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Total Free Living Energy Expenditure in Patients with Severe Chronic Obstructive Pulmonary Disease

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Resting energy expenditure (REE) is often elevated in patients with chronic obstructive pulmonary disease (COPD), but no data are available regarding total energy expenditure in free living conditions. We compared total daily energy expenditure (TDE) in eight COPD patients (FEV_1 36 ± 13%) admitted to a pulmonary rehabilitation center and eight independently living healthy subjects, matched for sex, age, and body mass index (BMI). TDE was measured over a 2-wk interval using doubly labeled water in combination with measurement of REE and body composition. The COPD patients had a significantly higher TDE than the healthy subjects (2,499 ± 320 kcal/d and 2,107 ± 88 kcal/d, respectively, $p < 0.01$). The nonresting component of TDE (TDE−REE: physical activity and diet-induced thermogenesis [DIT]) was significantly higher in the COPD patients than in the healthy subjects, resulting in a ratio between TDE and REE of 1.7 ± 0.2 and 1.4 ± 0.1, respectively ($p < 0.01$). The results indicate that COPD patients exhibit an increased TDE in comparison with healthy subjects. The difference could by attributed to an increase in the nonresting component of TDE, since REE was comparable between the groups. Baarends EM, Schols AMWJ, Pannemans DLE, Westerterp KR, Wouters EFM. Total free living energy expenditure in patients with severe Chronic Obstructive Pulmonary Disease.

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Weight loss is common in chronic obstructive pulmonary disease (COPD) (1, 2). It involves both a decrease in fat mass and wasting of fat-free mass (3). The influence of these changes in body composition on several important aspects of the disease is considerable. Weight loss and a low body weight correlate with morbidity and with a poor prognosis (2, 4). In addition, muscle wasting in COPD patents is associated with a decreased diaphragmatic size, a decrease in respiratory muscle strength and endurance (5, 6) and impaired physical fitness (7, 8).

The cause of weight loss in COPD patients is still not fully known, but has been predominantly ascribed to a disturbed energy balance. Because a reduction in energy intake has not been demonstrated in COPD patients (9, 10), increased attention has been focused on their energy expenditure. Several factors contribute to the amount of energy required by an individual: resting energy expenditure (REE), physical activity, and to a lesser extent the diet-induced thermogenesis (DIT). Because of the methodological difficulties in measuring total daily energy expenditure (TDE), generally only REE has been measured. Several studies have shown that a substantial percentage of COPD patients exhibit an increased REE (11, 12). Normal as well as increased DIT values have been found in COPD patients (13–15). However, since DIT accounts only for 10% of TDE, the influence of a possible increased DIT on TDE seems small. No data are available regarding reliable measured energy requirements of physical activity and TDE in free living conditions in COPD patients. In this study, TDE was measured by the doubly labeled water technique in COPD patients, and compared with TDE of healthy subjects matched for age, sex, and body mass index (BMI).

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METHODS

Patients

Eight patients with moderate to severe COPD (16) in stable clinical condition were studied. The patients were admitted to a pulmonary rehabilitation center. Only men were included in this study to exclude effects due to sex differences. Patients with a $Pa_{O_2} < 7.3$ kPa, or suffering from cancer, unstable cardiac condition (i.e., decompensated cor pulmonale), active gastrointestinal abnormalities, recent surgery, severe endocrine disorders, locomotor disease, or obesity (body weight > 120% of ideal weight) were excluded from the study. The patients were fully informed of the nature and purpose of the study and gave informed consent. The study was approved by the local ethical committee. Procedures followed were in accord with the Helsinki declaration from 1977 as revised in 1983.

Control Subjects

Control subjects were eight healthy men matched for age and BMI with the eight patients studied. They were selected from 16 free-living healthy elderly men who participated previously in a study by Pannemans and Westerterp (17). The eight remaining men had a significantly higher BMI (27.6 ± 1.1 kg/m^2) than the eight subjects selected as matched controls (22.4 ± 2.5 kg/m^2, $p < 0.001$).

TABLE 1

EXAMPLE OF STANDARD ACTIVITIES OF THE PULMONARY REHABILITATION PROGRAM (WEEKEND NOT INCLUDED)

	Activities of Daily Living	Everyday	Extras
Morning	6:00 A.M. awakened (medicine round)	Thorax massage	Visit of pulmonary physician (1/wk)
	Washing, dressing (1 h)	Gymnastics (½ h)	Test (1–2/wk)
	8:00 A.M. breakfast (½ h)	Cycling (¼ h)	
Midday	Lunch (1 h)	Cycling (½ h)	Exercise test† (2 or 4/mo)
	Sleeping/resting (½ h)	Relaxation (1 h)	Educational lectures (1 h/wk)
		Walking (1 h)	Visit disciplines‡ (1 h/wk)
			Extra training§ (3 × ½ h wk)
			Leisure activities (1 midday/mo)
Evening	22:00 h. Last medicine round		Watching television
	Undressing around 23:00 P.M. sleeping		Leisure activities

* Morning tests: pulmonary function, body composition, resting energy metabolism.
† Midday test: 1/mo incremental cycle ergometry test, 2/mo 12-min walking test.
‡ Visits of the psychologist, dietist, ergotherapist, social worker, etc.
§ Extra training possibilities such as quadriceps strength training, supported or unsupported arm exercise.

Total Daily Energy Expenditure

The premise of the doubly labeled water technique is that after a loading of water labeled with deuterium (^2H) and labeled oxygen (^{18}O), the ^2H is eliminated from the body as water, whereas the ^{18}O is eliminated from the body as water and carbon dioxide (CO_2). The difference between the elimination rates is therefore proportional to CO_2 production and hence energy expenditure (18).

Energy expenditure was determined following the standard Maastricht protocol as described by Westerterp and colleagues (19). In the late evening a baseline urine sample was collected. Then, a weighted isotope dose was administered at 10:00 P.M., a mixture of 10 atom percentage excess (APE) ^{18}O and 5 APE ^2H. Subsequently, the isotopes equilibrate with the body water (during equilibration the patient does not consume any food or drink) and the initial urine sample was collected the next morning (Day 1) from the second voiding. Further urine samples were collected in the evening of Day 1 and in the morning and evening of Days 8 and 15. In the evening of Day 15, at 10:00 P.M. after voiding, a weighted dose of ^2H_2O was administered and the second voiding on Day 16 (after ± 10 h of equilibration) was sampled for calculation of total body water. Isotope ratios in urine samples were measured by isotope ratio mass spectroscopy (VGA-Isogas Aqua Sira). Calculated carbon dioxide production was converted to energy expenditure assuming a respiratory quotient (RQ) of 0.85 (18).

Resting Energy Expenditure

REE was measured by an open-circuit indirect calorimetry system using a ventilated hood system (Oxyconbèta; Jaeger, Würzburg, Germany) (20). The principle of the measurement is that a stream of room air (40 L/min) is drawn through the hood, which mixes with the expired air, and is collected in the transparent Plexiglas hood placed over the subject's head. The oxygen consumption and carbon dioxide production are calculated from the difference between incoming and outcoming gases. Energy expenditure was calculated from the abbreviated Weir formula (21). Measurements were done in the early morning after an overnight fast, while the person was comfortable lying on a bed in supine position. The system was calibrated before measurements were taken, and the accuracy of the system was regularly tested with an ethanol combustion test.

Body Composition

Anthropometric data were collected following standard procedures. BMI was calculated as weight (kg) divided by height^2 (m). Total body water (TBW) was determined by deuterium dilution as described previously, and was calculated as the measured deuterium space divided by 1.04 (22). Fat-free mass (FFM) was calculated assuming a hydration factor of 73% of TBW.

Pulmonary Function Tests

Lung function measurements included flow volumes (FVC, FEV_1), and diffusion capacity of CO (DL_{CO}) measured by the single-breath method (Masterlab; Jaeger, Würzburg, Germany). The highest value of at least three measurements was used and expressed as a percentage of the reference value (23). Blood was drawn from the brachial artery at rest while breathing room air. Blood gases were analyzed on a blood gas analyzer (Model ABL 330; Radiometer, Copenhagen).

Activity Pattern

The healthy subjects completed a standardized activity questionnaire (24). In this questionnaire (Zutphen physical activity questionnaire, PA-Q) several standard activities are mentioned (walking, cycling, gardening, jobs around the house, household jobs, sport activities, hobbies, and walking stairs), and subjects were asked how long these activities were performed "last week".

The patients participated in a pulmonary rehabilitation regimen that includes a standard activity program on weekdays. The patients performed physical activities such as gymnastics, cycling and walking, strength training and/or upper extremity training, pulmonary and exercise test but also several sedentary activities are part of the program. These include educational lectures, relaxation sessions, and talks with the physician or other caretakers. In the evening no physical activities were scheduled and most patients performed sedentary leisure activities (reading, puzzlings, playing games, etc.). In Table 1 an example of a weekly activity schedule is presented. The prescribed activities were retrospectively filled in on the PA-Q, from which the estimated activity time of the patients was calculated.

Data Analysis

Results are described individually and as mean ± SD. Differences between the groups were tested with the Mann-Whitney U test; the level of significance was $p < 0.05$.

RESULTS

The characteristics of the study group as well as the results of the pairwise matching are shown in Table 2. The studied COPD patients suffered from a severe airflow obstruction. Except for one patient, all patients had an impaired diffusion capacity adjusted for alveolar volume (Kco). Measurements of body composition were not significantly different between patients and control subjects.

TABLE 2

LUNG FUNCTION AND BODY COMPOSITION: INDIVIDUAL AND MEAN VALUES OF PATIENTS AND CONTROL SUBJECTS

Age (*yr*)		BMI (*kg/m²*)		FFM (*kg*)		FM (*% weight*)		FEV_1 (%)	Kco (%)	Pa_{O_2} (*kPa*)
P*	H	P	H	P	H	P	H	P	P	P
74	66	19.0	18.8	41.1	52.9	18.1	18.9	37	61	10.0
71	77	24.2	24.9	46.3	50.8	29.6	35.0	49	65	12.2
62	65	18.0	18.7	45.9	46.3	16.8	18.1	27	42	8.5
67	69	25.0	25.1	53.7	47.9	29.2	25.3	25	53	10.0
59	69	20.7	22.0	47.6	45.6	22.2	22.9	30	35	8.5
71	79	22.9	22.9	46.8	52.3	24.2	22.6	61	109	12.1
58	77	20.7	23.4	47.0	43.7	18.2	27.2	21	55	10.8
70	80	23.4	23.5	40.3	48.1	33.9	25.8	37	35	10.3
66.5 ± 6.1	72.8 ± 6.1	21.8 ± 2.5	22.4 ± 2.5	46.1 ± 4.1	48.5 ± 3.3	24.0 ± 6.3	24.5 ± 5.3	35.8 ± 13.4	56.9 ± 23.9	10.3 ± 1.4

Definition of abbreviations: FEV_1 = forced expiratory volume in one second, as percentage of predicted; Kco = diffusion capacity of carbon monoxide, corrected for alveolar volume, as percentage of predicted; Pa_{O_2} = arterial oxygen pressure; BMI = body mass index (weight/length²); FFM = fat-free mass; FM = fat mass.

* P = patient; H = healthy subject.

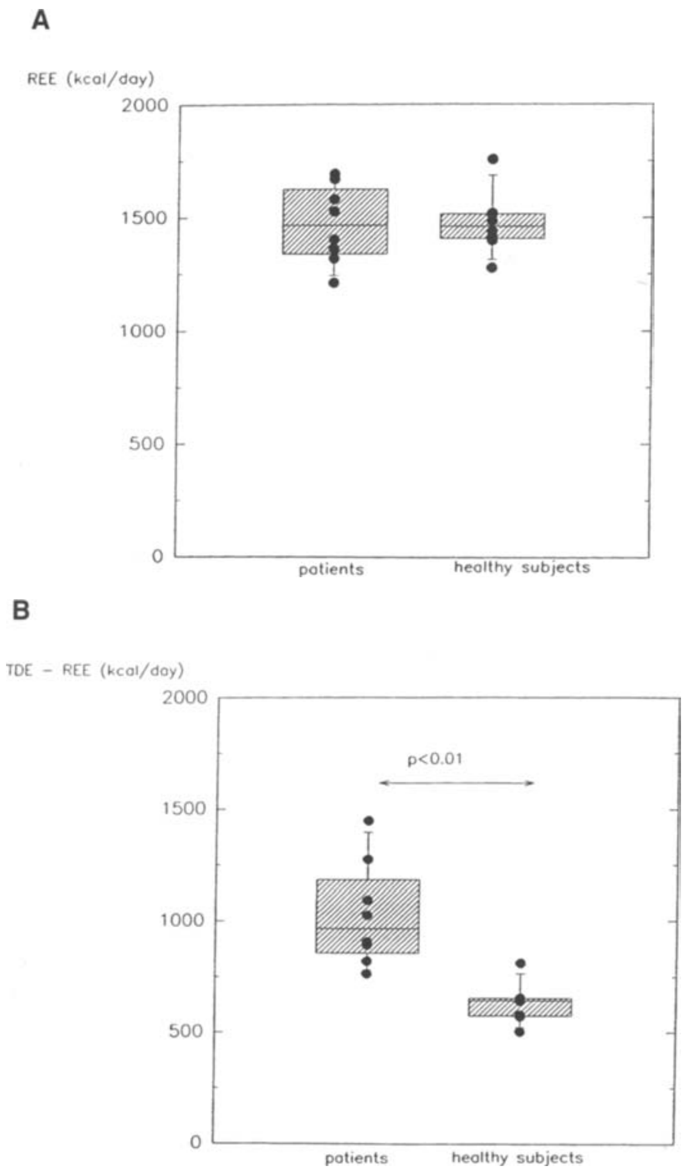

Figure 1. Resting energy expenditure (*A*) and the difference between total daily energy expenditure and resting energy expenditure (*B*) in the COPD patients and healthy subjects. Box plots indicate the 25th, 50th, and 75th percentile of the illustrated data.

Energy Expenditure

TDE was significantly higher ($p < 0.01$) in the COPD patients (2,499 ± 320 kcal/d) compared with the healthy subjects (2,107 ± 88 kcal/d). Figure 1 shows that resting energy expenditure (in absolute terms) was comparable in both groups (COPD: 1,471 ± 174 kcal/d; healthy: 1,474 ± 138 kcal/d). The nonresting component of TDE (TDE − REE) was significantly higher in the COPD patients (1.028 ± 236 kcal/d; healthy: 633 ± 90 kcal/d). Furthermore, the ratio TDE/REE was significantly higher in the COPD patients (Figure 2) ranging from 1.5 to 2.0 compared with a range from 1.3 to 1.6 in the healthy subjects ($p < 0.01$). According to Carpenter and coworkers (25) the relationship between TDE and REE is shown for patients and control subjects in Figure 3. This figure also demonstrates that the patients had an increased TDE relative to their REE.

Activity Pattern

Most patients rested or slept at 23.00 h and were awakened between 6.00 and 6.30 h which amounted to 7 to 7.5 h sleep/rest during the night. Most patients also rested/slept after lunch approximately 0.5 to 1 h. Therefore, total sleep time was estimated as approximately 7.5 to 8.5 h for the patients. The results of the PA-Q indicated that mean sleeping time amounted to 9 ± 2 h/d for the matched control subjects.

When prescribed activities for the patients were retrospectively filled in on the PA-Q, the average estimated activity time amounted to approximately 138 min/d. The matched control subjects reported a total physical activity time of 155 ± 57 min/d. Furthermore, following the PA-Q the eight healthy men not selected as control subjects (from the total of 16 elderly men studied previously [17]) had a total daily physical activity time of 121 ± 88 min, which was not significantly different from the physical activity time of the eight matched control subjects.

Because the TDE/REE of the healthy control subjects might have been lower than typical for this age group, we also compared with ratio with that of the remaining eight healthy elderly men (with a higher BMI) of the total group of 16 subjects from which the matched controls were selected. The average ratio TDE/REE for the eight subjects not selected as controls was significantly higher (1.6 ± 0.3) than the TDE/REE of the eight matched controls (1.4 ± 0.1, $p < 0.05$). However, when adjusted for FFM/height² the ratio TDE/REE was comparable between these groups (rest of healthy subjects: 1.51 ± 0.2, eight matched control subjects: 1.53 ± 0.2, ns).

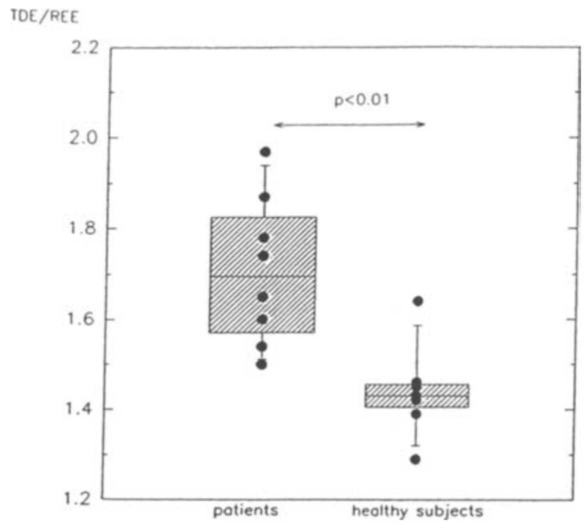

Figure 2. Ratio of total daily energy expenditure/resting energy expenditure in COPD patients and healthy subjects. Box plots indicate the 25th, 50th, and 75th percentile of the illustrated data.

DISCUSSION

The patients with COPD exhibited a higher TDE in comparison with healthy age-matched subjects when body composition was accounted for. The difference in the ratio TDE/REE between the groups can be attributed to the nonresting component of TDE, since REE was not significantly different.

Until now, no reliable measurements were available of TDE in free living conditions in COPD patients. Hugli and coworkers (26) studied TDE in a respiration chamber in COPD patients and preliminary results showed that the TDE corresponded to 1.1 to 1.4 of measured REE in these patients. This ratio is much lower than the mean ratio TDE/REE of 1.7 observed in this study. Measurements in the respiratory chamber and the doubly labeled water technique are the only ways available to measure TDE. Values of TDE obtained in the respiratory chamber may be low because the chamber allows only limited activity. Indirect evidence for a high TDE in patients with COPD was provided by several refeeding studies that did not result in satisfactory weight gain in COPD patients (27), despite an apparent adequate oral energy supplementation.

The comparable REE between COPD patients and healthy subjects in this study may appear different from previous reports

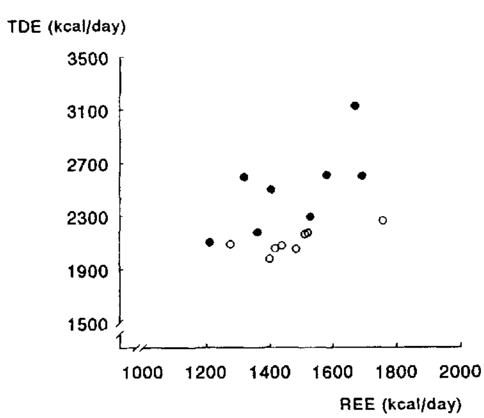

Figure 3. Relationship between TDE and REE for the patients (*closed circles*) and matched control subjects (*open circles*).

but could also be due to a selection "bias" since we deliberately selected normometabolic as well as hypermetabolic COPD patients to participate in this study. Furthermore, the comparable REE could be explained by a good pairwise match of BMI of the control group. It might also be a reflection of the fact that the studied healthy elderly were relatively active. Several studies have suggested that regular physical exercise may attenuate the age-related decline in REE (28, 29). Nevertheless, since in this study the REE was comparable in both groups, the increased TDE can clearly be attributed to the nonresting component.

The nonresting component of TDE is represented by the DIT, and energy expenditure associated with activities. The mean difference of the ratio TDE/REE between COPD patients and healthy subjects was 30% of REE. The DIT reported for COPD patients varies around 11 to 18% of baseline energy expenditure (30), and therefore cannot totally explain the high nonresting component. This suggests an increased energy expenditure for activities in COPD patients.

The cause for an elevated energy expenditure for activities is not known. Levison and Cherniack (31) reported an increased oxygen cost of breathing particularly during exercise in COPD patients, which may partly explain the increased energy expenditure during activities, since during exercise breathing accounts for a substantial part of total energy expenditure (32). However, it could also be hypothesized that the mechanical efficiency of peripheral skeletal muscle is decreased in COPD patients. Recent studies using nuclear magnetic resonance techniques observed an earlier anaerobic energy deliverance during exercise in COPD patients (33, 34). Because the efficiency of anaerobic work is 13% versus 23% for aerobic work (35), this may support the hypothesis of a decreased mechanical efficiency in COPD patients.

It could be argued that the COPD patients had a higher TDE because they were admitted to a pulmonary rehabilitation center, and therefore performed more activities than the healthy age-matched subjects. The estimated amount of sleep (rest) time for the patients was 8 h, and the healthy subjects reported approximately 9 h sleep. This suggests that the amount of time awake was comparable between the groups.

The eight matched control subjects completed a PA-Q and reported approximately 155 min/d physical activities (including gardening, etc.). We do not have comparable PA-Q data in the COPD patients, but in an earlier study we analyzed the amount of time spent in different activities (by activity diaries) in 11 other patients participating in the pulmonary rehabilitation program and found that the mean duration of the activities requiring physical performance (walking, gymnastics, cycling) was approximately 149 min/d (36). For the eight COPD patients in the present study, we estimated the total daily physical activities as 138 min/d, based on our interpretation of the clinical treatment program in the rehabilitation center. Although the difference in the methodology used limits an accurate comparison between the groups, these arguments support the suggestion that the time during which activities were performed was comparable between the groups.

We recognize that the eight matched control subjects had a relatively lower ratio TDE/REE (1.4 ± 0.1) compared with other studies (37, 38). However, these men were selected from a group of 16 healthy elderly. The remaining group of men (with a higher BMI) had a significantly higher ratio TDE/REE than the eight matched control subjects. However, when the ratio was adjusted for FFM/Height^2 (FFMI), the ratio TDE/REE of the matched controls was similar to that of the healthy men not selected as control subjects from the total of 16 men studied earlier (17). This observation confirms an earlier study in which a significant relationship between ratio TDE/REE and FFMI was reported (39). Furthermore, the amount of time spent on activities was comparable in all 16 healthy men. This comparison supports our choice to match patients and control subjects for BMI and shows that a lower ratio TDE/REE does not necessarily mean that fewer activities have been performed.

Although the above-stated arguments support the suggestion that the higher TDE of the COPD patients compared with the healthy subjects can at least not be fully explained by a difference in activity pattern between the studied groups, we acknowledge that the COPD patients participating in the rehabilitation program probably performed more activities than they would have done at home. Nevertheless, the high TDE that was found in this study has an important therapeutic implication. The higher energy needed for activities in the studied COPD patients compared with the healthy subjects despite (most likely) a comparable activity pattern suggests that physical activity represents a relatively high metabolic demand for COPD patients. This may explain partly why several refeeding studies in COPD patients were not able to result in a satisfactory weight gain and improvement of functional performance. In COPD patients, the energy requirements have to be taken into account for repletion of FFM as well as the extra energy needed for activity. Moreover, since we recently showed that in order to achieve a satisfactory increase in metabolic active tissue mass, oral supplementation should be given in combination with exercise (40).

In conclusion, this first study measuring TDE in free living conditions in COPD patients demonstrates that TDE is increased, which in this study could be attributed primarily to the nonresting component of TDE. In addition to our earlier reported nutritional intervention study, the results of this study provide important new therapeutic guidelines. In order to maintain or increase FFM in depleted COPD patients, a high metabolic demand of activities should be taken into account and oral supplementation in combination with exercise should be at least 1.7 of measured REE or more.

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