group (\(P < 0.05\)) and was related to the lower splanchnic extraction of phenylalanine in the patients. Consequently, net-WbPS increased more after feeding in the COPD group than in the control group (\(P < 0.05\)).

Conclusion: Feeding induces more protein anabolism in normal-weight patients with moderate COPD than in healthy control subjects. This is probably because these COPD patients are characterized by an adaptive interorgan response to feeding to prevent or delay weight loss at this disease stage.


KEY WORDS Chronic obstructive pulmonary disease, protein feeding, first-pass splanchnic extraction, whole-body protein turnover, endogenous protein metabolism

INTRODUCTION

Muscle wasting commonly occurs in patients with chronic obstructive pulmonary disease (COPD), but different patterns of tissue depletion are observed. A substantial part of the COPD population is characterized by a normal weight with a shift in body composition toward reduced fat-free mass (FFM) despite a relative or absolute increase of fat mass (1, 2). In this group, functional capacity (ie, exercise capacity, muscle strength) and health status (3) are even more impaired than in the underweight patients with COPD with a relative preservation of FFM. This body-composition pattern is also seen with aging and could therefore be described as (accelerated) sarcopenia that could be reflected in altered whole-body substrate metabolism. Indeed, we showed a reduced \(\beta\)-adrenoceptor–mediated lipolysis rate (4) and significantly higher amounts of whole-body protein turnover [protein synthesis (WbPS) and protein breakdown (WbPB) rates] in patients with COPD than in healthy, age-matched control subjects after overnight fasting (5). These data indicate that changes in intermediary metabolism are present in normal-weight patients with COPD that may trigger or reflect sarcopenia.

Although altered whole-body substrate turnover was observed in the postabsorptive state, no studies have yet examined the acute effect of feeding on substrate metabolism in COPD. Feeding is important because the fed state represents >50% of the 24-h metabolic activity and corresponds to the reconstitution of the protein lost during fasting. In COPD, the efficiency of maintaining body proteins may be declined as a result of a selective loss in the ability of skeletal muscle to efficiently use exogenous amino acids for protein anabolism. However, it is also possible that the splanchnic area is the compartment that is mainly contributing to the previously observed increased whole-body protein turnover in COPD (5, 6). The splanchnic tissues could limit the flow and the availability of alimentary amino acids to the peripheral tissues by influencing the absorption of the alimentary amino acids. In previous studies it has been shown that the first-pass splanchnic uptake of the amino acids leucine (7) and phenylalanine (8) increases with age. This means that if the splanchnic tissues use more amino acids, fewer amino acids will be available for the other (peripheral) tissues. Until now it was unknown whether chronic disease such as COPD further aggravated the age-related disturbances found in splanchnic extraction

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of amino acids, thereby negatively influencing the metabolic response to feeding in these patients.

Therefore, the purpose of the present study was to examine the response of whole-body protein turnover and splanchnic amino acid extraction to a given dose of a maltodextrin protein meal in patients with COPD. Milk-based protein (casein) was used because of its high nutritional value (protein quality) and because casein is the protein mostly used (and to the highest degree) in nutritional supplements.

SUBJECTS AND METHODS

Subjects

A group of 8 male patients with moderate airflow obstruction and 8 healthy male volunteers were studied. The patients had COPD according to American Thoracic Society guidelines (9) and chronic airflow limitation, defined as measured forced expiratory volume in 1 s (FEV1) < 70% of predicted FEV1. Furthermore, the patients had irreversible obstructive airway disease (<10% improvement of FEV1 predicted baseline after inhalation of β2-agonist) and were in clinically stable condition and had not experienced respiratory tract infection or exacerbation of their disease at least 4 wk before the study. The patients with COPD were outpatients, attending the hospital for routine pulmonary control every 6 or 12 mo. Exclusion criteria were malignancy, cardiac failure, recent surgery, and severe endocrine, hepatic, or renal disorder. Also, subjects who were using systemic corticosteroids within 3 mo before the beginning of the study were excluded. The number of present smokers in the COPD and control groups was 2. The number of former smokers in the COPD and control groups was 5 (average number of years stopped was 10.2) and 2 (average number of years stopped was 20.5), respectively. Body mass index (BMI; in kg/m2) was not significantly different between the groups (control group: 25.4 ± 0.9; COPD group: 27.2 ± 0.8). The maintenance treatment of the studied patients consisted of inhaled β2 agonists, inhaled anticholinergics, inhaled corticosteroids, oral theophylline, or a combination. Written informed consent was obtained from all subjects, and the study was approved by the medical ethics committee of the University Hospital Maastricht.

Pulmonary function tests

All patients and healthy volunteers underwent spirometry to determine FEV1, and the highest value from at least 3 technically acceptable assessments was used. Diffusing capacity of the lung for carbon monoxide was measured by using the single-breath method (Masterlab; Jaeger, Wurzburg, Germany). All values obtained were related to a reference value and expressed as percentages of the predicted value (10).

Study protocol

The protocol started at 0715 after an overnight fast from at least 0000. All subjects were in the supine position for 3 h. After insertion of a catheter into the right antecubital vein, the first blood sample was taken for baseline measurements. Immediately thereafter, a primed-constant intravenous infusion of stable isotopes (80 mL/h) was started with the use of a calibrated pump (IVAC Corporation, San Diego, CA). Primed and constant infusion of the stable isotopes L-[ring-2H4]-phenylalanine(2H4-Phe; prime: 2.19 μmol/kg body wt; infusion: 0.053 μmol · kg FFM—1 · min—1) and L-[ring-2H2]-tyrosine (2H2-Tyr; prime: 0.95 μmol/kg body wt; infusion: 0.018 μmol · kg FFM—1 · h—1) were given through the catheter in the antecubital vein. Primed infusion of L-[ring-2H4]-Tyr (2H4-Tyr; 0.31 μmol/kg body wt) was given in addition through the same catheter. 1-13C-Phe was given orally in the postabsorptive state and together with the liquid meal every 20 min (prime: 0.88 μmol/kg body wt; infusion: 0.055 μmol · kg FFM—1 · min—1).

Stable isotopes were purchased from Cambridge Isotopic Laboratories (Woburn, MA).

For sampling arterialized venous blood, a venous catheter was placed in a dorsal vein of the left hand, using the heated box technique (11), a technique to mimic direct arterial sampling. After 1.5 h of stable isotope infusion to reach steady state enrichments, enteral nutrition was started by sip feeding every 20 min, for a total duration of 2 h. The test meal involved a liquid casein-based protein meal and was given in an amount of 0.018 g · kg body wt—1 · 20 min—1. Total fluid intake was 0.67 mL · kg body wt—1 · 20 min—1 by enteral nutrition. Arterialized venous blood samples were taken at 80, 85, 90, 200, 205, and 210 min into infusion. Body composition was measured with the use of Bioelectrical Impedance Spectroscopy (BIS Xitron 4000B; Xitron Technologies, San Diego, CA) to express protein metabolism data per kilogram of FFM. FFM of the patients with COPD was calculated by using a patient’s specific regression equation as described by Steiner et al (12), whereas FFM of the healthy control subjects was calculated by using a specific equation for elderly men as described by Lukaski et al (13).

Enteral protein meals

To avoid metabolic changes as a result of recent modifications of the diet, the subjects were instructed to eat their usual diet at least 3 d before the study. The dietary protein intake of the study subjects was ascertainment retrospectively during 5 d by using the dietary history method (COPD group: 0.95 ± 0.10 g protein · kg body wt—1 · d—1, control group: 0.96 ± 0.07 g protein · kg body wt—1 · d—1).

The test meal on the experimental day consisted of 29.5 g sodium caseinate (casein protein meal: 4.0 g N) and 68.5 g maltodextrin dissolved in ultrapure water to 1000 mL fluid at 60 °C. For amino acid analysis, 301 mL enteral nutrition and 8.1 g protein (based on a 75-kg subject) was supplied during the study. The protein composition of the casein protein meal was a 1:1:1 mixture of commercially available French, Dutch, and Danish sodium caseinates. All meals were prepared at least 1 h before the start of the experiment. To ensure a complete dissolution of the proteins and to prevent bacterial growth, the meals were kept at 4 °C until use.

Sample processing

Analysis of arterialized venous blood

Promptly after sampling, blood was distributed in prechilled, heparinized tubes (Becton Dickinson Vacutainer System, Franklin Lakes, NJ) and kept on ice to minimize enzymatic reactions. All analyses were performed in plasma, obtained by centrifugation of whole blood at 4 °C for 10 min at 3120 × g. For amino acid analysis, 250 μL plasma was deproteinized by mixing it with 20 mg dry sulfosalicylic acid. For analysis of urea, glucose, lactate, and ammonia, 900 μL plasma was deproteinized by mixing with 90 μL of a 500 g/L trichloroacetic acid solution. All samples were stored at −80 °C until further analysis.
Biochemical analysis

The enrichments (tracer-to-tracee ratios) of the amino acids phenylalanine and tyrosine in arterialized venous plasma were analyzed by a liquid chromatography–mass spectrometry system (Thermoquest LCQ, Veennendaal, The Netherlands) (14). Plasma concentrations of amino acids were determined with the use of a fully automated HPLC (Pharmacia, Woerden, The Netherlands), after precolumn derivatization with o-phthalaldehyde (15).

Plasma glucose, lactate, urea, and ammonia were analyzed spectrophotometrically on a COBAS Mira S (Roche Diagnostics, Hoffmann-La Roche, Basel, Switzerland) by standard enzymatic methods (16). Plasma insulin was analyzed with a commercially available electrochemiluminescence immunoassay (Hitachi Modular Analyzer; Roche, Mannheim, Germany).

Calculations

The sum of amino acids (SUM AA) represents the sum of measurable α-amino acids (glutamine, glycine, threonine, histidine, citrulline, alanine, taurine, arginine, α-amino butyric acid, tyrosine, valine, methionine, isoleucine, phenylalanine, tryptophan, leucine, ornithine, and lysine). All the metabolic data were determined under steady state conditions. Tracer:tracee of phenylalanine reached an isotopic steady state within 1.5 h of infusion and within 2 h of feeding (data not shown) in both groups.

In the postabsorptive and prandial state, WbPS is calculated as follows (5):

$$WbPS = \text{whole-body Rd of Phe} - \text{hydroxylation of Phe to Tyr} \quad (1)$$

Whole-body rate of disappearance (Rd) of phenylalanine is equal to whole body rate of appearance (Ra) of phenylalanine under steady state. Whole-body Ra of phenylalanine (Ra_{2H5-Phe}) is the infusion rate/tracer:tracee of phenylalanine in plasma.

Splanchnic extraction (SPEPhe) represents the fraction (in %) of ingested phenylalanine, taken up by the gut and liver during its first pass and is calculated as follows (8, 17):

$$SPE_{\text{Phe}} = \left[1 - \left(\frac{Ra_{2H5-Phe}}{Ra_{13C-Phe}}\right)\right] \times 100\% \quad (2)$$

Ra_{2H5-Phe} and Ra_{13C-Phe} represent whole-body Ra of phenylalanine calculated from intravenous \(^{2}H_{5}\)-Phe and intragastric \(^{13}C\)-Phe isotopes, respectively.

Whole-body Ra of phenylalanine, not coming from phenylalanine in protein given by the diet [endogenous phenylalanine (Ra_{end-Phe})], is calculated as in equations (3) and (4).

Corrected Phe intake = dietary Phe intake \times [1 - (SPE_{\text{Phe}} \times 0.01)] \quad (3)

Ra_{end-Phe} = Ra_{2H5-Phe} - \text{corrected dietary Phe intake} \quad (4)

$$WbPB = Ra_{end-Phe} \quad (5)$$

netWbPS = WbPS - WbPB \quad (6)

Summary model used for the calculation of SPE of phenylalanine and protein kinetics is presented in Figure 1. Phenylalanine clearance is the amount of plasma that is completely cleared from tracee in 1 min and is calculated as follows (18):

$$Rd (Ra \text{ in steady state)/plasma concentration of the tracee} \quad (7)$$

Statistical analysis

Results are expressed as means ± SEs. The mean value of the measures of protein kinetics and the concentrations of amino acids at the time points 80, 85, and 90 min was used as the postabsorptive state and at 200, 205, and 210 min as the fed state. The unpaired Student’s t test was used to determine differences in general characteristics between the control and COPD groups and to test whether the changes in status (postabsorptive and prandial) in protein kinetics and amino acid concentrations were significantly different from zero. If the normality or equal variance test failed, data were log-transformed where appropriate. Furthermore, the two-factor analysis of variance (ANOVA; general linear model, SPSS version 12; SPSS Inc, Chicago, IL) was performed with a group (control and COPD) and status (postabsorptive and prandial) effect. The level of significance was set at P < 0.05, and P values are given for the group effect, status effect, and the group-by-status interaction. When an overall significance for group-by-status interaction was observed, unpaired Student’s t test was performed.

RESULTS

Eight male patients with COPD and 8 male healthy volunteers participated in the study (Table 1). Age, height, body weight, and BMI did not differ significantly between the groups, but a tendency toward a lower FFM index (NS) and higher fat mass index (NS) was found in the COPD group. In the control group, all lung function values were within the normal range. The patients with
feeding, although there was a tendency toward a reduction (\(\text{P} < 0.05\)). Moreover, feeding resulted in a decrease in SPE (\(\text{P} < 0.05\)) and an increase in WbPS (\(\text{P} < 0.05\)). The feeding-induced increase in WbPS (\(\Delta\text{WbPS}\)) was not different between the COPD and control groups. WbPB (Ra\(_{\text{end-Phe}}\); \(\text{P} < 0.01\)) was lower after feeding. The feeding-induced reduction in WbPB (\(\Delta\text{WbPB}\)) was significantly larger (\(\text{P} < 0.05\)) in the COPD group than in the control group. As a consequence, feeding resulted in a significant increase in netWbPS (\(\text{P} < 0.001\)). The increase in netWbPS (\(\Delta\text{netWbPS}\)) was higher in the COPD group than in the control group (\(\text{P} < 0.05\)), resulting in higher absolute values for netWbPS in the prandial state in the COPD group than in the control group (\(\text{P} < 0.05\)).

Phenylalanine concentration and phenylalanine clearance were not different between the COPD and control groups in the postabsorptive state. No significant group-by-status interaction was observed for both variables. There was a status effect for phenylalanine concentration (\(\text{P} < 0.001\)), indicating that feeding resulted in an increase in phenylalanine concentration. The increase in phenylalanine concentration after feeding (\(\Delta\text{Phe conc}\)) was higher in the control group than in the COPD group (\(\text{P} < 0.05\)). These findings were also present for SUM AA (data not shown). There was a status effect (\(\text{P} < 0.001\)), and, in addition, there was a tendency toward a difference in SUM AA between the COPD and control groups (\(\text{P} = 0.085\)). A group effect was observed for phenylalanine clearance (\(\text{P} < 0.01\)), indicating that phenylalanine clearance was lower in the COPD group than in the control group.

**DISCUSSION**

The ability to obtain homeostatic regulation of protein metabolic processes during the day is important to preserve muscle mass and to function long term. Insight into the protein metabolic response to feeding is of importance in COPD because low-intensity exercise has been shown to induce an increased amino acid release from muscle (19). This finding suggests that physical activity in daily life may induce protein catabolism in COPD. To maintain protein balance on a daily basis and to prevent muscle wasting in COPD for the longer term, a positive protein metabolic response to feeding is therefore of crucial importance. In the present study, feeding increased net WbPS to a higher extent in normal-weight patients with moderate COPD than in healthy control subjects, indicating an enhanced anabolic response to feeding in this patient group.

**TABLE 1**

Characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Control group ((n = 8))</th>
<th>COPD group ((n = 8))</th>
</tr>
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<tbody>
<tr>
<td>Age (y)</td>
<td>63.1 ± 3.0</td>
<td>68.1 ± 3.5</td>
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<tr>
<td>Height (m)</td>
<td>1.74 ± 0.02</td>
<td>1.74 ± 0.03</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.5 ± 3.7</td>
<td>81.8 ± 3.5</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>25.4 ± 0.9</td>
<td>27.2 ± 0.8</td>
</tr>
<tr>
<td>FFMI (kg/m(^2))</td>
<td>19.4 ± 0.9</td>
<td>17.7 ± 0.4(^a)</td>
</tr>
<tr>
<td>FMI (kg/m(^2))</td>
<td>6.1 ± 1.4</td>
<td>9.5 ± 0.8(^8)</td>
</tr>
<tr>
<td>FEV(_1) (% of predicted)</td>
<td>110 ± 5</td>
<td>50 ± 4(^a)</td>
</tr>
<tr>
<td>DLCO (% of predicted)</td>
<td>104 ± 9</td>
<td>78 ± 7(^a)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.7 ± 0.4</td>
<td>8.7 ± 3.9(^a)</td>
</tr>
</tbody>
</table>

\(^a\) All values are \(\bar{x} \pm \text{SEM}\). COPD, chronic obstructive pulmonary disease; FFMI, fat-free mass index (fat-free mass/height\(^2\)); FMI, fat mass index (fat mass/height\(^2\)); FEV\(_1\), forced expiratory volume in 1 s; DLCO, diffusing capacity of the lung for carbon monoxide; CRP, C-reactive protein.

**TABLE 2**

Plasma concentrations of glucose, lactate, urea, and ammonia in arterialized blood in the postabsorptive state and during feeding

<table>
<thead>
<tr>
<th></th>
<th>Control group ((n = 8))</th>
<th>COPD group ((n = 8))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Postabsorptive Prandial</td>
<td>Postabsorptive Prandial</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.4 ± 0.1</td>
<td>6.3 ± 0.1</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>5.2 ± 0.4</td>
<td>4.6 ± 0.3</td>
</tr>
<tr>
<td>Ammonia (μmol/L)</td>
<td>88 ± 3</td>
<td>78 ± 7</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>8.4 ± 1.2</td>
<td>21.5 ± 3.4</td>
</tr>
</tbody>
</table>

\(^a\) All values are \(\bar{x} \pm \text{SEM}\). COPD, chronic obstructive pulmonary disease. Data show postabsorptive values and values 2 h after the start of feeding. Two-factor ANOVA showed a significant status effect for glucose and insulin (\(\text{P} < 0.001\)). There was no significant group effect and no significant group-by-status interaction.
Effect of feeding on WbPS

Feeding induced an increase in WbPS, which is in line with data obtained in previous studies that showed a positive effect of mixed feeding on protein synthesis (20, 21). In the present study, 0.11 g protein/kg body wt was ingested in 2 h. On the basis of the fed state of 16 h/d, 0.87 g protein/kg body wt will be ingested, which is in line with the current recommended dietary allowances in the elderly (0.8 g protein · kg body wt \(^{-1} \cdot \)d \(^{-1}\)) (22) and slightly lower than the recorded daily dietary protein intake of the study groups. Earlier, it has been shown that to increase peripheral protein synthesis, high amino acid availability is important (23, 24). We observed a status effect for protein synthesis and the concentration of phenylalanine and SUM AA, indicating that feeding increased systemic amino acid availability and protein synthesis. However, despite the lower feeding-induced increase in the phenylalanine concentration in COPD, the increase in protein synthesis was not different between the groups.

First-pass splanchnic extraction of phenylalanine

The splanchnic tissues play an important role in the regulation of protein turnover because these tissues are responsible for absorption of the alimentary amino acids and their release to the peripheral tissues. In a study that compared elderly subjects with young healthy subjects, first-pass SPE of dietary leucine was twice as high in the elderly as in the young men (7). In line, a study by Volpi et al (8) showed that the SPE of oral phenylalanine was higher in the elderly than in the young. The exact reason for the elevated SPE of amino acids in the elderly is still unknown. However, it is believed that it may contribute to the development of sarcopenia because it reduces amino acid availability to the periphery.

We also measured SPE of phenylalanine after 2 h of feeding in the patients with COPD and the healthy control subjects using free 1-\(^{13}\)C-Phe given orally and together with the liquid meal. Because the meal as well as the oral tracers was administered in the same continuous feeding protocol, no differences in absorption kinetics between phenylalanine in the meal and the oral 1-\(^{13}\)C-Phe are expected. The data of Volpi et al (8) on SPE of phenylalanine in the healthy elderly are a bit higher than ours (47 ± 3% compared with 35 ± 7%). However, the meal composition used in the 2 studies was different (oral amino acid mixture compared with maltodextrin protein meal). Interestingly, there was a group effect for SPE of phenylalanine. SPE was lower in the patients with COPD than in the control group, indicating that there is lower phenylalanine extraction by the gut, liver, or both during feeding in the patients, which could lead to a higher peripheral availability of dietary phenylalanine. Therefore, it was expected that the lower SPE in COPD would induce a higher prandial phenylalanine concentration in these patients. In the present study, a feeding effect for phenylalanine concentration but no group effect was observed. Remarkably, the increase in phenylalanine concentration after feeding was lower in the COPD group than in the control group. As systemic phenylalanine concentration is mainly the result of the capacity of phenylalanine utilization for protein synthesis and hydroxylation, this finding suggests that, besides an increased phenylalanine release in the circulation, there is an increased phenylalanine removal from the circulation in COPD. In contrast, phenylalanine clearance was lower in the COPD group than in the control group and was not affected by feeding. We do not have a good explanation for this observation.

The lower SPE of phenylalanine in the COPD group was associated with a larger reduction of endogenous Ra of phenylalanine after feeding. Endogenous Ra of phenylalanine allows an accurate estimation of WbPB, because dietary phenylalanine sequestered by splanchnic tissues during the first pass cannot reach the metabolic pool where \(^{2}\)H\(_{2}\)-Phe is infused. The data suggest that the lower SPE in COPD positively influences their anabolic response to a given meal, and that the metabolic efficiency of feeding is therefore larger in the COPD group than in the control subjects.

Possible factors inducing a lower first-pass splanchnic extraction in COPD

At present, we can only speculate about possible mechanisms of the reduced SPE in COPD. Besides an adaptation to increased needs in the body elsewhere as mentioned previously, it is also possible that the reduced SPE in COPD is reflecting a reduced

| TABLE 3 | Measures of protein metabolism in the postabsorptive state and during feeding\(^1\) |
|----------------------------------------------|-----------------------------------------------|---------------------------------|-----------------------------------------------|
| | Control group | | COPD group |
| | (\(n = 8\)) | | (\(n = 8\)) |
| | Postabsorptive | Prandial | Postabsorptive | Prandial |
| WbPS (nmol · kg FFM \(^{-1} \cdot \)min \(^{-1}\)) | 727 ± 68 | 826 ± 64 | 805 ± 49 | 948 ± 43 |
| SPE (%) | 58 ± 7 | 45 ± 4 | 35 ± 7 | 28 ± 3 |
| WbPB (nmol · kg FFM \(^{-1} \cdot \)min \(^{-1}\)) | 803 ± 62 | 695 ± 50 | 892 ± 49 | 712 ± 50 |
| NetWbPS (nmol · kg FFM \(^{-1} \cdot \)min \(^{-1}\)) | −82 ± 11 | 156 ± 22 | −87 ± 7 | 226 ± 16\(^2\) |
| Pheconc (µmol/L) | 67 ± 3 | 85 ± 2 | 67 ± 3 | 79 ± 3 |
| Pheclear (µL · kg FFM \(^{-1} \cdot \)min \(^{-1}\)) | 8.4 ± 0.7 | 9.5 ± 0.5 | 7.3 ± 0.3 | 7.7 ± 0.3 |

\(^1\) All values are \(x \pm \) SEM. COPD, chronic obstructive pulmonary disease. Data show postabsorptive values and values 2 h after the start of feeding. WbPS, whole-body protein synthesis; SPE, relative splanchnic extraction of phenylalanine; WbPB, whole-body protein breakdown (reflecting rate of appearance of endogenous phenylalanine); NetWbPS, whole-body protein synthesis; Pheconc, phenylalanine concentration; Pheclear, phenylalanine clearance. Two-factor ANOVA showed a significant group effect for WbPS and NetWbPS (\(P < 0.05\)), Pheclear (\(P < 0.01\)), and SPE (\(P < 0.001\)). There was a significant status effect for WbPS and SPE (\(P < 0.05\)), WbPB (\(P < 0.01\)), and NetWbPS and Pheconc (\(P < 0.001\)). There was a significant group-by-status interaction for NetWbPS (\(P < 0.05\)).

\(^2\) Significantly different from the control group in the prandial state, \(P < 0.05\) (unpaired Student’s \(t\) test).
splanchnic protein turnover rate rather than a reduced splanchnic amino acid net utilization. However, the possibility that the splanchnic (liver + gut) protein turnover is reduced in COPD is remarkable when considering that this patient group is generally characterized by a low-grade systemic inflammatory state. In line, C-reactive protein concentrations tended to be higher in the studied patients with COPD than in the control subjects. However, because inflammation is associated with an increased hepatic protein synthesis, one should expect an elevated (but not reduced) protein synthesis in the splanchnic liver compartment in COPD. Other factors known to influence splanchnic protein turnover are nicotine use and intake of certain drugs. Nicotine can act as a splanchnic circulation constrictor because it has been shown that smoking aggravates liver injury and that intraportal nicotine infusion in rats decreases hepatic blood flow. However, smoking status and history were not different between the COPD and control groups. The studied patients were clinically stable for at least 3 mo before the study, exhibiting normal blood gases and only using inhalation medication. Still, it is important to highlight that this patient group is regularly experiencing an acute exacerbation of the disease, which is characterized by an increased inflammatory state, changes in blood gases, and use of systemic medication (i.e., oral corticosteroids and antibiotics). Nonsteroidal anti-inflammatory drugs are known to reduce blood flow in the splanchic region. Acute changes in the arterial partial pressures of oxygen and carbon dioxide do not reduce splanchnic blood flow but together with an increased inflammatory state may induce changes in insulin sensitivity and thus influence protein metabolism. A positive association has been found between SPE of dietary leucine and BMI. Currently, no relation was found between SPE of dietary phenylalanine and body weight or composition. However, it is important to notice that only normal-weight patients with COPD were studied without evidence of muscle wasting.

More research is warranted to get insight into the underlying factors responsible for the lower SPE of amino acids in COPD. The gut plays an important role as buffer of amino acids during fasting. The elevated initial release of amino acids into the arterial blood after feeding is a larger reduction of WbPB after feeding. This study was designed and data collection and analysis and reviewing the manuscript. None of the authors had a financial or personal interest in any company or organization sponsoring the research, including advisory board affiliations.  

REFERENCES


