Response of whole-body protein and urea turnover to exercise differs between patients with chronic obstructive pulmonary disease with and without emphysema[1–3]

Mariëlle PKJ Engelen, Nicolaas EP Deutz, Rob Mostert, Emiel FM Wouters, and Annemie MWJ Schols

ABSTRACT

Background: Exercise is known to improve physical capacity and muscle mass in patients with chronic obstructive pulmonary disease (COPD). However, recent evidence suggests that exercise may also negatively influence metabolism in COPD.

Objective: The objective was to investigate whether exercise influences whole-body protein metabolism differently in COPD patients and control subjects and to elucidate the effect of the specific underlying lung disease.

Design: Whole-body protein synthesis and breakdown and urea synthesis were measured by using stable-isotope methods in 14 male patients with severe COPD (forced expiratory volume in 1 s: $37 \pm 12\%$ of predicted) and in 8 male control subjects during and after 20 min of exercise. Subjects were normal weight [body mass index (in kg/m^2) of COPD patients and control subjects: 25.8 ± 3.9 and 25.7 ± 4.4, respectively]. The COPD group was selected to include patients with (Emph+, $n = 7$) and without (Emph−, $n = 7$) emphysema. Absolute workload was 35 ± 5 W, corresponding to $17 \pm 2\%$, $33 \pm 9\%$, and $52 \pm 14\%$ of the maximal obtained workload in the control, Emph−, and Emph+ groups.

Results: Exercise induced a 9% increase in protein synthesis and breakdown in the Emph− and control groups, which normalized postexercise. In the Emph+ group, protein turnover did not change significantly during exercise but decreased postexercise ($\pm 10\%$). Exercise did not change net protein breakdown (protein breakdown − synthesis) or urea synthesis, except in the Emph+ group, which showed a 14% reduction in urea synthesis postexercise ($P < 0.05$).

Conclusion: Low-intensity exercise suppresses whole-body protein and urea turnover in COPD patients with emphysema and needs to be considered when maximal anabolism is targeted through a combination of exercise and nutrition. *Am J Clin Nutr* 2003;77:868–74.

INTRODUCTION

It is generally accepted that physical exercise is an important element in the pulmonary rehabilitation of patients with chronic obstructive pulmonary disease (COPD). Exercise training, often combined with nutritional support, has been shown to increase body weight in patients with COPD and to result in significant increases in fat-free mass, muscle function, and exercise capacity (1, 2). However, recent evidence suggests that exercise may also have negative metabolic consequences in COPD. Low-intensity, constant cycle exercise induced significant alterations in plasma and skeletal muscle amino acid concentrations in COPD patients in whom fat-free mass was preserved (3), suggesting that exercise may be an important (protein) metabolic stressor even in patients with normal nutritional status.

Severe intrinsic alterations have been found in the skeletal muscle of COPD patients at rest. In COPD patients with emphysema, elevated concentrations of inosine monophosphate were found (4), suggesting an imbalance between ATP resynthesis and utilization. Moreover, a low proportion of type I fibers was found in emphysema patients (5), which is illustrative of a severely reduced oxidative capacity. Exercise in emphysema is often accompanied by accelerated anaerobic metabolism (6) and by arterial hypoxemia (7). All these factors may directly or indirectly influence protein metabolism through alterations in substrate metabolism.

The hypothesis of the present study was that physical exercise influences protein metabolism differently in COPD patients, particularly those with emphysema, than in healthy control subjects. Earlier studies in healthy subjects showed that protein metabolic changes often take place during recovery from exercise (8). This suggests that besides the actual exercise period, the postexercise (recovery) response to exercise is important to the overall state of protein metabolism in COPD. Studies of the effects of exercise on whole-body protein metabolism in patients with COPD may be clinically relevant because they indirectly provide information on the protein requirements of these patients in daily life and during pulmonary rehabilitation. If a catabolic effect of exercise is present as a result of altered substrate requirements, nutritional supplementation may be warranted to reach the expected anabolic effect of exercise in COPD patients.

In the present study, the metabolic effects of exercise in COPD were investigated by examining whole-body protein synthesis and breakdown in COPD patients and in healthy control subjects. Because urea is the predominant end product for the excretion of the nitrogen resulting from the catabolism of amino acids (and thus protein), whole-body urea synthesis was simultaneously determined. To elucidate the effect of the specific underlying lung disease, we studied COPD patients with and without radiologically proven emphysema who were able to preserve muscle mass.

SUBJECTS AND METHODS

Study population

Fourteen COPD patients with moderate to severe airflow obstruction and 8 healthy age-matched volunteers were studied. The COPD group was carefully selected to include 7 patients with macroscopic emphysema (Emph+) and 7 without (Emph−) on the basis of high-resolution computed tomography (9). All subjects were men. All patients had COPD according to the American Thoracic Society guidelines (10) and chronic airflow limitation, defined as a measured forced expiratory volume in 1 s (FEV_1) < 70% of reference FEV_1. Furthermore, the patients had irreversible obstructive airway disease (< 10% improvement in FEV_1 predicted baseline after inhalation of a $\beta_2$agonist), were clinically stable, and had not had a respiratory tract infection or exacerbation of their disease for ≥ 4 wk before the study. Exclusion criteria were malignancy; cardiac failure; distal arteriopathy; recent surgery; severe endocrine, hepatic, or renal disorder; and use of anticoagulant medication. Also, subjects who had used oral corticosteroids within 3 mo of the start of the study were excluded. The maintenance treatment of the studied COPD patients consisted of inhaled β_2-agonists, inhaled anticholinergics, inhaled corticosteroids, and oral theophylline. The COPD patients and control subjects were sedentary persons who were retired. Although most of the COPD patients were former smokers (80%), the current smoking status of the subjects was 3 in the patient group (21%) and 1 in the healthy control group (13%). Written informed consent was obtained from all subjects, and the study was approved by the medical ethical committee of the University Hospital Maastricht.

Study protocol

After fasting overnight, the subjects remained in a supine position for 3 h. A catheter was placed in an antecubital vein of the arm for infusion of the tracers. Each subject was given a priming dose, followed by continuous infusion until the end of the experiment. The following isotope infusion rates and priming doses were used (where FFM is fat-free mass): L-[ring-$^2H_5$]phenylalanine, infusion rate = 0.054 $\mu mol \cdot kg\ FFM^{-1} \cdot min^{-1}$, priming dose = 3.68 $\mu mol/kg$ FFM; L-[ring-$^2H_2$]tyrosine, infusion rate = 0.014 $\mu mol \cdot kg\ FFM^{-1} \cdot min^{-1}$, priming dose = 0.95 $\mu mol/kg$ FFM; L-[ring-$^2H_4$]tyrosine, priming dose = 0.3 $\mu mol/kg$ FFM; [$^{15}N_2$]urea, infusion rate = 0.186 $\mu mol \cdot kg\ FFM^{-1} \cdot min^{-1}$, priming dose = 44.42 $\mu mol/kg$ FFM. The tracers were obtained from Cambridge Isotope Laboratories (Woburn, MA).

A second catheter was placed in a superficial dorsal vein of the hand of the contralateral arm, which was placed in a thermostatically controlled hot box (internal temperature: 60 °C), a technique designed to mimic direct arterial sampling (11). Arterialized venous blood samples were taken at 2, 2.5, and 3 h during the infusion to ensure an isotopic steady state.

Subsequently, all subjects performed a submaximal exercise test on an electronically braked cycle ergometer (Cornival 400; Lode, Groningen, Netherlands) for 20 min, which is comparable to a single exercise (training) session used in patients with severe COPD. The work rate for each subject was calculated as 20% of the predicted maximum workload for height, age, and weight, according to the equations of Jones (12). The pedaling frequency was selected by the subjects between 60 and 70 rpm and was held constant throughout the test. An infrared electrode was placed on a finger to measure oxygen saturation (Fasttrac; Sensor Medics Co, Anaheim, CA). Heart rate was measured throughout the test with the use of a sport tester (PE3000; Polar Electro company, Kempele, Finland). Arterialized venous blood was sampled at 10, 15, and 20 min of exercise and at 15, 30, 45, and 60 min during recovery.

Analysis of arterialized venous blood

Arterialized venous blood was collected in a heparin-containing syringe, immediately put on ice, and subsequently centrifuged at 3120 × g and 4 °C for 10 min to obtain plasma. Plasma was deproteinized with sulfosalicylic acid (5%) and was stored at –80 °C until analyzed. Concentrations of phenylalanine and urea were analyzed by using an HPLC technique (13), and tracer-tracee ratios were analyzed by using a liquid chromatography–mass spectrometry system (14).

Calculations

We used a single pool model in which the whole-body amino acid pool is assumed to be homogeneous, with a constant exchange of amino acids entering and exiting from a metabolic pool of amino acids, because all proteins are constantly being synthesized and simultaneously degraded. Flux or protein turnover is defined under steady state conditions as the total flux into or out of the active metabolic amino acid pool. In our case, the influx into the metabolic pool is from the breakdown of body protein. The efflux from the metabolic pool includes the amino acids used for synthesis of protein and for hydroxylation (or oxidation). All other metabolic pathways are considered minor. Thus, in the postabsorptive state: protein turnover = protein breakdown = protein synthesis + hydroxylation (15, 16).

The following equations were used for the calculations in the postabsorptive state:

$$\text{Whole-body } R_a = \text{infusion rate/TTR in arterialized plasma} \quad (1)$$

where R_a is the rate of appearance and TTR is the tracer-tracee ratio.

$$\text{Hydroxylation of Phe into Tyr} = \text{whole-body}$$
$$R_{aTyr} \times (TTR_{Tyr4}/TTR_{Phe5}) \quad (2)$$

The hydroxylation of phenylalanine reflects net whole-body protein breakdown (= net protein breakdown).

$$\text{Whole-body protein breakdown}$$
$$\text{(protein breakdown)} = \text{whole-body } R_{aPhe} \quad (3)$$

$$\text{Whole-body protein synthesis} = \text{whole-body}$$
$$R_{aPhe} - \text{hydroxylation of Phe} \quad (4)$$

$$\text{Whole-body urea synthesis} = \text{whole-body } R_{aUrea} \quad (5)$$

For the calculations during exercise and postexercise, whole-body R_{aPhe}, the rate of disappearance of phenylalanine (R_{dPhe}), and R_{aUrea} were calculated by using the one-pool model non–steady state equations of Steele (17), modified for use with stable isotopes.

TABLE 1
General characteristics of the study population[1]

	Control subjects (n = 8)	EMPH⁻ patients (n = 7)	EMPH⁺ patients (n = 7)
Age (y)	66 ± 5	61 ± 3	62 ± 10
Height (cm)	172.4 ± 5.9	171.0 ± 4.7	173.9 ± 9.6
Weight (kg)	76.6 ± 11.9	76.2 ± 14.9	76.1 ± 10.5
BMI (kg/m²)	25.8 ± 3.9	26.0 ± 4.3	25.4 ± 4.7
FFM (kg)	55.9 ± 5.4	54.0 ± 9.2	51.8 ± 5.1
FM (kg)	20.7 ± 7.2	22.2 ± 5.9	24.3 ± 6.9
FEV₁ (% of predicted)	102[a] ± 19	44[b] ± 13	30[c] ± 6
DL_CO (% of predicted)	112[a] ± 20	89[b] ± 20	54[c] ± 16
RV (% of predicted)	119[a] ± 25	158[a] ± 44	215[b] ± 28
PaO₂ (kPa)	11.3[a] ± 1.0	9.7[b] ± 1.4	10.4[a,b] ± 1.8

[1] $\overline{x}$ ± SD. EMPH⁻ and EMPH⁺, patients with chronic obstructive pulmonary disease without and with emphysema, respectively; FFM, fat-free mass; FM, fat mass; FEV₁, forced expiratory volume in 1 s; DL_CO, diffusing capacity for carbon monoxide; RV, residual volume; PaO₂, arterial oxygen pressure. Means within a row with different superscript letters are significantly different, $P < 0.05$ (ANOVA followed by Tukey's test).

$$R_a = \{\text{infusion rate} - [pV_d \times (C_2 + C_1)/2 \times (TTR_2 - TTR_1)/(t_2 - t_1)]\}/(TTR_1 + TTR_2)/2 \qquad (6)$$

$$R_d = R_a - [pV_d \times (C_2 - C_1)/(t_2 - t_1)] \qquad (7)$$

Where p is the correction factor of the pool size for instant mixing [$p = 0.25$ for phenylalanine (plasma pool) and $p = 1$ for urea], V_d is the volume of distribution (total body water pool = 0.5 L/kg body wt), and $(TTR_2 - TTR_1)/(t_2 - t_1)$ and $(C_2 - C_1)/(t_2 - t_1)$ are the change in the tracer-tracee ratio and the change in plasma concentration of the tracee, respectively, between 2 time points.

To account for possible differences in fat-free mass between the study populations, whole-body fat-free mass was measured by bioelectrical impedance analyses (BIA 101; RJL Systems, Detroit) of the subjects in the supine position at the right site. The fat-free mass of the COPD patients was calculated by using a patient-specific regression equation (18), whereas the fat-free mass of the healthy control subjects was calculated by using a specific regression equation for elderly men as described by Lukaski et al (19). Fat mass was calculated by subtracting fat-free mass from body weight; the latter was measured by using an electronic beam scale with a digital readout to the nearest 0.1 kg (model 708; Seca, Hamburg, Germany) with patients and controls standing barefoot and wearing light indoor clothing. Protein synthesis, (net) protein breakdown, and urea synthesis were expressed in nmol · kg fat-free mass⁻¹ · min⁻¹.

Pulmonary function tests

All patients and healthy volunteers underwent spirometry for determination of FEV₁, with the highest value from ≥ 3 technically acceptable maneuvers being used. Residual lung volume was assessed by wholebody plethysmography (Masterlab; Jaeger, Wurzburg, Germany). Diffusing capacity for carbon monoxide was measured by using the singlebreath method (Masterlab; Jaeger). All values obtained were related to a reference value and are expressed as percentages of the predicted value (20).

Statistical analysis

Results are expressed as means ± SEs for arterial venous plasma determinations and as means ± SDs for other characteristics. The

TABLE 2
Exercise characteristics of the study population[1]

	Control subjects (n = 8)	EMPH⁻ patients (n = 7)	EMPH⁺ patients (n = 7)
WR (W)	33.5 ± 2.8	34.2 ± 6.5	35.8 ± 6.5
%WR_max (%)	16.9[a] ± 2.4	32.9[b] ± 8.5	51.5[c] ± 14.0
Oxygen saturation (%)			
Rest	95.6[a] ± 0.7	93.9[b] ± 1.2	93.1[b] ± 1.5
Postexercise	95.1[a] ± 0.7	93.1[b] ± 1.1	91.0[c] ± 1.7
Heart rate (beats/min)			
Rest	73.2 ± 5.9	79.9 ± 12.2	86.6 ± 13.7
Postexercise	91.6 ± 3.1	107.3 ± 19.2	116.7 ± 22.8

[1] $\overline{x}$ ± SD. EMPH⁻ and EMPH⁺, patients with chronic obstructive pulmonary disease without and with emphysema, respectively; WR, work rate; %WR_max, work rate as percentage of maximally achieved work rate in a previously performed exercise test. Means within a row with different superscript letters are significantly different, $P < 0.05$ (ANOVA followed by Tukey's test).

mean values of whole-body protein synthesis, (net) protein breakdown, and urea synthesis at 2, 2.5, and 3 h were used as the resting baseline values. If the normality or equal variance test failed, data were transformed or log transformed where appropriate. Analysis of variance (ANOVA), followed by Tukey's pairwise multiple comparison procedure, was used to determine differences in general and exercise characteristics between the Emph+ patients, Emph− patients, and control subjects. Because there was a significant difference in baseline values in protein metabolism among the study groups, the exercise-induced change in protein synthesis, (net) protein breakdown, and urea synthesis was calculated (by subtracting the baseline values). Subsequently, a two-way ANOVA (general linear model, SPSS version 7.5; SPSS Inc, Chicago) was performed with a time and group effect for the 2 different phases during the experiment [exercise ($t = 0–20$ min) and recovery ($t = 20–80$ min)]. The level of significance was set at $P < 0.05$, and P values are given for the time effect, group effect, and the time × group interaction. When an overall significance for time or group was observed, pairwise group (Emph+ compared with Emph− compared with controls) comparisons were performed with the use of Tukey's post hoc test to adjust for the multiple comparisons made. In the present study, no overall significant time × group interactions were observed.

RESULTS

Age, height, body weight, fat-free mass, and fat mass did not differ significantly between the COPD patients and the control group (**Table 1**). No recent involuntary weight loss was present in the patients or control subjects. On average, the studied COPD group had moderate to severe airflow obstruction (FEV₁: 37 ± 13% of predicted) and mildly to moderately reduced diffusing capacity (71 ± 25% of predicted). Stratification of the COPD group into the Emph+ ($n = 7$) and Emph− ($n = 7$) subgroups resulted in large differences in pulmonary function between the groups. The Emph+ group had more severe airflow obstruction and air trapping than did the Emph− patients ($P < 0.05$); there was no significant difference between the subgroups in arterial oxygen pressure. In the control group, all lung function values were within the normal range.

The absolute work rate used in the exercise test did not differ significantly between the study groups (**Table 2**) but when
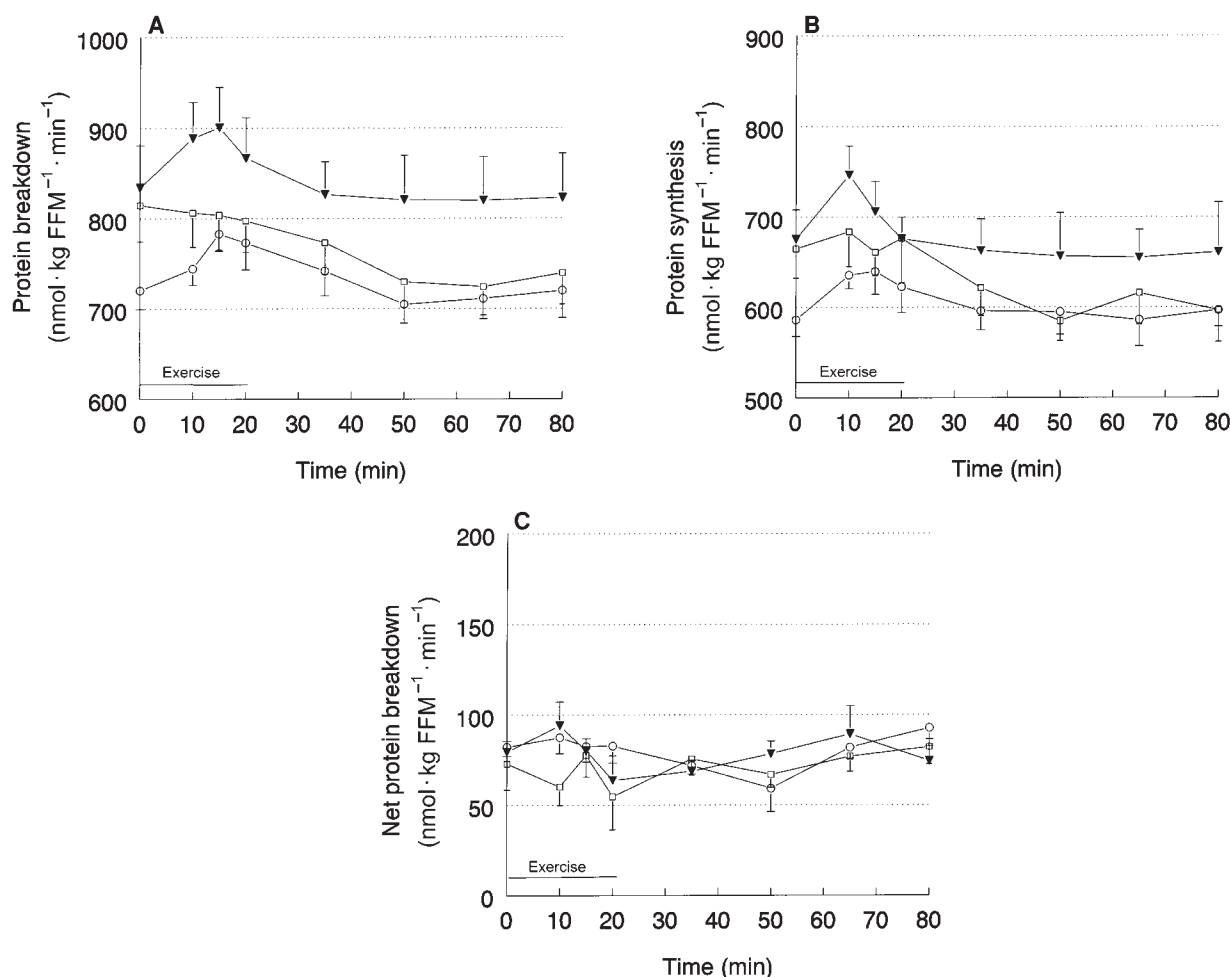
FIGURE 1. Mean (± SE) changes in whole-body protein breakdown (A), whole-body protein synthesis (B), and whole-body net protein breakdown in the healthy control group (○; $n = 8$), the patients with chronic obstructive pulmonary disease without emphysema (Emph− group; ▼; $n = 7$), and the patients with chronic obstructive pulmonary disease and emphysema (Emph+ group; □; $n = 7$) during 20 min of exercise and 1 h of recovery. FFM, fat-free mass. A: Two-factor ANOVA showed a significant group effect during exercise (control compared with Emph+, $P < 0.01$; Emph− compared with Emph+, $P < 0.01$) and recovery (control compared with Emph+, $P < 0.001$; Emph− compared with Emph+, $P < 0.05$). There was no significant time effect during exercise or recovery and no significant group × time interaction. B: Two-factor ANOVA showed a significant group effect during exercise (control compared with Emph+, $P < 0.05$; Emph− compared with Emph+, $P < 0.05$) and recovery (control compared with Emph+, $P < 0.001$; Emph− compared with Emph+, $P < 0.05$). There was no significant time effect during exercise or recovery and no significant group × time interaction. C: There was no significant group or time effect during exercise or recovery and no significant group × time interaction.

expressed as a percentage of a previously performed incremental exercise test was higher in both COPD subgroups than in the control subjects ($P < 0.01$). Moreover, the relative work rate was even higher in the Emph+ than in the Emph− group ($P < 0.05$). Transcutaneous oxygen saturation at rest and postexercise was lower in both COPD subgroups than in the control group. Moreover, oxygen saturation was lower postexercise in the Emph+ group than in the Emph− patients ($P < 0.05$). Heart rate did not differ significantly between the 3 groups at rest or postexercise.

As reported earlier (21), rates of protein turnover at rest were higher in the patients with COPD than in the healthy control subjects. Whole-body protein breakdown (**Figure 1**A) and protein synthesis (Figure 1B) increased (to a maximum of 9%) after the start of exercise in the control group. During recovery from exercise, protein synthesis and breakdown immediately normalized in the control group. Net protein breakdown (Figure 1C)

did not change significantly during exercise or recovery in the control group.

The protein metabolic response to exercise differed between the COPD subgroups. In the Emph+ patients, protein breakdown (Figure 1A) and protein synthesis (Figure 1B) did not change significantly during exercise and decreased below baseline values during recovery. This decrease (to a maximum of 10%) remained until at least 1 h into recovery. In contrast, the response in protein breakdown and synthesis of the Emph− group was not significantly different from that of the control group. The change in whole-body protein breakdown was significantly different during exercise and recovery between the Emph+ and the control groups ($P < 0.01$ and $P < 0.001$, respectively), and between the Emph+ and Emph− groups ($P < 0.01$ and $P < 0.05$, respectively).

A significant difference was also found for the change in whole-body protein synthesis during exercise (control compared
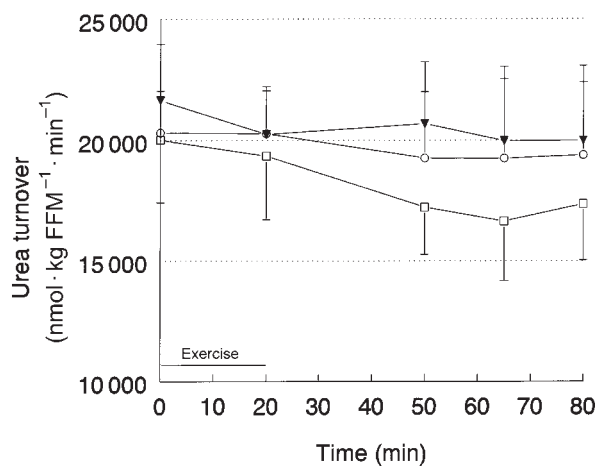
FIGURE 2. Mean (± SE) changes in whole-body urea turnover in the healthy control group (○; $n = 8$), the patients with chronic obstructive pulmonary disease without emphysema (Emph− group; ▼; $n = 7$), and the patients with chronic obstructive pulmonary disease and emphysema (Emph+ group; □; $n = 7$) during 20 min of exercise and 1 h of recovery. FFM, fat-free mass. Two-factor ANOVA showed a significant group effect during recovery (control compared with Emph+, $P < 0.05$) but not during exercise. There was no significant time effect during exercise or recovery and no significant group × time interaction.

with Emph+, $P < 0.05$; Emph+ compared with Emph−, $P < 0.05$) and recovery (control compared with Emph+, $P < 0.001$; Emph+ compared with Emph−, $P < 0.05$). There was a significant time effect for protein breakdown and synthesis during exercise (control compared with Emph−, $P < 0.05$) and recovery (control compared with Emph+, $P < 0.05$). Net protein breakdown (Figure 1C) did not change significantly during exercise or recovery in either COPD subgroup.

In line with the results for net protein breakdown, whole-body urea turnover (**Figure 2**) did not change significantly throughout the study in the Emph− and control groups. However, urea synthesis decreased from baseline after 30 min postexercise in the Emph+ group (to a maximum of 14%). The change in urea synthesis during recovery from exercise differed significantly between the control and Emph+ groups ($P < 0.05$). Plasma phenylalanine and urea concentrations did not change significantly during exercise or recovery in the control or COPD subgroups (data not shown).

DISCUSSION

The results of the present study indicate that exercise at a constant low work rate does not induce net protein catabolism in clinically stable, weight-stable patients with COPD but suppresses whole-body protein and urea turnover (by 10–14%) in those with emphysema. Until now, only a limited number of studies were available examining the acute effects of cycle exercise on whole-body protein metabolism in healthy subjects. To our knowledge, no studies are available concerning other chronic wasting diseases. In the present study, we chose to examine the response to exercise in COPD patients and control subjects by using absolute work rate values because in real-life situations, subjects perform absolute and not relative work. Moreover, relative exercise, which places an

identical metabolic strain on COPD patients and control subjects, is difficult to obtain because COPD patients stop cycling during maximal exercise tests mostly as a result of shortness of breath.

The increase in whole-body protein breakdown during low-intensity exercise found in the Emph− and control group agrees with some previous studies in healthy subjects (22–24) but is in contrast with others (25). Conflicting results have been reported regarding whole-body protein synthesis during endurance exercise in healthy subjects: both decreased (22, 26) and unchanged (23, 25) values have been observed. The differing findings are at least partly related to the different exercise protocols (intensities and durations) and study groups (mostly young and physically active) used. Remarkably, the response in whole-body protein turnover to exercise was similar between the Emph− group and the control group in the present study despite the difference in relative work intensity.

Protein turnover during exercise

Whole-body protein turnover was not increased in the Emph+ group during exercise. Several factors may theoretically contribute to this observation. Previously, we observed reduced muscle amino acid concentrations at rest in COPD patients with emphysema relative to those in patients without emphysema (27). When this indicates a reduction in amino acid availability, it may contribute to the fall in protein synthesis during exercise (28, 29). Moreover, significantly lower transcutaneous oxygen saturation was found during exercise in the Emph+ group than in the Emph− group. In fact, plasma lactate concentrations were higher at the end of exercise in the Emph+ group than in the Emph− group (3.8 compared with 3.0 mmol/L). When tissue hypoxia accompanies exercise in COPD patients with emphysema, the whole-body protein synthesis rate is expected to decrease (30). Moreover, the increase in protein turnover during exercise as seen in the Emph− group is an energy-consuming process (formation of peptide bonds, amino acid transport, RNA turnover, and protein breakdown). Recently, activity-related energy expenditure was found to be elevated in patients with emphysema (31), likely as the result of reduced skeletal muscle oxidative capacity (5). Moreover, the efficiency of breathing is decreased in COPD patients during exercise. In particular, patients with emphysema breathe at a higher inspiratory level as the result of dynamic hyperinflation of the diaphragm and therefore have to also use their shoulder-girdle muscle for breathing. Therefore, it can be hypothesized that patients with emphysema preferentially use their substrates (glucose and fat) for ATP production related to the enhanced work of breathing and anaerobic skeletal muscle contraction during exercise and less for protein turnover.

Protein turnover postexercise

Whole-body protein synthesis and breakdown returned to baseline values immediately in the Emph− group but decreased significantly below baseline values (by on average 10%) in the Emph+ patients. The reduced values in the Emph+ group remained until at least 1 h into recovery, which is remarkable because no energy is needed for muscle contraction. Although all COPD patients were ventilatory limited, the relative work intensity was slightly higher in the Emph+ than in the Emph− group. Previous studies in healthy subjects of whole-body protein synthesis and breakdown after high-intensity endurance exercise reported both unchanged (32, 33) and increased (22, 33) values. The latter was explained by the elevated free intracellular amino acid pool, which

resulted from an increased transport of amino acids into skeletal muscle (29) and to skeletal muscle proteolysis immediately after exercise (29, 34). To our knowledge, none of the studies observed a reduction in protein turnover postexercise. This suggests that the suppressed response in protein turnover to exercise in the Emph+ group was related to the underlying lung disease.

Urea synthesis during and after exercise

Net whole-body urea synthesis was not increased in the control and Emph− groups. Carraro et al (35) found in healthy subjects that low-intensity [40% of maximal oxygen uptake ($\dot{V}O_2$max)] and high-intensity (70% of $\dot{V}O_2$max) exercise did not significantly change the R_a of urea. Therefore, the decrease of 14% in urea synthesis in the Emph+ group postexercise was remarkable and not in line with the unchanged net protein breakdown. Evidence exists that over a short period of time the rate of urea production may not be a direct reflection of the net rate of protein breakdown because the urea pool is too large to immediately reflect changes in protein breakdown (26). It is also possible that the same processes that cause the reduction in whole-body protein turnover are responsible for the decrease in whole-body urea synthesis (ie, hypoxia).

Whole-body compared with muscle protein metabolism

It is still possible that net protein breakdown is enhanced in the skeletal muscle of COPD patients despite whole-body protein balance. Recently, a severe reduction in muscle amino acid concentrations and an increase in plasma amino acid concentrations were observed in stable patients with severe COPD after low-intensity exercise (3). This suggests an enhanced nitrogen efflux from muscle, indicating a potential catabolic effect of exercise. In line with this, studies in healthy subjects found an increased nitrogen efflux from muscle during low-intensity exercise (36). However, evidence also exists that the gut is a main source of the increased R_a during exercise (37). Quantification of the rate of protein synthesis and breakdown in the skeletal muscle of Emph+ patients will be an important step forward in the understanding these subjects' altered protein metabolic response to exercise.

Implications of the present findings

Earlier studies in healthy subjects showed that protein supplements taken immediately postexercise have greater anabolic effects than when taken preexercise, which is likely due to an accelerated amino acid transport into cells that increases the substrate availability of free amino acids for protein synthesis (8). The suppressed response in whole-body protein turnover in the Emph+ group in the present study could mean that amino acid transport into cells is reduced and that protein supplements taken postexercise are less effective in stimulating muscle protein synthesis in Emph+ than in Emph− patients. This means that the timing of feeding in Emph+ patients may be important in relation to muscle mass gain or preservation. Although the studied COPD patients were both clinically and weight stable at the time of measurement, an optimal anabolic stimulus of exercise and nutrition may be of particular importance during periods of involuntary weight loss and when factors are involved that are known to cause protein unbalance (ie, an acute inflammatory state). In conclusion, a suppressed response in protein turnover to exercise is present in patients with emphysema and needs to be considered in therapeutic interventions when the goal is to achieve maximal anabolism.

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