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Whole body resting and exercise-induced lipolysis in sarcopaenic patients with COPD

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SHORT TITLE

Lipolysis and body composition in COPD

ABSTRACT

Rationale: An impaired β-adrenoceptor-mediated lipolysis was reported in sarcopaenic COPD patients. This could play a role in the shift in body composition towards decreased fat-free mass (FFM) and relative maintenance of fat mass (FM). Lipolysis could be affected by chronic treatment with β_2-agonists or disease-related factors. Therefore, whole body resting and exercise-induced lipolysis was investigated in sarcopaenic COPD patients with moderate disease severity.

Methods: Seven sarcopaenic COPD patients (FEV_1: 53±5%, BMI: 27.5±0.9kg·m^{-2}) and 7 controls matched for age, gender and BMI were studied. In addition, 6 underweight COPD patients (FEV_1: 51±5%, BMI: 20.6±0.7kg·m^{-2}) matched for disease severity were recruited. Lipolysis and plasma levels of catecholamines were assessed during infusion of [$^2H_5$]glycerol at rest and during submaximal cycling exercise.

Results: Proportional FM was comparable between sarcopaenic patients and controls, while FFM-index was significantly reduced in patients. At rest, the rate of appearance (R_a) of glycerol (4.1±0.6µmol·kgFFM^{-1}·min^{-1} and 3.3±0.2µmol·kgFFM^{-1}·min^{-1}, respectively) was not significantly different. In underweight patients, glycerol R_a (4.3±0.5µmol·kgFFM^{-1}·min^{-1}) was also comparable. End-of-exercise lipolytic rates were not significantly different between groups. Glycerol R_a was not related to fat mass. Resting epinephrine levels were significantly increased in underweight COPD patients and were related to resting lipolysis ($r=0.520$, $p<0.05$).

Conclusions: Sarcopaenia in COPD patients with moderate disease severity is not characterized by abnormal lipolytic rate. Altered regulation of muscle protein turnover seems to be the trigger in the body compositional shift observed in these patients.

KEYWORDS

Chronic obstructive pulmonary disease, body composition, fat mass, lipolysis, intermediary metabolism, exercise

INTRODUCTION

Cachexia, defined as weight loss with a disproportional loss of fat-free mass (FFM), occurs in a substantial number of patients with chronic obstructive pulmonary disease (COPD) and is an independent predictor of mortality [1]. Its prevalence depends on the population analysed and varies from 11% in moderate to severe COPD out-patients [2] to 26% in severe patients eligible for pulmonary rehabilitation [3]. Furthermore, in a substantial proportion of normal weight COPD patients (10–15%) [3, 4] hidden depletion of fat-free mass occurs, also referred to as sarcopaenia. The clinical implications of this body compositional shift towards decreased FFM and relative or even absolute abundance of fat mass were illustrated in a study showing a greater degree of physical impairment in normal weight COPD patients with low FFM compared to underweight patients with preserved fat-free mass [3]. We hypothesized that sarcopaenia in COPD is associated with alterations in intermediary metabolism, towards accelerated net muscle protein breakdown and impaired fat oxidation or decreased lipolysis. There are some indications that depletion of FFM is indeed associated with altered regulation of protein turnover towards increased protein breakdown [5-7]. Also, reduced skeletal muscle activity of 3-hydroxyacyl CoA dehydrogenase (HADH), which regulates the β-oxidation of fatty acids, has consistently been shown in normal weight COPD patients [8]. Finally, an impaired β-adrenoceptor-mediated increase in plasma levels of nonesterified fatty acids was reported in sarcopaenic COPD patients [9], which is suggestive for a reduced lipolysis. However, whole body lipolytic rate and differences in lipid kinetics between sarcopaenic and underweight COPD patients have not been studied until now.

The primary aim of the present study was to investigate resting whole-body lipolysis in sarcopaenic COPD patients versus healthy controls, matched for age and BMI. Secondary, potential differences in lipolytic rate between normal and underweight COPD patients matched for disease severity were explored, since loss of fat mass may be due to increased lipolysis, as previously observed in cancer patients [10]. Since oxidation of free fatty acids accounts for the major portion of energy requirements during low intensity exercise, submaximal bicycle exercise was used as metabolic stressor for whole body lipolysis.

METHODS

Study population

Seven male and clinically stable COPD out-patients [11] with moderate airflow obstruction and seven healthy controls, matched for age, sex and body mass index (BMI) volunteered for this study. Additionally, six COPD patients with low BMI were recruited, matched for FEV_1. Details on body composition of the groups are shown in figure 1. Exclusion criteria for participation were glucose intolerance, diabetes mellitus, thyroid or other endocrine disorders, recent involuntary weight loss, malignancies, chronic heart failure, renal, hepatic or other gastro-intestinal disease or recent surgery. Patients did not exhibit chronic respiratory insufficiency or receive supplemental oxygen therapy. The following pulmonary maintenance medications were used: inhaled short- and long-acting β2-adrenoceptor agonists, 54%; anticholinergics by inhalation, 54%; combined inhalers of short-acting β2-adrenoceptor agonists and short-acting anticholinergics, 8%; inhalation corticosteroids, 8%; combined inhalers of sympathicomimetics and corticosteroids, 46%; xanthines, 31%; and oral N-acetylcysteine, 23%. The use of pulmonary medications was equally distributed between COPD subgroups. On the evening before the test day and on the morning of the study, pulmonary maintenance medications were suspended in order to avoid potential acute effects of these on lipolysis. Written informed consent was obtained from all subjects and the study was approved by the medical ethical committee of the University Hospital Maastricht.

Study design

The study was performed at the out-patient metabolic ward of the University Hospital Maastricht on two separate occasions. During the first visit, medical history was checked and physical examination was performed by a physician. Furthermore, body composition was measured and lung function and incremental exercise tests were carried out. Eligible subjects subsequently participated in the glycerol stable isotope tracer protocol, as described below.

Lung function tests

Subjects underwent spirometry for measurement of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). The highest value of at least three technically acceptable maneuvers was used. Total lung capacity (TLC) and residual volume (RV) were determined by whole body plethysmography (MasterLab Body, Jaeger, Würzburg, Germany). Diffusing capacity for carbon monoxide (DL_{CO}) was assessed by the single-breath method

(MasterLab Transfer, Jaeger, Würzburg, Germany). All values obtained were related to a reference value and expressed as a percentage of the predicted value. In patients, arterial blood gases were determined on a blood gas analyzer (ABL 700, Radiometer, Copenhagen, Denmark).

Body composition

Body height was determined to the nearest 0.5 cm with subjects standing barefoot. Body weight (BW) was measured with a beam scale (SECA, Hamburg, Germany) without shoes and in light clothing to the nearest 0.1 kg. Body mass index was calculated as the ratio of weight to height in meters squared. Fat-free mass (FFM) was measured by bioelectrical impedance analysis at a spectrum of 48 frequencies ranging from 5 to 500 kHz (Xitron 4000b, Xitron technologies, San Diego, California, USA). Resistance was measured in supine position at the right side as described by Lukaski [12]. In subjects with COPD, FFM was estimated from impedance measurements using the sex-specific regression equation described by Steiner [13], while the equation of Dey [14] was used for the healthy elderly controls. Fat-free mass index (FFMI) was calculated as the ratio of FFM to height in meters squared.

Exercise capacity

In order to determine the submaximal bicycle exercise load for each individual, subjects performed a standardized incremental exhaustive exercise test on an electrically braked cycle ergometer, as previously published [15].

Glycerol stable isotope tracer protocol

After an overnight fast, subjects reported at the laboratory at 07.30 h and were studied at rest in the supine position. A catheter was placed in an antecubital vein of the arm for stable isotope infusion. A second catheter for sampling of arterialized venous blood was placed retrograde in a dorsal hand vein of the contralateral arm and maintained at 60ºC in a thermoregulated box. At 08.00 h, after taking a blood sample for background enrichment of plasma glycerol, subjects were administered a single intravenous dose of [$^2H_5$]glycerol (1.5 μmol·kgBW^{-1}, >99% enriched; Cambridge Isotopes Inc, Andover, Massachusetts, USA) in order to prime the glycerol pool. Thereafter (t=0), a continuous infusion of [$^2H_5$]glycerol (0.1 μmol·kgBW^{-1}·min^{-1}) dissolved in 0.9% saline was started via a calibrated pump (IVAC 560, San Diego, California, USA). Resting blood samples were taken at t=110 and 120 minutes. In each experiment, the exact [$^2H_5$]glycerol infusion rate was determined from the glycerol

concentration and enrichment in the infusate. At t=120 minutes COPD patients started to exercise on a cycle ergometer at a workload of 50% W_{max} for 20 minutes, while controls exercised at an identical absolute work load (30 W = 50% of mean W_{max} in COPD patients) for the same duration. Blood samples were drawn at t=125, 130, 135 and 140 minutes. The protocol continued with one hour recovery period, during which blood samples were taken at t=155, 170, 185 and 200 minutes. Thereafter, controls performed a second 20 minute exercise test at 50% of their individual W_{max} in order to study potential alterations in glycerol kinetics at identical relative submaximal work load. Blood samples were taken at t=205, 210, 215 and 220 minutes during exercise and at t=235, 250, 265 and 280 minutes during a second recovery period of one hour. Plasma levels of regulatory hormones were determined at t=110, 140, 200, 220 and 280 minutes. During the study, subjects were allowed to drink water only.

Analytic procedures

Blood samples (5ml) for [$^2H_5$]glycerol enrichment and glycerol concentration were collected on heparin, immediately put on ice, and centrifuged at 4000 rpm at +4ºC for 10 minutes. Samples for catecholamines were collected in iced EDTA tubes, centrifuged at 4000 rpm for 10 minutes at +4ºC and stored in a glutathione containing tube. For determination of insulin, 3 ml of arterialized-venous blood were put into a coagulation tube, which was centrifuged for 10 minutes at 3000 rpm at room temperature. Serum was separated and centrifuged again for 5 minutes at 3000 rpm. All aliquots of plasma and serum were frozen immediately in liquid nitrogen, stored –80°C and transported on dry ice before assay.

Isotope enrichment of glycerol in plasma was determined by gas chromatography-mass spectrometry, as described by Ackermans et al [16]. Serum free fatty acids (FFA) were measured by an enzymatic colorimetric method (NEFAC; Wako Chemicals GmbH, Neuss, Germany). Catecholamines were determined by an in-house reversed phase HPLC method with fluorescence detection. Plasma insulin concentrations were determined by radioimmunoassay (RIA) (Immulite, Diagnostic Products Corporation, Los Angeles, California, USA).

Calculations

Rate of appearance (R_a) of glycerol at rest was calculated by dividing the infusion rate of [$^2H_5$]glycerol by the plasma glycerol enrichment. During submaximal exercise glycerol R_a was calculated using the single-pool non-steady state Steele equation, adapted for stable isotope methodology as described elsewhere [17]:

$R_a = (F - V_d[(C_2+C_1)/2][(E_2-E_1)/(t_2-t_1)])/((E_2+E_1)/2)$,

where F is the infusion rate (μmol·kgFFM^{-1}·min^{-1}), V_d is the distribution volume of glycerol, C_1 and C_2 are glycerol concentrations at times 1 (t_1) and 2 (t_2), respectively, and E_1 and E_2 are the glycerol enrichments at t_1 and t_2, respectively. The effective V_d was assumed to be 230 ml·kgBW^{-1} [18]).

Statistics

Results are expressed as mean ± standard error of the mean (SEM). One way analysis of variance (ANOVA) was used to determine differences in baseline characteristics and substrate and hormone concentrations between normal weight patients, underweight patients and controls. LSD multiple comparison test was used as post hoc test. Mixed design ANOVA for repeated measures was performed in order to analyse potential differences in glycerol R_a between the three study groups. Groups were entered as between-group variables, while individual glycerol R_a's at various timepoints of the protocol were used as within-group variables. This analysis was performed for each of the phases of the protocol (rest, submaximal exercise and recovery) and specifically focussed on significant between-group differences in glycerol R_a during any of these phases. Levene's test showed homogeneity of variance of repeated measures of glycerol R_a's. In order to assess the variation explained by between-group differences and the variation explained by unsystematic factors, *F*-ratios were calculated. Mauchly's test of sphericity was performed to assess equality of variances of the differences between groups. Since the condition of sphericity was not met, Greenhouse-Geisser correction was applied in the production of *F*-ratios.

RESULTS

General characteristics of all subjects are shown in Table 1. As expected, the normal weight COPD patients could be typified as sarcopaenic based on a comparable FM but reduced fat-free mass index in comparison to controls. In the underweight COPD patients, fat mass (index) and fat-free mass (index) were significantly decreased in comparison to the other COPD group and controls (Figure 1). Lung function and arterial blood gases were equally impaired in both COPD groups. Functional capacity was impaired in COPD and was more

reduced in underweight patients compared to sarcopaenic patients. This was probably the result of the difference in fat-free mass, since $V'O_{2max}$ was related to FFMI ($r = 0.679$, $p < 0.05$).

Resting postabsorptive rate of appearance of glycerol was comparable in sarcopaenic COPD patients (4.1 ± 0.6 μmol·kgFFM^{-1}·min^{-1}) and controls (3.3 ± 0.2 μmol·kgFFM^{-1}·min^{-1}, $p = 0.25$) (Figure 2). Glycerol R_a in underweight COPD patients (4.3 ± 0.5 μmol·kgFFM^{-1}·min^{-1}, ns) was comparable to the other groups. Mixed design ANOVA for repeated measures revealed a non-significant effect of study group on whole body glycerol R_a at rest ($F(1, 2) = 308.47$, ns). Fasting plasma levels of FFA and glycerol were comparable in the three groups (Table 2). In underweight COPD patients, catecholamine concentrations were significantly increased compared to sarcopaenic patients and controls. Also, insulin levels were significantly increased in sarcopaenic patients, while insulin concentrations in underweight COPD patients were decreased.

Submaximal bicycle exercise resulted in significant increases in glycerol R_a in all three groups (Figure 2). The proportional increase in glycerol R_a during submaximal exercise was slightly less in sarcopaenic COPD patients (59 ± 18 %) in comparison to underweight patients (82 ± 22 %, ns). In controls, the relative increment in glycerol R_a was even greater during submaximal exercise at both identical absolute workload (107 ± 22 %, ns) as well as identical proportional load (177 ± 39%, $p < 0.05$ for both COPD groups). As a consequence, the end-of-exercise values for glycerol R_a were lower in sarcopaenic patients (6.8 ± 1.2 μmol·kgFFM^{-1}·min^{-1}), than in underweight patients (7.6 ± 1.0 μmol·kgFFM^{-1}·min^{-1}) and controls (30 Watt: 7.7 ± 1.3 μmol·kgFFM^{-1}·min^{-1}; 50% W_{max}: 7.9 ± 1.1 μmol·kgFFM^{-1}·min^{-1}), but differences were not significant (Figure 2). After exercise, glycerol R_a recovered to baseline in all groups and values were comparable (Figure 2). No significant effects of study group on whole body glycerol R_a was observed during submaximal exercise at identical absolute work load ($F(1, 2) = 201.96$, ns) and identical relative work load ($F(1,2) = 213.76$, ns) and during recovery periods ($F(1,2) = 189.71$, ns and $F(1,2) = 212.86$, ns, respectively). Plasma concentrations of FFA, glycerol and catecholamines increased significantly after submaximal exercise in all groups, and end-of-exercise values were also identical (Table 2).

In bivariate correlation analysis in the total study population, resting glycerol R_a was related to plasma epinephrine concentration ($r = 0.520$, $p < 0.05$) and basal glycerol level ($r = 0.760$, $p < 0.001$), while correlations with body mass index, fat-free mass (index) and fat mass

(index) were absent. End-of-exercise glycerol R_a was significantly related to post-exercise glycerol ($r = 0.762$, $p < 0.01$) and FFA ($r = 0.631$, $p < 0.05$) plasma levels and to resting norepinephrine concentration ($r = 0.618$, $p < 0.05$) in COPD patients.

DISCUSSION

This is the first study that investigated lipid kinetics using glycerol stable isotope tracer methodology in patients with COPD. Also, the contribution of derangements in whole body lipolysis to body composition was not previously studied in COPD. No differences in resting and exercise-induced lipolysis were observed between sarcopaenic COPD patients and age-matched controls. Thus, in normal weight and clinically stable COPD patients, (relative) maintenance of fat mass with evidence of muscle wasting is not related to altered adipocyte lipolysis.

Total body fat mass is determined by the balance between lipid synthesis and degradation. Lipids are stored in the adipocytes as triglycerides and constitute the main fuel reserve of the body. Following hormonal stimulation, the stored triglycerides are hydrolyzed to their components fatty acids and glycerol and this process is called lipolysis. The released fatty acids are either used for mitochondrial beta-oxidation to produce ATP or reesterified to triacylglycerol and restored. FFA are the major source of energy for resting muscle. It has been consistently shown that muscle fat oxidative capacity is reduced in COPD patients [8], partly as an adaptation to a more sedentary lifestyle due to disease related symptoms. Although the effects of physical inactivity on adipose tissue lipolysis in COPD have not been studied, available evidence suggests that whole body lipolytic rate is not related to training status [19]. No difference in exercise-induced lipolysis was observed between untrained and endurance-trained healthy subjects, although fat oxidation was enhanced in the latter group [20].

Previously, Schiffelers et al. [9] reported a reduced increase in plasma fatty acid levels and a blunted thermogenic response during β-adrenergic stimulation in normal weight COPD patients with high fat mass compared to controls. The authors suggested that disturbed lipolytic responsiveness contributes to the development or maintenance of increased fat mass in the subgroup of sarcopaenic COPD patients. In contrast to the present study, no patients

with a reduced fat mass were studied and whole body lipolysis was not assessed. However, the results of the present study are in line with these previous observations. Although whole body lipolytic rate was comparable between groups, homeostatic control of lipolysis was altered in sarcopaenic COPD patients, as indicated by hyperinsulinaemia. Thus, the inhibitory effect of insulin on lipolytic rate seemed impaired in sarcopaenic COPD patients. Also, the lipolytic response to exercise tended to be decreased in this subgroup.
In contrast to the present results, Jakobsson et al. [21] reported increased turnover rate and plasma levels of free fatty acids in normal weight COPD patients (BMI 23.6 $kg \cdot m^{-2}$), suggestive for increased state of lipolysis. The fact that included patients were chronically hypoxaemic may account for the distinct results compared to the normoxaemic patients in the present study. In healthy subjects, elevated levels of FFA were observed during chronic hypobaric hypoxia, probably related to enhanced epinephrine-induced lipolysis [22].

Lipolytic rate was not enhanced in underweight COPD patients in comparison to normal weight patients or controls, despite significantly elevated catecholamine levels. Since catecholamines are the primary stimulators of lipolysis via β-adrenoceptors, alterations in sympathetic tone may result in changes in fat mass and body weight in COPD patients. Indeed, Hofford et al. [23] reported nearly doubled plasma norepinephrine levels in underweight patients with severe COPD in comparison to healthy normal weight control subjects. However, results of the present study suggests a reduced sensitivity to circulating catecholamines and confirm the observations by Schiffelers et al. [9]. Due to chronic overstimulation of the sympathic nervous system in COPD [24] and the long-term usage of β_2-agonists for bronchodilatation, β-adrenoceptors may become desensitized and subsequently the lipolytic response following hormonal stimulation might be reduced [25].

Since the contribution of impaired lipolysis to the sarcopaenic phenotype of COPD patients is unlikely, selective wasting of fat-free mass rather than preservation of fat mass seems to be the predominant pathophysiological mechanism. Indeed, increased whole body myofibrillar protein breakdown, assessed by a methylhistidine stable isotope tracer protocol, has been reported in underweight COPD patients with reduced fat-free mass and fat mass, in comparison to normal weight patients and controls with preserved fat-free mass [5]. In addition, increased cellular [6] and muscular protein catabolism [7] was observed in COPD patients with evidence for muscle atrophy. This suggests that increased muscle protein

breakdown is the trigger in the body compositional shift in COPD, towards reduced fat-free mass.

This study assessed potential differences in lipolytic rate in clinically stable sarcopaenic COPD patients without recent weight loss. However, the present body composition of these COPD patients may result from foregoing episodes of shifts in body fat and fat-free tissues. During acute exacerbations of the disease a combination of enhanced hypoxemia, increased sympathetic tone, more frequent use β_2-agonists as reliever therapy, administration of systemic corticosteroids and a reduced dietary intake may induce short-term bursts of increased lipolysis resulting in degradation of body fat mass and weight loss. Thus, it might be interesting to study potential periods with deranged lipid metabolism during acute exacerbation in relation to longitudinal changes in body composition in COPD in the future.

In summary, resting and exercise-induced whole body lipolytic rate was comparable in sarcopaenic COPD patients, underweight patients and matched controls, despite significant alterations in endocrinological control of lipolysis. Disturbances in lipolytic rate do not contribute to alterations in body composition in COPD.

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TABLES

TABLE 1. Baseline characteristics of the study groups (mean ± SEM). BMI: body mass index; FFM: fat-free mass, assessed by bioelectrical impedance analysis; FFMI: fat-free mass index; FM: fat mass; FMI: fat mass index; FEV_1: forced expiratory volume in one second; DL_{CO}: diffusing capacity for carbon monoxide; RV: residual volume; P_aO_2: arterial oxygen tension; P_aCO_2: arterial carbon dioxide tension; $V'O_{2max}$: maximal oxygen consumption. Significance of differences between COPD patients and controls is indicated as: #: $p < 0.05$, ##: $p < 0.01$, ###: $p < 0.001$. Significant differences between sarcopaenic and underweight COPD patients are shown as: *: $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.

	Controls (n = 7)	Sarcopaenic COPD (n = 7)	Underweight COPD (n = 6)
Age, yrs	64 ± 2	64 ± 4	70 ± 4
Body composition			
Height, cm	173.7 ± 2.2	172.9 ± 1.9	168.1 ± 1.5 #
Weight, kg	85.5 ± 5.6	82.5 ± 3.5	58.2 ± 2.1 ### **
BMI, $kg \cdot m^{-2}$	28.2 ± 1.2	27.5 ± 0.9	20.6 ± 0.7 ### ***
FFM, kg	62.6 ± 2.7	56.1 ± 2.4 $^{p=0.06}$	45.3 ± 1.5 ### **
FFMI, $kg \cdot m^{-2}$	20.7 ± 0.5	18.8 ± 0.8 #	16.0 ± 0.4 ### *
FM, kg	22.9 ± 3.3	26.4 ± 2.9	12.9 ± 0.8 # **
FMI, $kg \cdot m^{-2}$	7.5 ± 0.9	8.8 ± 0.9	4.6 ± 0.3 # **
Pulmonary function			
FEV_1, %predicted	105 ± 4	53 ± 5 ###	51 ± 5 ###
FEV_1/FVC%	73.0 ± 1.8	43.0 ± 1.9 ###	34.4 ± 4.6 ###
DL_{CO}, %predicted	117 ± 5	62 ± 7 ###	62 ± 4 ###
RV/TLC%	36.3 ± 1.6	43.2 ± 3.5	51.0 ± 10.0
P_aO_2, kPa	-	8.5 ± 7.4	8.5 ± 7.8
P_aCO_2, kPa	-	5.1 ± 0.2	5.1 ± 0.1
Exercise capacity			
Peak work rate, %predicted	129 ± 9	48 ± 5 ###	44 ± 4 ###
$V'O_{2max}$, %predicted	110 ± 6	62 ± 5 ###	57 ± 3 ###

TABLE 2. Resting and end-of-exercise plasma free fatty acid (FFA), glycerol and hormone concentrations (mean ± SEM). [1]: for controls values after exercise at identical absolute workload are shown. Significance of differences between patients and controls is indicated as: #: $p < 0.05$. Significant differences between COPD subgroups are shown as: *: $p < 0.05$ and **: $p < 0.01$.

	Controls (n = 7)	Sarcopaenic COPD (n = 7)	Underweight COPD (n = 6)
Resting state			
FFA ($mmol \cdot l^{-1}$)	1.04 ± 0.14	1.08 ± 0.13	0.99 ± 0.11
Glycerol ($mmol \cdot l^{-1}$)	79.9 ± 6.4	85.0 ± 9.5	97.1 ± 11.1
Insulin ($pmol \cdot l^{-1}$)	47 ± 9	76 ± 12 #	22 ± 6 **
Epinephrine ($nmol \cdot l^{-1}$)	0.45 ± 0.07	0.52 ± 0.12	1.01 ± 0.24 # *
Norepinephrine ($nmol \cdot l^{-1}$)	0.35 ± 0.09	0.85 ± 0.21	1.22 ± 0.46 #
End-of-exercise[1]			
FFA ($mmol \cdot l^{-1}$)	1.79 ± 0.28	1.45 ± 0.15	1.42 ± 0.25
Glycerol ($mmol \cdot l^{-1}$)	230.6 ± 41.2	207.7 ± 40.5	229.1 ± 49.7
Insulin ($pmol \cdot l^{-1}$)	51 ± 8	66 ± 13	19 ± 3 # **
Epinephrine ($nmol \cdot l^{-1}$)	0.85 ± 0.18	3.68 ± 2.40	2.88 ± 1.00
Norepinephrine ($nmol \cdot l^{-1}$)	1.34 ± 0.21	2.41 ± 0.51	2.18 ± 0.86

FIGURE LEGENDS

Figure 1. Body composition of the study groups, displayed in stacked bars. The contribution of fat mass index (FMI, grey area) and fat-free mass index (FFMI, black area) to the body mass index (BMI) is shown. BMI of sarcopaenic COPD patients was comparable to controls, although fat-free mass index was significantly reduced. Underweight COPD patients were characterized by reduced BMI, FFMI and FMI. Standard errors of the mean and p-values are displayed in table 1.

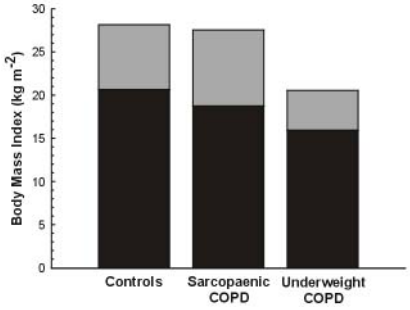
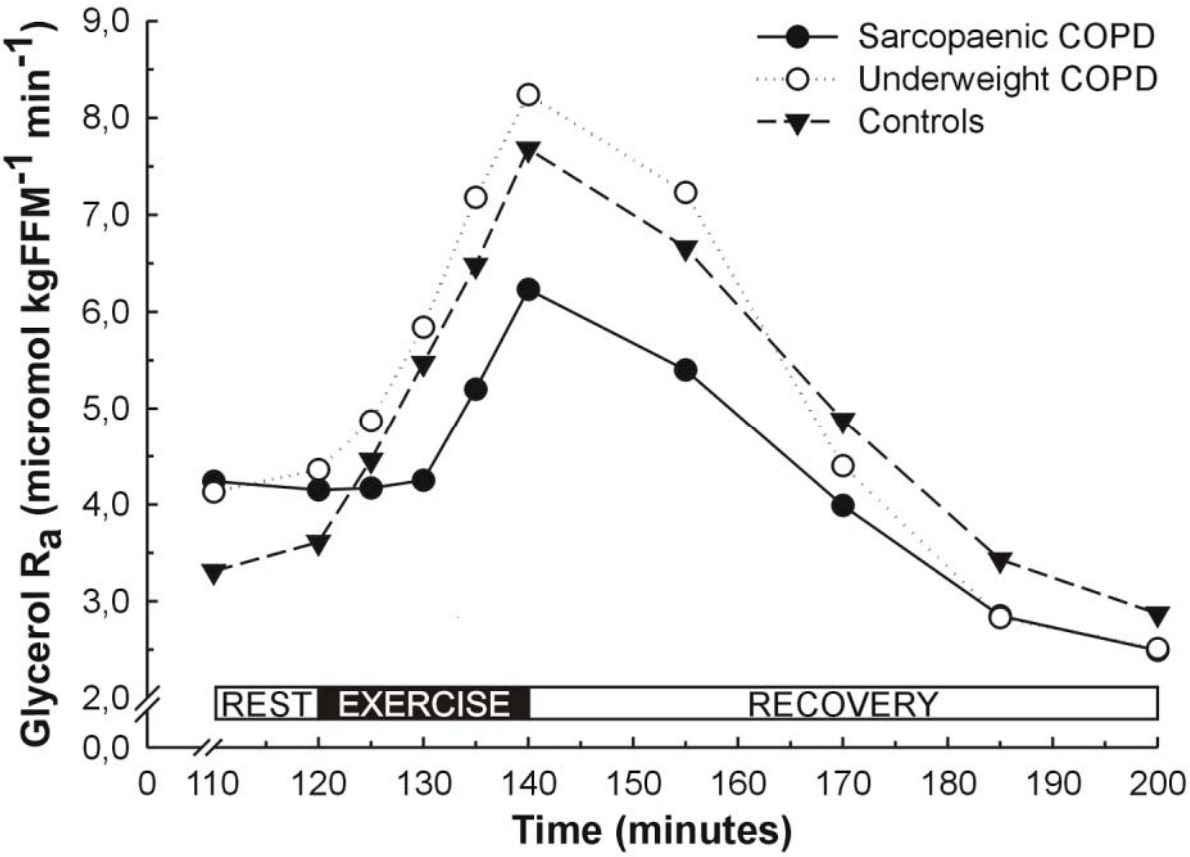


Figure 2. Whole body lipolysis measured by rate of appearance (R_a) of glycerol at rest, during submaximal cycle exercise and during recovery from exercise. Healthy controls (n=7), closed triangles; sarcopaenic COPD patients (n=7), closed circles; underweight COPD patients (n=6), open circles. No significant differences were observed between groups at any part of the study. For clearity, standard errors of the mean are not shown.


Sarcopaenic COPD
Underweight COPD
Controls
Glycerol R_a (micromol kgFFM^{-1} min^{-1})
9,0
8,0
7,0
6,0
5,0
4,0
3,0
2,0
0,0
REST
EXERCISE
RECOVERY
0
110
120
130
140
150
160
170
180
190
200
Time (minutes)