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Original Research

Association of resting energy expenditure and nutritional substrate oxidation with COPD stage and prediction indexes

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ABSTRACT

While increase in resting energy expenditure (REE) of COPD patients is generally accepted, there is a lack of information about nutritional substrates oxidation (NSO) in this specific population. The aim of this study was comparison of REE and NSO from indirect calorimetry between COPD patients and control subjects and to evaluate possible associations with the disease stage and prediction indexes.

In this observational study, 50 consecutive outpatients with stable COPD (COPD group) were examined and compared with 25 volunteers without respiratory problems (control group). Body composition, REE and NSO were determined in all study participants. All COPD subjects underwent a comprehensive examination to determine COPD severity and prognostic scales.

Measured REE values adjusted for body weight, fat-free mass (FFM), and body surface were approximately 10% higher in COPD patients than in the control group. Respiratory quotient (RQ) and non-protein RQ (nRQ) values were respectively 5% and 10% higher in the COPD group. Adjusted carbohydrate oxidation was almost two times higher in comparison with the control group. We found no differences in absolute values of lipid and protein oxidation between the groups. Correlation analysis proved a positive association of relatively expressed REE and oxidation of lipids, and a negative association of RQ, nRQ and oxidation of carbohydrates with the value of prediction indexes.

In conclusion, our study demonstrated metabolic changes in COPD patients leading to increased values of REE and changes in NSO which were associated with the disease stage, and which can be applied for nutritional support in clinical practice.

1. Introduction

Patients with chronic obstructive pulmonary disease (COPD) suffer not only from impairment of respiratory function but also often from energy metabolism disturbances. Increased resting energy expenditure (REE) has been found in COPD patients in many studies [1–3]. Hypermetabolism together with compromised nutritional status could be associated with malnutrition and sarcopenia, independent predictors of morbidity and mortality [4–6].

While an increase in REE of COPD patients is generally accepted, there is a lack of information about nutritional substrates oxidation (NSO) in this specific population. Only a few studies have been concerned with this topic. Kao et al. found by isotope tracer technique increased whole-body protein turnover which correlated with REE in COPD patients [7]. They also described increased whole-body glucose production, clearance, oxidation and rate of glycolysis [8]. Ramires et al. demonstrated by means of indirect calorimetry increased values of respiratory quotient and carbohydrate oxidation, and only a trend in decrease of lipid oxidation [9]. Also found was a correlation between REE and lipid oxidation in ventilated COPD patients [10].

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Indirect calorimetry is the gold standard for determination of energy expenditure. Advantage of this method is also quantification of NSO. The ratio of carbon dioxide produced, and oxygen consumed varies by type of substrate being oxidized. During carbohydrates metabolism, there is an equal amount of carbon dioxide produced and oxygen consumed, while during lipid metabolism, there is less carbon dioxide produced than oxygen consumed. Knowledge of metabolic changes in COPD patients could help to achieve appropriate dietary intervention necessary to prevent sarcopenia, tailored to their individual needs (it could reflect not only energy but also macronutrients demands).

The aim of this study was comparison of REE and NSO from indirect calorimetry between COPD patients and controls without impairment of respiratory function, and to evaluate possible associations with disease stage and prediction indexes: BODE (**B**ody-mass index, the degree of airflow **O**bstruction and **D**yspnea, and **E**xercise capacity), updated BODE ($_{U}$BODE) and ADO (**A**ge, **D**yspnea, and airflow **O**bstruction). To the best of our knowledge there is to date no study determining these associations in COPD patients.

2. Patients and methods

2.1. Study participants and design of the study

In this observational study, we compared two study groups. The first group (COPD group) consisted of 50 consecutive outpatients with stable COPD, 37 men and 13 women; and a second control group of 25 volunteers without respiratory problems, 20 men and 5 women. Detailed basic anthropometric characteristics of both groups are presented in Table 1.

COPD patients were recruited from the Department of Pneumology, University Hospital Hradec Kralove, Czech Republic (most of them from the Czech multicentric research database of COPD – Registry of the Czech Pneumological and Physiological Society). The details concerning inclusion and exclusion criteria, and the relevant items of a patient's history including comorbidities and medications used were described by Novotná et al. [11]. Briefly, the main inclusion criteria were a diagnosis of COPD, stable patient condition (free of acute exacerbation of COPD more than 8 weeks prior to study enrolment) and post-bronchodilator forced expiratory volume in 1 s (FEV_1) $\leq$ 60%. The main exclusion criteria were presence of comorbidities affecting the energy metabolism (eg. malignancy, diabetes and other endocrine disorders) and/or systemic corticosteroid use. All COPD subjects underwent a comprehensive examination to determine prognostic scales (BODE, $_{U}$BODE, and ADO indexes) and COPD severity: Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage and ABCD assessment.

The main inclusion criterion for the control group was the absence of respiratory problems (normal value of spirometric parameters). The exclusion criteria were identical to the COPD group.

Body composition, REE and NSO were determined for all study participants. All measurements were taken in the morning after a fast of 12 h (in COPD patients before rehabilitation commenced).

The study was reviewed and approved by the Ethical Committee of University Hospital in Hradec Kralove and performed in accordance with the Declaration of Helsinki. All subjects gave written informed consent.

2.2. COPD severity and prognostic scales

The BODE index was calculated according to Celli et al. [12] and the $_{U}$BODE and ADO indexes according to Puhan et al. [13]. Patients were divided into four grades in line with the GOLD classification according to post-bronchodilator airflow limitation [14]. The ABCD assessment was used to distinguish patients to four categories according to risk and level of symptoms [15].

2.3. Body composition

Body weight was measured in underwear to the nearest 0.1 kg (Tanita Corporation, Japan). Height was measured with a stadiometer to the nearest 0.5 cm. Both were used to calculate body mass index, BMI (kg m^{-2}). Body composition was determined by means of skin-fold anthropometry (SFA), because this method has been proven as appropriate for COPD patients [16]. Triple measurements were taken in four standard places (triceps, biceps, subscapular and suprailiac) using a caliper (Best K-501, Trystom, Czech Republic). All measurements were performed by a sole trained examiner. Body density was estimated according to the method of Durnin and Womersley [17], and the Siri equation was used to calculate fat mass [18]. Fat-free mass (FFM) was calculated by subtracting the amount of fat mass from body weight. FFM was corrected for height to produce the fat-free mass index (FFMI), expressed in kg m^{-2}. Body surface area (BSA) in m^2 was calculated by the equation of DuBois and DuBois [19].

2.4. Indirect calorimetry

Energy metabolism was measured by indirect calorimetry (Vmax Series, V6200 Autobox, SensorMedics Corporation, Yorba Linda, CA, USA). Before each examination the indirect calorimeter was calibrated according to standard procedures for the machine: the flowmeter was calibrated using a 3 L calibration syringe (Viasys, Germany) and the gas analysers were calibrated using a two-point calibration method with certified gases (Carefusion, USA). Accuracy of the calorimeter was tested by an ethanol burning kit (Cosmed, Italy). Measurements were obtained under conditions of ambient temperature (21–22 °C) and relative humidity (60–80%), with the subject in a relaxed, supine position under the canopy hood. Participants were at rest for at least 30 min before the assessment. The measurements were taken over approximately a 30-min period, until the steady state condition was reached.

Oxygen consumption per minute (VO_2) and carbon dioxide production per minute (VCO_2) were measured by indirect calorimetry. Urine samples were collected 24 h before the measurement and urinary nitrogen (UN) concentration, quantifying protein metabolism, was determined by a standard kinetic ultraviolet assay (Roche/Hitachi 917 Analyzer, Roche Diagnostics, Indianapolis, IN, USA) at University Hospital. From the obtained parameters, REE was calculated by the Weir equation [20]. This equation applies a correction for nitrogen expenditure (NE). NE was calculated as the sum of UN and non-urea nitrogen from feces, skin, and miscellaneous, predicted from the weight [21]. REE values were adjusted for weight, FFM and BSA. The predicted REE was evaluated using the Harris-Benedict equation from weight, height, age and gender [22]. Respiratory quotient (RQ) and non-protein respiratory quotient (nRQ) were calculated from VO_2 and VCO_2 (nRQ also from NE) [23]. For NSO determination, specific formulae were used

Table 1
Basic anthropometric characteristics.

Parameter	$Control_{total}$ (n = 25)	$Control_{male}$ (n = 20)	$COPD_{total}$ (n = 50)	$COPD_{male}$ (n = 37)
Age [years]	65 ± 6	66 ± 6	67 ± 7	66 ± 7
Height [cm]	174 ± 7	176 ± 7	170 ± 8	174 ± 6
Weight [kg]	88.0 ± 17.7	91.3 ± 17.5	82.8 ± 20.4	89.6 ± 17.2
BMI [kg·m^{-2}]	29.0 ± 5.0	29.6 ± 5.1	28.4 ± 6.1	29.7 ± 5.4
FFMI [kg·m^{-2}]	20.5 ± 3.1	21.4 ± 2.7	19.2 ± 3.2	19.6 ± 3.0[a]
BSA [m^2]	2.02 ± 0.20	2.07 ± 0.19	1.93 ± 0.25	2.03 ± 0.20

COPD – chronic obstructive pulmonary disease; BMI – Body mass index; FFMI – fat-free mass index; BSA – body surface area.
Results are expressed as mean ± standard deviation.
[a] Unpaired t-test COPD vs. control group ($P \leq 0.05$).

Table 2
Equations for determination of nutritional substrates oxidation according to nonprotein respiratory quotient value.

	nRQ value	Nutritional substrates oxidation
Carbohydrates [g·day^{-1}]	<0.706	$-3.590 \times VCO_2 \times 1440 + 2.540 \times VO_2 \times 1440 + 2.050 \times NE$
	0.706–1.000	$4.115 \times VCO_2 \times 1440 + 2.909 \times VO_2 \times 1440 + 2.539 \times NE$
	>1.000	$-0.187 \times VCO_2 \times 1440 + 1.393 \times VCO_2 \times 1440–6.892 \times NE$
Lipids [g·day^{-1}]	<0.706	$0.700 \times VCO_2 \times 1440 – 3.390 \times NE$
	≥0.706	$1.689 \times VO_2 \times 1440 – 1.689 \times VCO_2 \times 1440–1.539 \times NE$
Proteins [g·day^{-1}]	0.650–1.250	$6.250 \times NE$
Carbohydrates [kcal·day^{-1}]	<0.706	1.720 × Carbohydrates [g·day^{-1}]
	≥0.706	4.180 × Carbohydrates [g·day^{-1}]
Lipids [kcal·day^{-1}]	<1.000	9.460 × Lipids [g·day^{-1}]
	≥1.000	1.089 × Lipids [g·day^{-1}]
Proteins [kcal·day^{-1}]	0.650–1.250	4.320 × Proteins [g·day^{-1}]

nRQ – nonprotein respiratory quotient; VCO_2 [l·min^{-1}] – volume of carbon dioxide production; VO_2.
[l·min^{-1}] – volume of oxygen utilization; NE – nitrogen excretion [g·day^{-1}].
Adapted from Hronek and Zadak 2011 [24].

according to nRQ value from VO_2, VCO_2 and NE (see Table 2) [24]. NSO was expressed in grams or kilocalories per day or as a relative value in %. NSO values were adjusted for weight, FFM and BSA.

2.5. Statistical analysis

The calculation of sample size was performed using OpenEpi online calculator (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01, updated 2013/04/06: www.OpenEpi.com). The mean differences in REE adjusted for FFM evidenced in the study by Sergi et al., 2006 [3] and in RQ and carbohydrate oxidation evidenced in the study by Ramires et al., 2012 [9] were considered for calculation (as the association of REE and NSO with disease stage and prediction indexes in COPD patients is not known, we could not take this into account in the calculation). Considering these differences and when setting power of 80%, two-sided confidence interval of 95%, and ratio of COPD and control group 2:1, the largest estimated sample size was 66 patients (44 for COPD and 22 for control group).

The acquired data were analysed using the programs GraphPad Prism 8.2.1 (GraphPad Software, La Jolla, CA, USA) and Excel 2016 (Microsoft, Redmond, WA, USA). All parameters were evaluated by descriptive statistics. Normality of the data was assessed by D'Agostino and Pearson omnibus normality test. The unpaired *t*-test or Mann–Whitney *U* test were used for determining differences between COPD and control groups or groups according to the ABCD assessment. The ordinary one-way analysis of variance with Tukey's multiple comparisons test or Kruskal–Wallis test was applied to determine differences in the observed parameters among the four GOLD stages. Spearman's correlation coefficient was used for demonstration of relationships between parameters. Significance was accepted at $P \leq 0.05$. Results are expressed as mean ± SD or median (25th percentile; 75th percentile). There are presented results in male only group in addition to total group due to relatively small proportion of women in the study.

3. Results

3.1. Basic characteristics

Basic anthropometric characteristics of the study groups are summarized in Table 1. The mean value of BMI 28.4 ± 6.1 kg m^{-2} corresponds to overweight, while the mean value of FFMI 19.2 ± 3.2 kg m^{-2} corresponds to a normal level of FFM. No significant differences between the study groups were found in any of the basic anthropometric characteristics. The only exception was FFMI in the male-only COPD group, which was about 8% lower in comparison with the male-only control group.

According to the study design, the basic spirometric parameters in the control group were close to the predicted values, while being significantly impaired in the COPD group. For example, the FEV_1 values were 101 ± 14% and 54 ± 20% of predicted values for the control and COPD groups, respectively.

According to the GOLD classification, 6 COPD patients were of stage 1, 23 of stage 2, 16 of stage 3 and 5 patients of stage 4. According to ABCD assessment, 4 patients were of group A, 22 of group B and 24 of group D.

3.2. Resting energy expenditure

The absolute values of measured and predicted REE were not different between the study groups (see Table 3). However, measured REE values adjusted for body weight, FFM and body surface in the COPD patients were significantly higher than in the control group (approximately 10% increase). The median of relatively expressed REE (as a percentage of the estimated values) in COPD patients corresponds to hypermetabolism, while in the control group is in the normal range. Although volumes of oxygen utilization and carbon dioxide production were not significantly different between the study groups (only carbon dioxide production was about 14% higher in the male-only COPD group in comparison with the male-only control), both RQ and nRQ values were higher in the COPD group (5% increase for RQ and 10% for nRQ).

3.3. Nutritional substrates oxidation

Determination of NSO is summarized in Table 4. We found no differences in absolute values of lipid and protein oxidation between COPD and control group, neither unadjusted nor adjusted for body weight, FFM and body surface. Only lipid oxidation was 15% lower in the COPD group when expressed relatively. The most developed changes were

Table 3
Resting energy expenditure.

Parameter	$Control_{total}$ (n = 25)	$Control_{male}$ (n = 20)	$COPD_{total}$ (n = 50)	$COPD_{male}$ (n = 37)
VO_2 [l·min^{-1}]	0.27 ± 0.05	0.29 ± 0.05	0.28 ± 0.06	0.30 ± 0.05
VCO_2 [l·min^{-1}]	0.20 ± 0.04	0.21 ± 0.04	0.23 ± 0.05	0.24 ± 0.04[a]
RQ	0.74 (0.69; 0.79)	0.73 (0.68; 0.78)	0.78 (0.72; 0.84)[a]	0.79 (0.74; 0.84)[a]
nRQ	0.71 (0.67; 0.79)	0.70 (0.65; 0.77)	0.78 (0.71; 0.85)[a]	0.79 (0.71; 0.85)[a]
REE [kcal·day^{-1}]	1835 ± 343	1919 ± 309	1910 ± 410	2048 ± 353
REE [kcal·day^{-1} kg^{-1}]	20.9 (19.2; 23.3)	21.3 (19.0; 23.7)	22.6 (21.4; 25.5)[a]	22.5 (21.4; 25.6)
REE [kcal·day^{-1} kg^{-1} FFM]	29.7 ± 3.3	29.1 ± 2.9	33.2 ± 3.9[a]	32.3 ± 3.6[a]
REE [kcal·day^{-1} m^{-2}]	930 (812; 992)	950 (838; 1015)	998 (891; 1061)[a]	1022 (945; 1071)[a]
REE_{PR} [kcal·day^{-1}]	1682 ± 275	1753 ± 256	1595 ± 321	1720 ± 264
REE [% predicted value]	109 ± 13	110 ± 14	120 ± 15[a]	120 ± 14[a]

COPD – chronic obstructive pulmonary disease; VO_2 – volume of oxygen utilization; VCO_2 – volume of carbon dioxide production; RQ – respiratory quotient; nRQ – nonprotein respiratory quotient; REE – resting energy expenditure; FFM – fat-free mass; REE_{PR} – predicted value of resting energy expenditure by Harris-Benedict equation.
Results are expressed as mean ± standard deviation or median (25% percentile; 75% percentile).
[a] *t*-test or Mann-Whitney test COPD vs. control group ($P \leq 0.05$).

Table 4
Nutritional substrates oxidation.

Parameter	$Control_{total}$ (n = 25)	$Control_{male}$ (n = 20)	$COPD_{total}$ (n = 50)	$COPD_{male}$ (n = 37)
Carbohydrates [g·day^{-1}]	66 (46; 104)	58 (27; 98)	101 (43; 212)	124 (45; 213)
Carbohydrates [kcal·day^{-1}]	153 (94; 395)	100 (73; 340)	411 (94; 886)[a]	517 (93; 888)[a]
Carbohydrates [%]	8 (5; 25)	6 (4; 19)	23 (5; 42)	24 (6; 41)[a]
Carbohydrates [g·day^{-1} kg^{-1}]	0.9 (0.5; 1.2)	0.7 (0.3; 1.2)	1.4 (0.5; 2.2)[a]	1.3 (0.5; 2.1)
Carbohydrates [g·day^{-1} kg^{-1} FFM]	1.1 (0.6; 1.8)	0.9 (0.4; 1.6)	2.1 (0.8; 4.1)[a]	2.1 (0.8; 4.1)[a]
Carbohydrates [g·day^{-1} m^{-2}]	38 (21; 53)	29 (14; 50)	57 (21; 107)[a]	64 (21; 100)[a]
Lipids [g·day^{-1}]	121 (99; 161)	144 (110; 167)	118 (62; 155)	131 (72; 159)
Lipids [kcal·day^{-1}]	1148 (939; 1523)	1363 (1043; 1576)	1116 (587; 1467)	1239 (680; 1505)
Lipids [%]	71 (56; 77)	74 (62; 78)	60 (39; 75)[a]	57 (39; 76)[a]
Lipids [g·day^{-1} kg^{-1}]	1.6 (1.2; 1.8)	1.6 (1.3; 1.9)	1.5 (0.9; 1.8)	1.4 (1.0; 1.7)
Lipids [g·day^{-1} kg^{-1} FFM]	2.2 (1.9; 2.5)	2.2 (1.8; 2.5)	2.2 (1.3; 2.7)	2.2 (1.5; 2.7)
Lipids [g·day^{-1} m^{-2}]	64 (50; 78)	74 (55; 79)	65 (37; 77)	66 (40; 78)
Proteins [g·day^{-1}]	84 (65; 101)	86 (66; 101)	70 (56; 99)	73 (57; 106)
Proteins [kcal·day^{-1}]	363 (279; 433)	373 (287; 437)	303 (240; 430)	317 (246; 459)
Proteins [%]	19 (14; 24)	19 (14; 23)	17 (11; 20)	15 (11; 20)
Proteins [g·day^{-1} kg^{-1}]	0.9 (0.7; 1.1)	1.0 (0.7; 1.1)	0.9 (0.7; 1.1)	0.8 (0.6; 1.1)
Proteins [g·day^{-1} kg^{-1} FFM]	1.3 (1.0; 1.7)	1.3 (1.0; 1.5)	1.4 (0.9; 1.8)	1.3 (0.9; 1.9)
Proteins [g·day^{-1} m^{-2}]	42 (31; 47)	42 (31; 47)	37 (28; 49)	37 (28; 50)

COPD – chronic obstructive pulmonary disease; FFM – fat-free mass.
Results are expressed as median (25% percentile; 75% percentile).
[a] Mann-Whitney test COPD vs. control group ($P \leq 0.05$).

related to carbohydrate oxidation: expressed in kcal per day this was almost three times higher in the COPD group. Even when we adjusted carbohydrate oxidation for body weight, FFM and BSA, it remained almost two times higher in comparison with the control group. Also, relative oxidation of carbohydrates was almost three times higher in the COPD group.

3.4. COPD severity and prediction indexes

When we stratified the COPD patients according to GOLD stage, we did not find any differences in REE values among the subgroups. However, Kruskall-Wallis test revealed differences in NSO, specifically in lipid oxidation expressed in kilocalories per day ($P = 0.049$), lipid oxidation adjusted for FFM ($P = 0.022$) and protein oxidation adjusted for body weight ($P = 0.029$). The lowest lipid oxidation was found in the GOLD 1 subgroup of COPD patients.

Comparison of COPD patients in the two most frequent subgroups of ABCD assessment, D and B, revealed differences in REE. Group D (more symptoms, high risk) had approximately 10% higher relatively expressed REE ($P = 0.031$) than group B (more symptoms, low risk). Also, REE adjusted for FFM was 10% higher ($P = 0.005$) and for BSA 5% higher ($P = 0.044$) in the D group (see Figs. 1 and 2). We found that values of NSO did not differ between B and D groups.

Correlation analysis proved a positive association for relatively expressed REE and oxidation of lipids, and a negative association of RQ, nRQ and oxidation of carbohydrates with the prediction indexes (BODE, $_{U}$BODE and ADO). For details see Table 5.

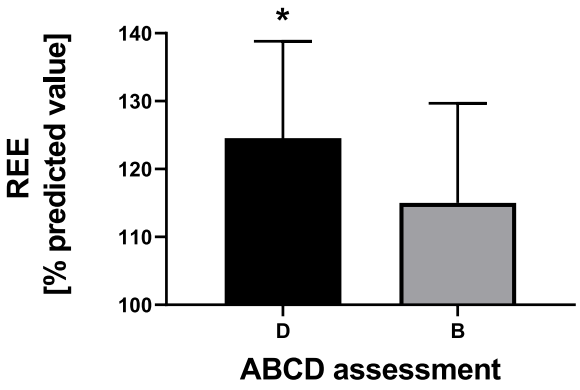

Fig. 1. Relatively expressed resting energy expenditure in COPD groups divided according the ABCD assessment.
REE – resting energy expenditure
Results are expressed as mean ± standard deviation.
* - *t*-test D vs. B group of ABCD assessment ($P \leq 0.05$)

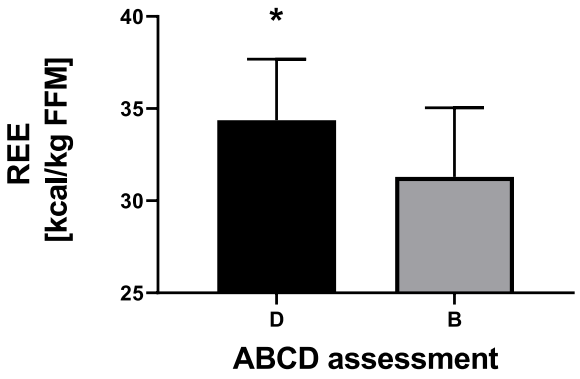

Fig. 2. Resting energy expenditure adjusted for fat-free mass amount in COPD groups divided according the ABCD assessment.
REE – resting energy expenditure; FFM – fat-free mass.
Results are expressed as mean ± standard deviation.
* - t-test D vs. B group of ABCD assessment ($P \leq 0.05$)

4. Discussion

The results of our study confirmed previous observations of increased values of REE in COPD patients. The increase in the COPD group was present only after adjustment, while absolute values of REE did not differ between the study groups. This is in accordance with Schols et al. [1], whereas Sergi et al. [3] found increased values of REE even without adjustment. The REE value of 33.2 ± 3.9 k cal·day^{-1} kg^{-1} FFM in COPD patients is very similar to that in other studies (32.1 by Schols et al. [1] and 35 by Sergi et al. [3]). Regardless of the type of adjustment, there was approximately a 10% increase of REE (8% for body weight, 12% for FFM and 7% for body surface). In addition, there was only a trend toward lower FFM in COPD patients. From this it can be concluded that the FFM changes only partially explain the differences in REE.

Using the Harris-Benedict equations, 76% of COPD patients were considered hypermetabolic (more than 110% of predicted value). This is an even higher prevalence of hypermetabolism than published by Creutzberg et al. [2] or Sergi et al. [3], respectively 54% and 60% of the patients. On the other hand, 52% of subjects in the control group should also be considered as hypermetabolic. The median of relatively

Table 5
Correlation of energy metabolism parameters with values of multivariable prediction indexes.

Parameter		BODE	$_{U}$BODE	ADO
RQ	**r**	**−0.312**	**−0.309**	−0.276
	P	**0.027**	**0.029**	0.053
nRQ	**r**	**−0.338**	**−0.340**	**−0.290**
	P	**0.016**	**0.016**	**0.041**
REE [% predicted value]	**r**	0.255	**0.287**	**0.293**
	P	0.074	**0.043**	**0.039**
Carbohydrates [kcal·day^{-1}]	**r**	−0.277	**−0.300**	**−0.291**
	P	0.051	**0.034**	**0.040**
Carbohydrates [%]	**r**	**−0.299**	**−0.324**	**−0.296**
	P	**0.035**	**0.022**	**0.037**
Lipids [g·day^{-1} kg^{-1}]	**r**	**0.313**	**0.298**	**0.286**
	P	**0.027**	**0.035**	**0.044**
Lipids [g·day^{-1} kg^{-1} FFM]	**r**	**0.334**	**0.321**	**0.297**
	P	**0.018**	**0.023**	**0.036**

RQ – respiratory quotient; nRQ – nonprotein respiratory quotient; REE – resting energy expenditure; FFM – fat-free mass; BODE – value of BODE (**B**ody-mass index, the degree of airflow **O**bstruction and **D**yspnea, and **E**xercise capacity) index; $_{U}$BODE – value of updated BODE index; ADO – value of ADO (**A**ge, **D**yspnea, and airflow **O**bstruction) index
R – Spearman correlation coefficient; *P* – probability values of correlation test. Bolded values reached statistical significance ($P \leq 0.05$).

expressed REE of 120% in COPD patients is similar to the weight-losing COPD patients (118%) by Schols et al. [1] and the hypermetabolic COPD patients (121%) by Sergi et al. [3]. Only 5 COPD patients (10%) and 1 subject in the control group (4%) have a low FFMI value (<16 for men and <15 for women). This suggests that changes in metabolism precede changes in body composition (loss of muscle mass).

We demonstrated that COPD patients have 5% higher RQ values, suggesting increased oxidation of carbohydrates. This is in agreement with work of Ramires et al. [9], although other studies found higher values of RQ in the COPD group (Ramires at al [9]. Almost 1, Efthimiou et al. [25] 0.88) than in our study (0.78). Differences in nRQ were almost twofold higher than in RQ between the groups, suggesting that nRQ could be a more sensitive parameter. We know of no other study on COPD patients determining this parameter, and so this should be verified in other studies.

This is the first study that establishes oxidation of all three main nutritional substrates in COPD patients at one time. We have used formulae which are used in indirect calorimetry but are not specific to COPD patients. On the other hand, the results for NSO are consistent with results of RQ and nRQ. We found almost two times higher carbohydrate oxidation in the COPD group, while lipid oxidation was not significantly different in the COPD group, findings similar to those of Ramires et al. [9]. However, absolute values of carbohydrate oxidation were almost three times lower (0.07 versus 0.20 g per minute) and lipid oxidation two times higher (0.08 versus 0.04 g per minute) in our study in comparison with Ramires' results [9]. Relative changes of carbohydrate and lipid oxidation are described for the first time. However, it is logical that no changes in lipid oxidation together with increased REE values should lead to a decrease in relative lipid oxidation in COPD patients. We found also no changes in protein oxidation, which is in accordance with results by Kao et al. [7], who described no change in leucine oxidation notwithstanding faster rates of whole-body protein breakdown and synthesis.

When we examined the gender differences in the parameters of energy metabolism, we found that the absolute REE values were 35% higher in male than in female subgroup of COPD patients (2048 ± 353 and 1518 ± 300 kcal·day^{-1} in male and female subgroup, respectively; $P < 0.0001$). Higher REE values in male subgroup were probably due to higher weight and height compared to female subgroup. This is consistent with the fact that after adjustment to weight or when expressed relatively (in % of the predicted value), the differences were no longer statistically significant. We found no significant gender differences in RQ, nRQ and NSO values.

Very interesting and quite new is the proving of an association between REE and NSO and COPD severity and prediction indexes. While the highest rate of carbohydrate oxidation was in patients with the lowest scores of prediction indexes, the highest rate of lipid oxidation was in patients with high scores of prediction indexes. This is in agreement with the finding that the lowest rate of lipid oxidation was in the subgroup of patients with GOLD stage 1 (four times lower rate than in the subgroup with GOLD stage 3). We can only suggest that the changes in NSO were affected by differences in nutrient intake, as this was not monitored in our study. On the other hand, REE and NSO determination was performed in fasting state so acute effect of diet was minimized. We have not demonstrated differences in NSO between subgroups classified according to ABCD, although we found that in patients with more symptoms and high risk (group D), the relatively expressed REE value was 10% higher than in patients with more symptoms and low risk (group B). Schols et al. [1] demonstrated that in weight-losing COPD patients relatively expressed REE was higher than in weight stable patients.

The limits of the study include relatively small proportion of women in the study, which is corresponding to a lower incidence of COPD among females. Also, the proportion of COPD patients according to GOLD stages was not uniform. Another limit is that nutrient intake was not monitored in this study. Because we used the SFA for determination of body composition, it is difficult to make comparisons with studies that used other methods. According to the results of our previous study [16] SFA has a higher degree of agreement than bioelectrical impedance analysis (BIA) compared to dual energy X-ray absorptiometry for FFM determinations in COPD patients. In fact, we determined body composition in patients from this study using both SFA and BIA. However, adjusting the REE and NSO to the amount of FFM determined by BIA only changes the absolute value of these parameters (amount of FFM determined by BIA was lower than by SFA), it does not affect the conclusions of this study. The main strengths of this study are assessment of oxidation of all three main nutritional substrates in COPD patients at one time and finding associations between REE and NSO and COPD severity and prediction indexes.

Although there are no specific recommendations for the diet of COPD patients, some studies have demonstrated a short-term effect of diet composition in this specific population. Efthimiou et al. [25] described attenuation of the 6-min walking test distance after administration of a carbohydrate-rich meal, which was correlated with an increase in carbon dioxide production. This effect was not observed after administration of a fat-rich meal with low carbohydrate content. Tumer et al. [26] demonstrated an improvement in lung functions (increased tidal volume and forced vital capacity) after 10 days of a high fat content diet in COPD patients in acute exacerbation, which was not observed after a standard diet (with high carbohydrate content). The question must be asked whether increased fat oxidation is beneficial for COPD patients. Jiang et al. [27] described a link between increased fatty acid beta-oxidation due to cigarette smoke and increased cell death through the increased production of reactive oxygen species. Activation of fatty acid beta-oxidation was connected also with *FAM13A* (family with sequence similarity 13 member A), a well-replicated COPD genome-wide association studies gene. Silencing of *FAM13A* and pharmacological inhibition of fatty acid beta-oxidation reduced cell death.

Accurate estimation of REE by means of indirect calorimetry is an important factor when calculating energy requirement in nutritional care of COPD patients, yet it is rarely used in routine clinical practice. This study demonstrated the alteration in NSO of COPD patients in addition to increase in REE. Therefore, we believe that a specific diet tailored for COPD patients according to their actual needs (both energy and the proportion of individual nutritional substrates) could be a potential benefit, especially for patients with malnutrition.

5. Conclusion

In conclusion, our study demonstrated metabolic changes in COPD patients leading to increased values of REE and changes in NSO which were associated with disease stage. Future large-scale studies are needed to confirm the effect of disease stage or patient phenotype on NSO. Also, the potential benefit of a specific diet tailored for COPD patients should be studied.

CRediT authorship contribution statement

Miroslav Kovarik: Conceptualization, Methodology, Investigation, Resources, Formal analysis, Data curation, Writing - original draft. **Simona Najpaverova:** Investigation, Writing - review & editing. **Vladimir Koblizek:** Conceptualization, Investigation, Resources, Writing - review & editing. **Zdenek Zadak:** Conceptualization, Writing - review & editing, Supervision. **Miloslav Hronek:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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