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Resting energy expenditure and protein turnover are increased in patients with severe chronic obstructive pulmonary disease

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ABSTRACT

The mechanisms leading to weight loss in patients with chronic obstructive pulmonary disease (COPD) are poorly understood. Changes in protein metabolism and systemic inflammation may contribute to increased resting energy expenditure (REE) in COPD, leading to an energy imbalance and loss of fat and fat-free mass. The objective of this study was to determine first whether REE was increased in patients with COPD and, second, whether this was associated with increased protein turnover and/or systemic inflammation. Resting energy expenditure was determined using indirect calorimetry in 14 stable outpatients with severe COPD (7 with low and 7 with preserved body mass indices) and 7 healthy controls. Endogenous leucine flux, leucine oxidation, and nonoxidative disposal, indices of whole-body protein breakdown, catabolism, and synthesis, were measured using intravenous infusions of ^{13}C-bicarbonate and 1-^{13}C-leucine. Total body water, from which fat-free mass and fat mass were calculated, was determined using an intravenous bolus of deuterated water. Plasma markers of systemic inflammation were also measured. As a group, subjects with COPD had increased REE adjusted for fat-free mass ($P < .001$) and faster rates of endogenous leucine flux ($P = .006$) and nonoxidative leucine disposal ($P = .002$) compared with controls. There was a significant correlation between REE and both endogenous leucine flux ($P = .02$) and nonoxidative leucine disposal ($P = .008$). Plasma concentrations of the inflammatory markers C-reactive protein and interleukin-6 were not different between COPD subjects and controls. Increased rates of protein turnover are associated with increased REE and loss of fat-free mass in COPD.

1. Introduction

Weight loss and peripheral muscle wasting and dysfunction are common findings in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and are associated with poor quality of life [1], impaired exercise tolerance, and increased mortality [2]. In general, weight loss occurs when there is an imbalance between energy intake and energy

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expenditure. However, decreased intake does not seem to be the primary cause of weight loss in COPD [3]. Increased resting energy expenditure (REE) has been found in some patients with COPD [4,5], suggesting that it may also contribute to weight loss.

Increased REE in COPD may result from systemic inflammation. Evidence of systemic inflammation, including increased concentrations of proinflammatory cytokines such as tumor necrosis factor–α (TNF-α) [6] and interleukin-6 (IL-6) and acute phase proteins such as C-reactive protein (CRP) [7], has been found in patients with COPD and muscle wasting. In addition, changes in macronutrient metabolism may also lead to increased REE. Because synthesis and breakdown of muscle protein are primarily responsible for the energy expenditure of resting muscle [8], increased REE in COPD may be associated with increased protein breakdown and/or synthesis. However, studies of in vivo protein metabolism in COPD have had conflicting results. Whereas one study reported that subjects with emphysema had similar rates of protein breakdown but decreased rates of protein synthesis compared with healthy controls [9], another reported increases in both whole-body protein synthesis and breakdown rates, suggesting an overall increase in whole-body protein turnover in subjects with COPD compared with healthy controls [10]. Inflammation and protein breakdown may also be linked, as one study found increased concentrations of inflammatory markers and increased whole-body protein breakdown in COPD patients compared with controls [11]. In this study, we aimed to determine first whether REE was increased in patients with COPD and, second, whether this was associated with increased protein turnover and/or systemic inflammation. Resting energy expenditure, in vivo whole-body protein kinetics, and plasma markers of systemic inflammation were measured in subjects with severe COPD and in healthy controls.

2. Methods

2.1. Subjects

Fourteen clinically stable adult outpatients with severe COPD (postbronchodilator forced expiratory volume in 1 second [FEV_1] <50% of predicted) were enrolled in the study. Seven subjects had body mass index (BMI) less than 21 kg/m^2 (low-BMI group), and 7 subjects had BMI greater than or equal to 21 kg/m^2 (preserved-BMI group). In previous studies, this BMI threshold has been associated with increased risk of mortality [12]. Fat-free mass (FFM) was not determined before enrollment in the study. None of the subjects had suffered from upper respiratory tract infection or exacerbation of disease at least 8 weeks before the study. Exclusion criteria included malignancy; cardiac failure; and severe endocrine, hepatic, or renal disorders. In addition, subjects receiving systemic corticosteroids within 3 months before the study were excluded. Maintenance therapy of the COPD subjects consisted of inhaled β_2-agonists, anticholinergics, and/or corticosteroids.

Seven healthy adult volunteers who were current or former smokers participated in the study as control subjects. All controls had at least a 10-pack-year smoking history. They were all in good health as established by medical history, physical examination, and blood chemistry measurements. They were selected to be similar in age as the COPD patients. All patients and controls were enrolled after written, informed consent was obtained. The study was reviewed and approved by the Institutional Review Board at Baylor College of Medicine in Houston, TX. This study was part of a larger study of metabolic alterations in patients with COPD.

2.2. Isotope tracer infusions

Tracer infusions were performed in all subjects in the adult General Clinical Research Center of Baylor College of Medicine. All tracers were obtained from Cambridge Isotope Laboratories (Woburn, MA), and sterile solutions for intravenous administration were prepared by the investigational pharmacy. After an overnight fast of at least 8 hours, subjects were admitted to the General Clinical Research Center; and an intravenous catheter was placed in an antecubital vein for isotope infusions and a hand vein of the contralateral arm for blood sampling. The hand was heated to arterialize the blood samples. After baseline blood and breath samples were obtained, a primed, constant infusion of ^{13}C-bicarbonate (prime = 7 μmol/kg in COPD subjects and 5 μmol/kg in controls, infusion = 6 μmol/[kg h]) was administered for 2 hours. A larger priming dose was required in the COPD subjects compared with controls because of a larger bicarbonate pool. After 1 hour, an intravenous bolus of deuterium oxide (D_2O) (100 mg/kg) was given; and REE was measured by indirect calorimetry (Deltatrac; Sensormedics, Fullerton, CA) for 0.5 hour. Additional breath samples were obtained at 60, 80, 100, and 120 minutes into the ^{13}C-bicarbonate infusion. After 2 hours, the ^{13}C-bicarbonate infusion was stopped; and a primed continuous infusion (prime = 6 μmol/kg, infusion = 6 μmol/[kg h]) of 1-^{13}C-leucine was started and maintained for 3 hours. Additional blood and breath samples were obtained every 15 minutes during the last 45 minutes of the 1-^{13}C-leucine infusion.

2.3. Additional tests

All subjects with COPD underwent spirometry with determination of FEV_1 and forced vital capacity (FVC) according to the guidelines set by the American Thoracic Society.

2.4. Sample analyses

The blood samples were drawn into tubes containing EDTA or sodium fluoride and potassium oxalate. The tubes were centrifuged immediately at 4°C, and the plasma was removed and stored immediately at –70°C for later analysis. Commercially available enzyme-linked immunosorbent assay kits were used to measure the plasma concentrations of CRP (Millipore, Temecula, CA), TNF-α (R&D Systems, Minneapolis, MN), and IL-6 (R&D Systems); and prealbumin was measured by radial immunodiffusion (The Binding Site Group, Birmingham, UK).

Breath samples were analyzed for ^{13}C abundance in carbon dioxide by gas isotope ratio–mass spectrometry,

with monitoring of ions at *m/z* 44 and 45. The plasma isotopic enrichment of α-ketoisocaproic acid (KICA), a surrogate of intracellular leucine enrichment, was measured by negative chemical ionization gas chromatography–mass spectrometry on its pentafluorobenzyl derivative and monitoring of ions at *m/z* 129 and 130. The $^2H_2$ content of plasma water was measured by reducing water extracted from 10 μL of plasma with zinc in quartz vessels and measuring the $^2H_2$ abundance of the resulting hydrogen gas by gas isotope ratio–mass spectrometry.

2.5. Calculations

Rates of appearance of CO_2 and leucine were calculated from the steady-state equation:

$$\mathrm{Ra}\left(\mu\mathrm{mol\,kg^{-1}\,h^{-1}}\right) = (\mathrm{IE_{inf}} / \mathrm{IE_{Plateau}}) \times \mathrm{i},$$

where IE_{inf} is the isotopic enrichment (mole percentage excess) of bicarbonate or leucine in the infusate and $IE_{plateau}$ is the isotopic enrichment of CO_2 in the expired air or KICA in plasma at isotopic steady state, and *i* is the infusion rate of the tracer in micromoles per kilogram per hour. By linear regression, the slope of the plateau enrichment of $^{13}CO_2$ in breath samples or ^{13}C-KICA in plasma for each subject was not significantly different from zero.

Endogenous flux was determined by subtracting the infusion rate, *i*, from Ra. In the fasted state, endogenous leucine flux is equal to leucine derived from protein breakdown (Leu_{brk}).

Leucine oxidation (Leu_{ox}) was calculated as follows:

$$\mathrm{Leu_{ox}}\left(\mu\mathrm{mol\,kg^{-1}\,h^{-1}}\right) = \mathrm{Ra}^{13}\mathrm{CO_2} / \mathrm{IE_{plateau}},$$

where $Ra^{13}CO_2$ is the rate of production of labeled CO_2 (obtained from the product of $RaCO_2$ and the plateau isotopic enrichment of expired CO_2 during the ^{13}C-leucine infusion) and $IE_{plateau}$ is the plasma isotopic enrichment of α-KICA at isotopic steady state.

Nonoxidative leucine flux, that is, leucine used for protein synthesis (Leu_{syn}), was calculated as leucine flux minus leucine oxidation.

Total body water (TBW) was calculated as follows:

$$\mathrm{TBW}(mL) = E_{D20} \times (dose / E_{pD20}) \times 1.04,$$

where E_{D2O} is the enrichment of the deuterium oxide dose, E_{pD2O} is the plasma water enrichment, and 1.04 is the factor that converts deuterium dilution space to total water [13].

Fat-free mass and fat mass (FM) were calculated as follows:

$$\mathrm{FFM\,(kg)} = \mathrm{TBW} / 0.73$$
$$\mathrm{FM\,(kg)} = \mathrm{total\,weight} - \mathrm{FFM},$$

where 0.73 is the water content or hydration of FFM in adult humans [14]. All kinetic data are expressed per kilogram of FFM.

2.6. Statistics

Data are expressed as means ± SEMs unless otherwise noted. Differences in subject characteristics and metabolic parameters between the 3 groups of subjects were assessed by 1-way analysis of variance (ANOVA) using the Tukey test for post hoc comparisons for parametric variables and the Kruskal-Wallis test for nonparametric variables. Analysis of covariance was performed to determine the effect of age on outcome variables. When data from the 14 COPD subjects were combined, differences between the 2 groups were made by nonpaired *t* test. Correlations were performed using Pearson correlation. Linear regression was used to determine the effect of body composition on REE. Tests were considered statistically significant if $P < .05$. Data analysis was performed with STATA software (version 9, College Station, TX).

3. Results

The general characteristics and anthropometric parameters of all subjects are shown in Table 1. Controls were younger than COPD subjects with low BMI ($P = .01$ ANOVA, $P < .05$ post hoc Tukey). Low-BMI subjects had lower FFM than controls ($P < .01$ ANOVA, $P < .05$ post hoc Tukey). Both groups of COPD subjects had lower fat-free mass index (FFMI) compared with controls ($P < .001$ ANOVA, $P < .05$ post hoc Tukey), and all subjects with COPD but one had low FFMIs (defined as <15 kg/m^2 for women and <16 kg/m^2 for men [15]). The COPD subjects with low BMI had lower FM compared with those with preserved BMI (ANOVA $P = .02$, $P < .05$ post hoc Tukey).

The clinical characteristics and spirometric values of subjects with COPD are given in Table 2. Treatment with inhaled corticosteroids and with oxygen therapy was similar between the 2 groups.

The plasma concentrations of 4 markers of systemic inflammation—2 cytokines, IL-6 and TNF-α; a positive acute phase protein, CRP; and a negative acute phase protein, prealbumin—are presented in Table 3. There were no differences in the plasma concentrations of CRP, TNF-α, IL-6, and prealbumin among the 3 groups.

Table 1 – Subject characteristics and anthropometric parameters of all subjects

	COPD with low BMI (n = 7)	COPD with preserved BMI (n = 7)	Controls (n = 7)
Age (y)	67 ± 5 *	61 ± 9	55 ± 6
Sex			
Male	5	6	5
Female	2	1	2
Height (in)	67.4 ± 3.1	67.9 ± 5.7	68.9 ± 3.4
Weight (kg)	55.0 ± 7.5 *,†	75.4 ± 13.1	81.3 ± 16.6
BMI (kg/m^2)	18.7 ± 1.1 *,†	25.4 ± 3.5	26.4 ± 3.9
FFM (kg)	36.9 ± 6.1 *	45.2 ± 10.2	55.2 ± 11.0
Percentage FFM (%)	67 ± 7	60 ± 9	68 ± 8
FFMI (kg/m^2)	12.6 ± 1.6 *,†	15.2 ± 1.2 *	18.5 ± 3.3
FM (kg)	18.1 ± 4.2 †	31.5 ± 9.8	26.3 ± 8.9
Percentage FM (%)	0.33 ± 0.07	0.40 ± 0.09	0.32 ± 0.08
Smoking status			
Current	4	4	5
Former	3	3	3

Data expressed as mean ± SD.
* $P < .05$ compared with control group.
† $P < .05$ compared with preserved-BMI group.

Table 2 – Spirometric values and clinical characteristics of subjects with COPD

	COPD with low BMI (n = 7)	COPD with preserved BMI (n = 7)
FEV_1 (L)	0.84 ± 0.20	0.91 ± 0.13
FEV_1 (% predicted)	26 ± 11	30 ± 10
FVC (L)	1.79 ± 0.27	2.26 ± 0.17
FVC (% predicted)	46 ± 4	57 ± 6
FEV_1/FVC ratio	45 ± 5	42 ± 4
GOLD stage		
Stage III	2	3
Stage IV	5	4
Medications		
β-Agonist	7/7	7/7
Inhaled steroid	5/7	5/7
Anticholinergic	4/7	6/7
Home oxygen use	3/7	3/7

GOLD Stage III disease is defined by FEV_1<50% predicated and ≥30% of predicted. GOLD stage IV disease is defined by FEV_1<30% predicted. All *P* values nonsignificant.

All REE and protein kinetic data are expressed per kilogram of FFM. Two subjects with COPD and low BMI were unable to complete indirect calorimetry measurements. Data on energy expenditure are shown in Fig. 1. Two subjects with COPD and one control subject were hypermetabolic as defined by measured REE greater than 110% of REE as predicted by Harris-Benedict equations. As shown in Fig. 1, the mean REE of the COPD subjects with preserved BMI was not different from that of the COPD subjects with low BMI (32.9 ± 0.8 vs 34.0 ± 1.36 kcal/kg FFM per day). Both groups, however, had REEs that were significantly higher than control values (27.9 ± 0.7 kcal/kg FFM per day) when compared individually ($P = .001$) and when combined ($P < .001$). Fat-free mass was a significant predictor of REE (kilocalories per day) in both COPD subjects and controls, explaining 91% of interindividual variation in REE in the healthy control group and 84% of the variation in the COPD group. When all subjects were combined, FFM explained 84% of the variation in REE. When REE was adjusted for FFM, FM, and age, REE was higher by 204 kcal/d in the COPD group compared with controls; and this difference was significant ($P < .01$). However, the interaction term between subject type (COPD vs control) and FFM was nonsignificant.

As shown in Table 4, both endogenous leucine flux and its nonoxidative disposal, indices of whole-body protein breakdown and synthesis rates, were significantly faster in the combined COPD subjects compared with control values ($P = .006$ and $P = .002$ respectively). Endogenous leucine flux remained higher in COPD subjects compared with controls after adjustment for age ($P = .008$). However, leucine oxidation, an index of net protein loss, was not different in COPD patients compared with controls. When the COPD subjects were separated into individual groups, both endogenous leucine flux and its nonoxidative disposal were significantly faster in the COPD subjects with preserved BMI compared with control values ($P < .05$ for both). In addition, endogenous leucine flux was also higher in COPD subjects with preserved BMI compared with those with low BMI. The differences in endogenous leucine flux remained significant after adjustment for age ($P = .01$). Furthermore, leucine oxidation, although not statistically significant, was 21% faster in the COPD subjects with preserved BMI compared with control values. With respect to the COPD subjects with low BMI, although both endogenous leucine flux and its nonoxidative disposal trended higher when compared with control values, only the difference in nonoxidative leucine disposal reached statistical significance ($P < .05$). In all subjects, REE was significantly correlated with protein breakdown ($r = 0.53$, $P = .02$) as well as protein synthesis ($r = 0.59$, $P = .008$).

Table 3 – Plasma concentrations of CRP, TNF-α, IL-6, and prealbumin

	COPD with low BMI (n = 7)	COPD with preserved BMI (n = 7)	Controls (n = 7)
CRP (μg/L)	2.4 (1.5, 6.0)	2.6 (1.7, 3.9)	1.7 (0.8, 7.1)
TNF-α (pg/mL)	4.4 (3.5, 8.3)	5.3 (4.3, 7.5)	7.7 (5.2, 8.9)
IL-6 (ng/L)	9.7 (1.9, 11.3)	3.7 (1.1, 6.8)	3.6 (2.2, 8.4)
Prealbumin (mg/L)	202 (173, 259)	222 (191, 293)	226 (202, 280)

Values are expressed as median (interquartile range). All *P* values nonsignificant by Kruskal-Wallis test.

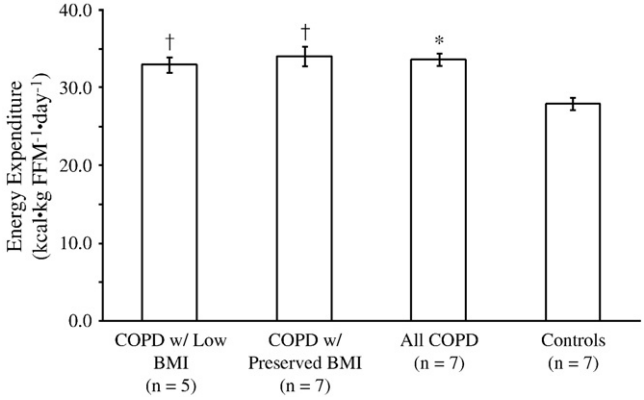

Fig. 1 – Resting energy expenditure in healthy controls (n = 7) and in COPD patients (n = 12) with either low BMI (n = 5) or preserved BMI (n = 7). *Significantly different from controls using unpaired *t* test; †significantly different from controls using ANOVA and post hoc Tukey test.

4. Discussion

The primary goal of this study was to determine first whether REE was increased in patients with COPD and, second, whether this was associated with increased protein turnover and/or systemic inflammation relative to the values of healthy controls. We found that COPD subjects had loss of FFM even with preservation of BMI. Furthermore, our results show that, as a group, COPD subjects had increased REE and faster rates of protein breakdown and synthesis compared with controls. Protein catabolism was not significantly different between the groups. There were no differences in the plasma concentrations of the inflammatory markers TNF-α, CRP, and IL-6 between COPD subjects and controls, although the variability in the concentrations was high and the sample size was small.

Table 4 – Leucine kinetics in COPD patients and healthy controls

Leucine kinetics (μmol/kg FFM per hour)	COPD with low BMI (n = 7)	COPD with preserved BMI (n = 7)	All COPD (n = 14)	Controls (n = 7)
Endogenous flux	145.80 ± 7.85	164.87 ± 7.14 *,†	155.34 ± 5.74 *	129.54 ± 2.46
Oxidation	49.75 ± 5.15	63.83 ± 7.63	56.79 ± 4.84	51.57 ± 2.16
Flux to protein synthesis	105.06 ± 6.32 *	111.28 ± 4.13 *	108.17 ± 3.73 *	86.86 ± 3.13

Data expressed as mean ± SEM.
* $P < .05$ compared with controls.
† $P < .05$ compared with low-BMI group by ANOVA and post hoc Tukey test.

These findings suggest that increased REE and protein turnover are involved in the loss of FFM in patients with severe COPD.

To negate the influence that the different body composition of the 3 groups of subjects may have on the metabolic measurements, REE and protein kinetics were expressed per unit of FFM, a proxy for body cell mass. All but one subject with COPD in this study had low FFMI. The low FFM of this sample may be related to the severity of COPD because previous studies have shown that FFMI is associated with the degree of airflow obstruction [15], with the highest prevalence of cachexia (defined as low BMI and low FFMI) in GOLD stage IV disease [12]. Fat-free mass was a major determinant of REE in the COPD subjects. This is in accordance with population studies showing that FFM is the major determinant of REE [16,17]. Our finding of a greater REE in COPD subjects compared with controls after adjustment for FFM is in agreement with earlier findings [4,5] and strongly suggests that COPD is associated with hypermetabolism. Even the COPD subjects with low BMI, who should have a lower REE because of the hypometabolic adaptation to undernutrition [18], had an REE that was 18% greater than that of the controls. Although reduced dietary energy may also be a contributing factor in the weight loss of COPD, most nutritional studies have reported that the measured dietary energy intake of COPD subjects, including those who have not lost weight, is greater than their recommended energy requirement [19,20], suggesting a compensatory response to an elevated energy requirement.

Alterations in metabolic processes that consume energy may also contribute to an increased REE in COPD. Because synthesis and breakdown of muscle protein are primarily responsible for the energy expenditure of resting muscle [8], increased whole-body protein breakdown and synthesis in COPD may be contributing significantly to the higher REE. In COPD subjects, we found that whole-body protein breakdown and synthesis rates are faster than in controls. These results corroborate the findings of an earlier study using a different tracer approach. Engelen et al [10] found increased whole-body protein synthesis and breakdown when using phenylalanine, but not leucine, tracers. However, leucine oxidation was not measured; and KICA was not used as a surrogate for intracellular leucine, which may have affected the results [21]. In support of protein synthesis and breakdown contributing to the increased REE of COPD, there was a significant correlation between REE and both the rate of protein breakdown and the rate of protein synthesis in all subjects.

Both this study and the prior study by Engelen et al [10] failed to show a significant difference in net protein loss (leucine oxidation in this study) between COPD and control subjects. This was unexpected because muscle protein wasting can only occur when there is an increase in net protein catabolism. There are several possible explanations for this unexpected finding. First, both studies were performed in the fasted state only, when there is usually a downregulation of amino acid oxidation and ureagenesis in an attempt to conserve protein [22]. This is not true in the fed state. Hence, one cannot rule out the possibility that a difference in protein catabolism between COPD subjects and controls does exist in the fed state. Second, because both studies were performed when the patients were clinically stable, the actual period of protein loss, such as during exacerbation, may have been missed. When divided by BMI, the mean leucine oxidation of the COPD subjects with low BMI was actually similar to the mean value of the 7 control subjects, suggesting that these patients may have already established a new homeostasis between protein breakdown and synthesis to conserve body protein content. On the other hand, the subjects with preserved BMI but with low FFMI were probably still losing muscle mass; and they had mean leucine oxidation that was 24% faster than the mean value of the controls. Finally, measurement of leucine oxidation may not accurately reflect protein catabolism if there is an adaptation to restrain oxidation of branched-chain amino acids, by downregulation of branched-chain aminotransferase and branched-chain α-keto acid dehydrogenase, in an attempt to maintain their availability for protein synthesis, thereby slowing down protein loss in COPD patients.

The protein metabolic response and body composition were different in the 2 groups of COPD subjects. The majority of subjects with preserved BMI had low FFMI, indicating selective loss of FFM. On the other hand, subjects with low BMI had low FFM and FM, indicating loss of both fat and muscle. Whole-body protein breakdown was higher in the COPD group with preserved BMI than in both controls and COPD subjects with low BMI. These results suggest that although the selective loss of FFM may be associated with increased whole-body protein breakdown, loss of both FFM and FM may represent a distinct metabolic syndrome.

This study was limited by the use of the leucine tracer technique to measure whole-body protein turnover instead of muscle protein synthesis and breakdown rates. Although the ^{13}C-leucine tracer method is considered the reference method to estimate whole-body protein metabolism in most conditions, it may not have been the most ideal method to use in this study because it does not provide specific information on muscle protein synthesis and breakdown rates. Obtaining fractional

muscle protein synthesis rate in the current ^{13}C-leucine tracer infusion protocol would have required timed skeletal muscle biopsies, which were not performed in this study. Furthermore, muscle protein breakdown rate could have been easily estimated by co-infusing $^{2}H_3$-3-methylhistidine to calculate 3-methylhistidine flux as an index of myofibrillar protein breakdown rate [23]. Alternatively, the pulse tracer injection of L-[*ring*-$^{13}C_6$]phenylalanine and L-[*ring*-^{15}N]phenylalanine could have been used to measure muscle protein fractional synthesis and breakdown rates simultaneously as described by Zhang et al [24]. We plan to use this approach in future studies to address muscle protein metabolism in COPD.

Our findings of an increased REE and protein turnover in the COPD patients point toward the presence of systemic inflammation. However, given the wide range of concentrations of the inflammatory markers, this study was underpowered to detect a difference between groups. Furthermore, the controls were current and former smokers; and smoking even in the absence of lung disease can lead to systemic inflammation. A study of current and former smokers demonstrated that 20.6% of those subjects without COPD had CRP between 3 and 10 mg/L and 5.2% had CRP greater than 10 [26]. Current and former smokers have also been found to have increased concentrations of IL-6 compared with nonsmokers [27]. Smoking can also affect protein turnover. Petersen et al [25] found that whole-body leucine flux was similar between smoker and nonsmokers, but mixed muscle protein fractional synthesis rate was significantly less in smokers compared with nonsmokers. However, all COPD subjects were also current or former smokers; yet they had increased, rather than decreased, whole-body protein synthesis. This finding suggests that the presence of COPD affects protein turnover independent of smoking.

This is the first study to investigate the link between REE and protein turnover in patients with severe COPD. However, the study is limited by a small sample size. It is possible that this subgroup of COPD patients is not representative of the disease as a whole because COPD is a very heterogeneous disease. Furthermore, use of ^{13}C-leucine as a tracer allows for estimation of whole-body protein breakdown, but does not specifically measure skeletal muscle protein synthesis.

In summary, subjects with COPD have increased REE and increased whole-body protein synthesis and protein breakdown when compared with controls. Because protein synthesis and breakdown are a major component of REE, increased protein turnover may be a major contributor to a higher REE in COPD. In addition, COPD subjects with low BMI and those with preserved BMI appear to have different metabolic changes, which may be contributing to different body composition in these 2 groups. Finally, our findings of a higher REE in all COPD subjects, together with changes in protein turnover, strongly suggest that supplemental dietary energy and protein should be part of routine therapy even in those COPD patients with normal BMIs.

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