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Body composition and resting energy expenditure in elderly male patients with chronic obstructive pulmonary disease

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KEYWORDS
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Summary
Study objective: Our study investigates nutritional status, resting energy expenditure (REE) and physical performance in elderly patients with stable COPD to identify any early conditions of hypermetabolism, malnutrition and sarcopenia.
Methods: Eighty-six males (40 stable COPD and 46 healthy subjects) over 65 years old were studied. All subjects underwent spirometry, blood gas analysis and a 6-min walking test (6MWT). Fat-free mass (FFM) and appendicular skeletal muscle mass (ASMM) were measured by dual energy X-ray absorptiometry (DEXA). REE was measured by indirect calorimetry.
Results: COPD patients had a lower FFM both expressed in kilograms and after correction for height squared. The prevalence of sarcopenia was higher for COPD subjects (38% vs 31%). REE, both in absolute values and adjusted for FFM was significantly higher in COPD patients. Hypermetabolism was found in 60% of COPD cases and 13.7% ($P<0.01$) of healthy subjects. No relationship was found in COPD patients between the measured/predicted REE ratio (REE_m/REE_p) and FEV_1. In the hypermetabolic COPD subgroup, the REE_m/REE_p ratio correlated with 6MWT.
Conclusions: Elderly patients with stable COPD develop an increased REE. This hypermetabolism seems to be independent of the severity of the pulmonary obstruction and to influence the patient's physical performance.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating condition often associated with physical impairment and worse quality of life, particularly in old age.[1,2]

A poor nutritional status is common among individuals suffering from COPD and is an independent predictor of mortality and increased morbidity.[3] This is supported by the energy imbalance due to a low dietary intake[4] and a higher resting energy expenditure (REE).[5] This hypermetabolic state is determined by the chronic inflammatory condition[6] and the effort that goes into breathing.[7]

Previous studies mainly investigated the nutritional status in COPD patients over a wide age range[8,9] and consequently did not consider the possible effects of a longer-standing disease on REE and body composition of elderly COPD subjects.

In the elderly, the relationship between nutritional status and COPD is more complex because malnutrition associated with the illness overlaps the physiological decline of lean and muscle mass, called sarcopenia, typical of aging.[10] COPD exacerbates this muscle mass wasting, which affects both peripheral and respiratory muscle performance, leading to a reduction in ventilation and physical exercise.[11] The reduction in fat-free mass (FFM) and muscle mass in these older patients may be balanced be an increase in their metabolic activity to sustain the greater respiratory work. It is therefore feasible for hypermetabolism to affect older COPD patients more than younger ones.

Severe malnutrition, as well as underweight status and low visceral proteins, have been demonstrated in elderly COPD patients in advanced stages of the disease,[12] often in association with disability. It is hard to say, however, whether the energy imbalance already exists in the intermediate stages of the condition and whether it influences nutritional status, respiratory function and physical performance.

The aim of our study was to investigate nutritional status, REE and physical performance in a sample of elderly patients with stable COPD who were normalweight or overweight according to the WHO criteria[13] to identify any early hypermetabolism, malnutrition and sarcopenia and their possible relationship with physical and pulmonary performance.

Methods

Study subjects

This survey was performed at the Geriatric Department of Padua University on 86 males over 65 years of age. Forty subjects had COPD diagnosed on the basis of a respiratory functional impairment measured according to the European Respiratory Society criteria.[14] Only patients with COPD in a stable clinical condition were considered. Patients with fever, worsening respiratory symptoms, leukocytosis, changes in medication in the previous 30 days, or hospital admissions in the previous 6 weeks were considered clinically unstable and excluded. Subjects with cognitive or physical impairments severe enough to prevent the performance of pulmonary function tests were also ruled out. COPD patients meeting the inclusion and exclusion criteria were recruited consecutively from among the outpatients at the Respiratory Pathophysiology Department in Padua during regular check-ups.

Forty-six healthy elderly subjects were evaluated as a control group, recruited on a voluntary basis from elderly people coming to the Department of Geriatrics for a check-up. Their healthy condition was established from their clinical history, clinical examination and normal biochemical test results.

For all subjects, the exclusion criteria were: severe underweight condition (BMI $< 18.5\,kg/m^2$) or obesity (BMI $> 30\,kg/m^2$); acute disease, liver, heart or kidney failure, endocrine disease, cancer and inflammatory conditions. The use of drugs (oral or systemic corticosteroids, theophylline, hormones, benzodiazepines and antipsychotic medication) that could interfere with REE was a reason for exclusion. For COPD patients, allowable drugs were beta 2 agonists, inhaled corticosteroids and anticholinergic agents.

The study design was approved by the local Ethical Committee. Patients were fully informed as to the nature and purpose of the study and gave their informed consent.

All subjects took several tests on the same morning, as follows:

Biochemical analyses: Blood samples were obtained in the morning after a 12-h overnight fast; routine biochemical analyses included hemochrome, urea, electrolytes, liver and kidney function indices, thyroid-stimulating hormone levels, and erythrocyte sedimentation rate (ESR). The blood was also analyzed for albumin, prealbumin and retinol-binding protein (RBP).

Pulmonary function *tests*: Lung function was evaluated using a computerized water-sealed Stead-Wells spirometer (BAIRES System, Biomedin, Padua, Italy), which meets the 1994 ATS recommendations for diagnostic spirometry. The customized software assists the operator during the test and enables on-line compliance monitoring according to ATS criteria by displaying all parameters relevant to the start and end of the test, as well as

those relevant to the reproducibility of the FEV_1 and FVC[15] recordings.

An arterial blood sample was drawn from the radial artery for blood gas analysis of PaO_2 and $PaCO_2$ (ABL 300 blood gas analyzer, Radiometer, Copenhagen, Denmark).

Physical performance: This was evaluated on the basis of the distance covered during a 6-min walking test (6MWT) according to Guyatt et al.[16] Patients were asked to walk as far as possible in 6 min in a hospital corridor 100 m long. They could set their own pace, stopping if necessary, and they were told that at the end they should feel as though they could not have walked any further. No encouragement was given during the test. Since learning effects have been known to occur quickly with repeated walking tests, the patients performed one practice 6MWT 30 min prior to the test.[16]

Anthropometry: Body weight was measured to the nearest 0.1 kg and height was determined to the nearest 0.1 cm with a standard balance and stadiometer (Seca; Germany) with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared.

Body composition: FFM and fat mass (FM) were obtained by Dual Energy X-ray Absorptiometry (DEXA) with fan-beam technology (Hologic QDR 4500 W, Inc). A standardized procedure was used for positioning the patient and using the QDR software. The DEXA scans were analyzed with the Hologic software for body composition assessment, rel. 8.21. DEXA has a good reproducibility in determining soft tissue composition and a good agreement has been found in elderly subjects.[17] FFM and FM were expressed as absolute values, as a percentage of body weight, and adjusted for height squared as the FFM index (FFMI) and FM index (FMI). Appendicular skeletal muscle mass (ASMM) was also measured as the sum of the fat-free soft tissue masses of the arms and legs, as described by Heymsfield et al.[18] Finally, the ASMM index (ASMMI) was calculated as the ASMM divided by height squared.[10] As a cut-off for defining sarcopenia, we used two standard deviations below the sex-specific ASMMI mean values of the Rosetta Study on young adults (7.26 for males), as proposed by Baumgartner et al.[10]

Resting energy expenditure: REE was measured with an open-circuit indirect calorimeter (Sensor Medics V_{max}-229 Metabolic System, CA) and a ventilated hood system.

The patients arrived to the Department in the early morning and lay supine for 30 min before beginning the test. The measurements were taken after an overnight fast, under standardized conditions, with the person lying awake and emotionally undisturbed, completely at rest, comfortably supine on a bed, their head under a transparent ventilated canopy, in a thermally neutral environment, and after at least 8 h of sleep. Respiratory gas samples were taken minute by minute for 30–40 min and only measurements from steady states were considered for the analysis. Steady states were defined as time intervals of at least 5 min, during which every average minute of oxygen consumption and carbon dioxide production changed by less than 10%, and the average respiratory quotient changed by less than 5%.

The calorimeter was calibrated each day before the tests using a two-point calibration method based on two separate mixtures of known gas content. Carbon dioxide and oxygen concentrations were compared with span gas (with known oxygen and carbon dioxide fractions) and pure nitrogen (as the zero level gas). Flow rate was calibrated with a 3-L syringe, according to the manufacturer's instructions. The accuracy of the system was tested regularly, twice a month, by repeated measures of acetone combustion and showed a good accuracy (2.4% error) and precision (CV 0 1.5%).

The energy expenditure was calculated from the VO_2 and VCO_2 in the stationary states of the recording using the abbreviated Weir equation.[19]

Statistical analysis: Data were analyzed using Systat statistical software, rel. 8.01 for Windows (SPSS Inc., Chicago). The results were expressed as means $\pm$ the standard deviation. Differences in the variables between COPD and healthy subjects were evaluated using Student's unpaired two-sided *t*-test. Differences between prevalences were tested by the χ^2 test. REE was normalized for FFM variations in COPD and healthy subjects by analysis of covariance, as suggested by previous Authors.[20] The level of statistical significance for each test was set at $P<0.05$.

REE was also predicted using an unpublished formula generated in a sample of 100 local healthy elderly subjects, using the same methods to measure REE (indirect calorimetry) and FFM (DEXA).

Patients were considered hypermetabolic when the measured REE was more than 110% of the predicted REE.[8] The measured/predicted REE ratio (REE_m/REE_p) was correlated with FEV_1, FEV_1% predicted, FEV_1/FVC ratio and 6MWT by simple regression analysis.

Results

Spirometric and blood gas values for the COPD patients and normal subjects are given in Table 1. As expected, the spirometric values (FEV_1, FEV_1%pred, FEV_1/FVC%) were significantly lower in COPD subjects than in controls, the former being more hypoxemic and hypercapnic. ESR (42.5 ± 24.1 vs 38.4 ± 22.4 mm/h) and leukocyte (6.69 ± 2.0 vs $6.26 \pm 1.88 \times 10^3/\mu L$) mean values did not differ significantly in COPD and healthy subjects.

Nutritional and body composition parameters are shown in Table 2. Age and anthropometric indexes are similar in the two groups. The elderly COPD subjects had similar mean BMI values, but a lower FFM both in kg (50.7 ± 6.3 vs 53.9 ± 6.9 kg; $P<0.05$) and after correction for height squared (18.0 ± 2.0 vs 19.0 ± 1.9; $P<0.05$). The mean ASMM and ASMMI values were similar in patients and controls. The prevalence of sarcopenia was 38% among COPD subjects and 31% in the healthy group (*P*: ns).

Among the visceral proteins, mean albumin, prealbumin and RBP values were lower in patients than in controls, but the difference was only statistically significant for albumin (38.2 ± 5.4 vs 40.8 ± 5.6 g/L; $P<0.05$). The prevalence of hypoalbuminemia (<35 g/L) was 30% in COPD and 22% in healthy subjects (*P*: ns).

Unadjusted mean REE values (1774 ± 334 vs 1570 ± 272 kcal/24 h; $P<0.01$) were significantly higher in COPD patients than healthy subjects, even after adjusting for FFM using the covariance method (1772 ± 193 vs 1623 ± 212 kcal/24 h; $P<0.01$) (Table 3) or expressed per kg of body weight (24.9 ± 4.1 vs 22.9 ± 3.4 kcal/day/kg; $P<0.05$).

Hypermetabolism, considered as a measured REE > 110% of the predicted REE,[8] was seen in 60% of COPD cases and 13.7% of healthy subjects ($P<0.01$).

In the hypermetabolic COPD subgroup, REE_m/REE_p ratio (REE_m/REE_p) correlated inversely with 6MWT (r: −0.57; $P<0.01$) (Fig. 1), whereas no relationship was found in the non-hypermetabolic COPD subgroup (r: 0.08; *P*: ns) or the control group (r: 0.20; *P*: ns).

Nor was any relationship found in the COPD patients between REE_m/REE_p and spirometric indices of lung function as FEV_1 (Fig. 2), $FEV_{1\%}$ predicted (r−0.09; *P*: ns), and FEV_1/FVC ratio (r−0.12; *P*: ns).

Table 1 Spirometric, blood gas analytical parameters and 6-min walking test (6MWT) in COPD patients and controls. Values are presented as mean (SD).

	COPD patients ($n = 40$)	Controls ($n = 46$)
PaO_2 (mmHg)	75.0 (13.1) **	95.3 (13.1)
$PaCO_2$ (mmHg)	41.6 (5.2) *	37.1 (5.5)
pH	7.4 (0.039)	7.4 (0.055)
FEV_1 (L)	1.3 (0.5) **	2.8 (0.6)
FEV_1% predicted	52.6 (17.5) **	103.2 (17.8)
FEV_1/FVC%	48.8 (9.8) **	73.4 (9.0)
6MWT (m)	286.0 (76.2) *	405.4 (77.7)

COPD vs controls (*$P<0.05$,**$P<0.01$).

Table 2 Age, anthropometric and body composition indices for COPD patients and controls. Values are presented as mean (SD).

	COPD ($n = 40$)	Controls ($n = 46$)
Age	75.7 (5.3)	77.7 (7.0)
Height (cm)	167.8 (6.8)	168.0 (6.3)
Weight (kg)	71.9 (12.2)	71.3 (10.7)
BMI (kg/m^2)	25.5 (3.6)	25.2 (3.2)
FFM (kg)	50.7 (6.3) *	53.9 (6.9)
FM (kg)	18.1 (6.2)	16.4 (5.6)
FFMI	18.0 (2.0) *	19.0 (1.9)
FMI	6.4 (2.0)	5.8 (1.9)
ASMM	20.9 (3.2)	21.5 (3.5)
ASMMI	7.39 (0.9)	7.55 (1.0)
Albumin	38.2 (5.4) *	40.8 (5.6)
Prealbumin	277.0 (62.9)	294.2 (90.5)
RBP	47.6 (12.7)	50.2 (17.6)

COPD vs Controls (*$P<0.05$). FFM: fat-free mass; FM: fat mass; ASMM: appendicular skeletal muscle mass; FFMI: FFM index; FMI: FM index; ASMMI: ASMM index; RBP: retinol-binding protein.

Table 3 Resting energy expenditure (REE) in COPD patients and controls. Values are presented as mean (SD).

	COPD patients ($n = 40$)	Controls ($n = 46$)
Measured REE (Kcal/day)	1774 (334)**	1570 (272)
†Adjusted REE (Kcal/day)	1772 (193)**	1623 (212)
††REE-BW (Kcal/day)	24.9 (4.1)*	22.9 (3.4)

COPD vs Controls (*$P<0.05$,**$P<0.01$).
†REE adjusted for FFM using covariance method
††REE expressed per kilogram of body weight

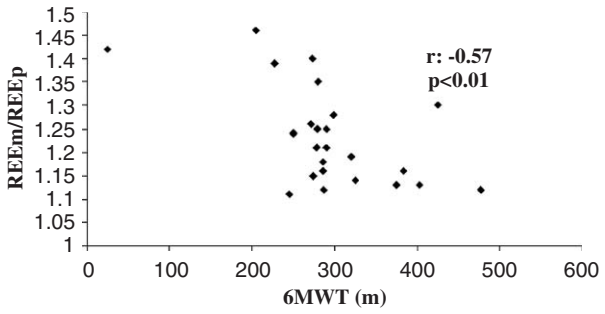

Figure. 1 Relationship between REE measured/REE predicted ratio (REE_m/REE_p) and 6-min walking test (6MWT) in the hypermetabolic COPD subgroup.

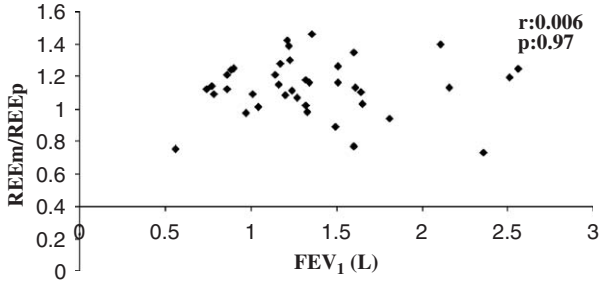

Figure. 2 Relationship between REE measured/REE predicted ratio (REE_m/REE_p) and FEV_1 in COPD patients and controls.

Discussion

This study investigated nutritional status, body composition and REE in normal-weight or overweight elderly COPD patients to identify any early conditions of hypermetabolism, sarcopenia and malnutrition.

Our sample of COPD cases was small because we adopted strict selection criteria to rule out other factors that might interfere with nutritional status and REE. The groups of healthy elderly subjects and COPD patients were similar in terms of age, weight, height and BMI, so any differences between their nutritional parameters can be attributed to the COPD rather than to any other factors.

As expected, our COPD patients fared significantly less well in the pulmonary function tests and blood gas parameters than the healthy controls, though their mean PaO_2 and $PaCO_2$ were still acceptable for elderly people. This may be due to the fact that patients unable to perform the 6MWT were ruled out.

COPD patients are known to be generally thin, underweight, with a reduced FFM.[21] Previous studies on moderate or severe COPD showed that FFM loss affected 20% of outpatients and 35% of those eligible for pulmonary rehabilitation.[22]

Though their mean anthropometric values were similar to those of the healthy group, our elderly COPD patients had a significantly lower FFM in kg and after correction for height squared (FFMI).

Several studies have already shown that age-related FFM loss particularly involves peripheral skeletal muscle and gives rise to weakness.[10] This process, called sarcopenia, is being recognized as a major cause of disability and mortality in the elderly population.[23] Indeed, 30% of our healthy elderly people were sarcopenic using Baumgartner criteria.[10] Though sarcopenia is part of the normal aging process, muscle wasting is accelerated by chronic diseases. COPD accelerates muscle loss, particularly in the acute phase, due to higher levels of circulating proinflammatory cytokines (IL1, TNF, IL6) prompting an increase in protein turnover, hypoxemia and acidosis, and further restricting physical activity.[24]

In our study, the mean ASMM and ASMMI values used to define sarcopenia were not statistically different between the control and COPD groups. The prevalence of sarcopenia was only 7% greater in the COPD patients than in controls. ASMMI only evaluates the muscle mass of limbs and probably underestimates sarcopenia in cases of COPD, whose chest muscle mass may also be affected.[25] On the basis of our results, we can nonetheless assume that it is difficult to detect COPD-attributable muscle wasting in elderly COPD patients because loss of FFM only occurs in a minority of outpatients with COPD and older patients lose muscle anyway as part of the aging process.

Our elderly COPD patients had lower mean albumin values than controls. These results are consistent with those reported in previous studies[26,27] where hypoalbuminemia was prevalent in COPD. The lower mean albumin values may be due to malnutrition and/or chronic inflammation.[28] Our patients had slightly, but not significantly higher values for ESR and leukocytes, adding support to the clinical impression that their COPD was stable.

Unfortunately, more specific markers of inflammation, such as high-sensitivity CRP, IL1–IL6, etc., were not measured in our patients, so it is hard to pinpoint the cause of their mild hypoalbuminemia to a worse nutritional status or chronic inflammation.

Previous studies have already demonstrated that a low dietary energy intake is certainly a problem in COPD, and particularly in the more severe cases.[8] Malnourished subjects suffer more from anorexia, early satiety, dyspnea and dry mouth,[4] and medication plays an important part.

Another reason for a negative energy balance in COPD patients is the increase in REE, affecting about one third of adult patients. As already confirmed in younger patients, COPD causes several metabolic adjustments that lead to an increased metabolic activity to ensure adequate ventilation.[29] Moreover, the drugs used to treat COPD (beta 2 agonists, corticosteroids and theophylline) also increase REE.[30]

Our study shows that 60% of elderly COPD had associated hypermetabolism, while only about one third of them had low albumin and sarcopenia. This might suggest that hypermetabolism in elderly COPD subjects precedes nutritional decline and contributes to malnutrition and FFM and muscle mass loss.

The prevalence of hypermetabolism was greater among our COPD patients than in other studies. Two reports on COPD patients who were 10 years younger on average found the prevalence of hypermetabolism to be 26%[8] and 34%.[9] Schools reports that hypermetabolism is overestimated when REE is predicted using equations (Harris Benedict) that consider only anthropometric indices rather than FFM. For this reason, to predict REE we used a formula derived from a linear regression of REE on FFM generated in a healthy elderly population. Our COPD cases were probably more hypermetabolic for different reasons. It is feasible to suggest that REE increases particularly in old people with COPD to guarantee respiratory function despite a lower muscle mass. But these differences can be due to the different methods used to estimate body composition. In previous investigations, FFM was determined by bioelectrical impedance analysis (BIA), which is less reliable than DEXA in assessing body composition.[31,32] Conversely, we believe that our results underestimate hypermetabolism in elderly COPD because our study ruled out patients with other conditions that raise REE (multiple comorbidities, acute exacerbation of disease and oral or systemic intake of corticosteroids or theophylline).

Hypermetabolism seems to be independent of the severity of COPD, since no correlation was found between the ratio of measured/predicted REE and lung obstruction parameters such as FEV_1 and FEV_1/FVC ratio. These results are consistent with other studies, where FEV_1 was higher in hypermetabolic than in normometabolic COPD.[9] Unfortunately, the investigation on the relationship between hypermetabolism and lung performance is limited because indices of lung function, other than spirometry, were not measured.

Hypermetabolism, however, has a negative fallout on physical performance in any case. In our subgroup of hypermetabolic COPD cases, the measured/predicted REE ratio correlated inversely with the walking test results and accounted for more than 30% of the variability in the distance covered. The physical performance of elderly COPD patients seems to depend on numerous factors, among which hypermetabolism can have an important role, but it is difficult to grasp the foundations for this relationship and further studies are needed to confirm and clarify it.

In conclusion, our study demonstrates that elderly patients with stable COPD have an increased resting metabolic rate. This hypermetabolism seems to be independent of the severity of the pulmonary obstruction and to influence the patient's physical performance.

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