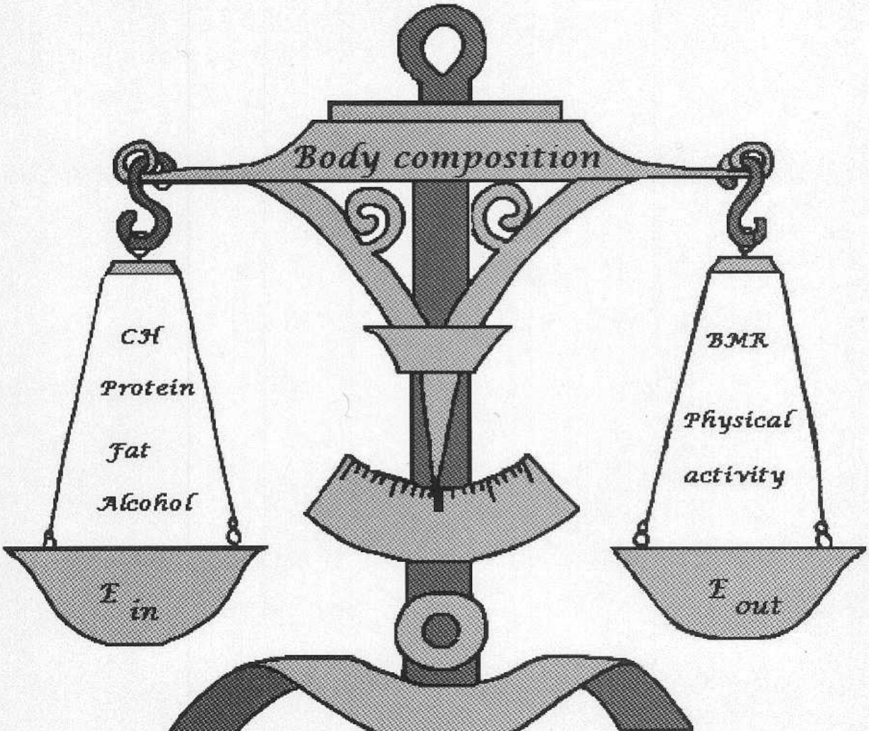
Body Composition and Energy Expenditure in Patients with Chronic Obstructive Pulmonary Disease



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Göteborg 2004

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Body composition and energy expenditure in patients with chronic obstructive pulmonary disease (*In Swedish:* Kroppssammansättning och energiförbrukning hos patienter med kroniskt obstruktiv lungsjukdom)

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Preface

In 1996 I finished my education as a clinical nutritionist. As a part of the final term, I was supposed to do a small research project. My colleague Marianne Tronrud and I decided to develop and validate a new, simple screening tool, which could be used in hospitals to detect malnutrition already at the patient's first contact with the nurse.

To be able to validate the screening tool, which we named "The less complicated nutritional assessment (LCNA)", we needed to include patients that really had nutritional problems. Our supervisor, Ingvar Bosaeus, suggested using a population of patients with chronic obstructive pulmonary disease (COPD), since they had a high prevalence of malnutrition.

During four weeks, Marianne and I performed the Subjective Global Assessment tool (which was the tool toward we validated LCNA) in 29 COPD patients admitted to Sahlgrenska University Hospital. This was my first encounter with COPD patients.

After one year of military service and two years as a dietitian in Norway, I got the possibility to work in a research project at the Department of Clinical Nutrition, Göteborg University. The aim of the project was to investigate the physical activity in Swedish adolescents. My interest in COPD patients had been triggered during my final year as undergraduate student, and contacts were therefore taken between the Department of Clinical Nutrition and the Department of Respiratory Medicine and Allergology. This thesis is a result of the cooperation between the two departments.

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"In 1955, I was 23 years old, and I just had started working as an assistant in a butcher's shop. We were seven girls working there. The others were older than me, between 30 and 40 years old. They all smoked. On Saturdays we closed at 3 PM and we cleaned the shop for about an hour. We really worked hard, we had a lot of customers. When we were finished for the day, we sat down in the coffee room and had a nice time with coffee, a glass of something and the others also had a cigarette. They wanted me to smoke too, but I did not accept the offer. After a couple of weeks I didn't want to feel so out of it – so I accepted the offer. It really tasted horrible, but still it continued for some weeks. After some more weeks I felt it was my turn to buy the cigarettes and I bought a package of ten cigarettes. Since we were seven, three cigarettes were left over, which I brought home with me. One night, I felt the lure. I had the three left-over cigarettes in my bag. It still didn't taste good. However, that was how it all started. I was a regular smoker for 42 years and I quit smoking when I had surgery for my 'fönstertittarsjuka' (intermittent claudication). Two years later I got my COPD diagnosis."

One of the patients in paper V

Abstract

The prevalence of chronic obstructive pulmonary disease (COPD) is increasing in Sweden as well as worldwide. The main cause of the disease is cigarette smoking. Almost 50 % of all COPD patients become underweight. The questions addressed in this thesis are:

(1) Does body composition measured by bioelectrical impedance predict mortality in patients with COPD?
(2) How large variation can be seen in humans' body composition measured by bioelectrical impedance during 24 hours?
(3) How much energy do underweight patients with COPD expend when they are living their normal lives at home and during a physiotherapy program?

Methods used in this thesis were bioelectrical impedance analysis and dual-energy X-ray absorptiometry to assess body composition, doubly labelled water to measure total daily energy expenditure, indirect calorimetry to measure basal metabolic rate, and seven-day dietary registrations to measure energy intake.

This thesis shows that within a sample of COPD patients, who have been included in a one-year multidisciplinary rehabilitation program, those patients with a high proportion of fat-free mass – measured by bioelectrical impedance – lived longer than those with a low proportion of fat-free mass. This thesis also shows that standardization of the measurements of body composition by bioelectrical impedance is of importance. Measurements should be done in the fasting state after the subject has been in the supine position for ten minutes. Additionally, underweight COPD patients were found to have a large variation in energy expenditure. A variation in total daily energy expenditure from 1.2 to 1.8 times basal metabolic rate is reported. Some patients increased their total daily energy expenditure during two weeks of training with a physiotherapist, whilst others decreased their total daily energy expenditure. Energy intake of the patients can not be used as a measure of their energy expenditure, since in most cases these two do not agree.

Conclusions: This thesis shows that bioelectrical impedance might be a prognostic tool in COPD, but the measurements need to be standardized. COPD patients at the same level of disease and body weight may have totally different levels of energy expenditure. The energy requirement of underweight COPD patients should therefore be assessed individually. New methods for assessing energy requirement/expenditure are needed to be developed for use in COPD patients. These methods need to be able to be used in the clinical setting, since the main conclusion is that calculation or prediction of energy requirements in COPD patients with current methods has limited value.

Sammanfattning

Kroniskt obstruktiv lungsjukdom (KOL) är en allt vanligare sjukdom i Sverige och i övriga världen. Sjukdomen orsakas huvudsakligen av cigarrettrökning och nästan hälften av alla patienter med KOL blir underviktiga. Frågeställningarna som besvaras i avhandlingen är:

(1) Påverkar patienternas kroppssammansättning – mätt med bioelektrisk impedans – deras överlevnad?
(2) Hur stor är variationen i människors kroppssammansättning – mätt med bioelektrisk impedans – under dagen?
(3) Hur mycket energi förbrukar underviktiga KOL-patienter dels i den vanliga vardagen, dels under ett träningsprogram hos sjukgymnast?

För att mäta kroppssammansättning har bioelektrisk impedans och dual-energy X-ray absorptiometry använts. Total energiförbrukning har mätts med dubbelmärkt vatten medan indirekt kalorimetri har använts för att mäta energiförbrukning i vila. Sju-dagars kostregistrering har nyttjats för att mäta energiintag.

Avhandlingen visar att hos en grupp KOL-patienter som genomgått ett års multidisciplinär rehabilitering, levde de patienter med hög andel fettfri massa – mätt med bioelektrisk impedans – längre än dem med låg andel fettfri massa. Avhandlingen visar också att det är viktigt med *standardiserade* mätningar av kroppssammansättningen med bioelektrisk impedans. Mätningarna bör göras när den som skall mätas är fastande samt har legat och vilat i tio minuter. Underviktiga KOL-patienter uppvisar en mycket stor variation i sin energiförbrukning. Deras totala energiförbrukning varierade från 1,2 till 1,8 gånger viloenergiförbrukningen. Under två veckor med träning hos sjukgymnast ökade några patienter sin totala energiförbrukning medan andra minskade sin totala energiförbrukning. Patienternas energiintag kunde inte användas som mått på deras energiförbrukning, då energiintaget och energiförbrukningen i de flesta fall inte överensstämde med varandra.

Slutsatser: Bioelektrisk impedans kan vara ett prognostiskt verktyg hos KOL-patienter, men då måste mätningarna standardiseras. Avhandlingen visar att KOL-patienter som är lika sjuka och underviktiga kan uppvisa totalt olik energiförbrukning. Underviktiga KOL-patienters energibehov bör därför värderas individuellt. Nya metoder behöver utvecklas och testas för att mäta energibehov/-förbrukning hos patientgruppen. Dessa metoder måste också kunna användas i den kliniska vardagen, då den viktigaste slutsatsen är att beräkning av KOL-patienters energibehov, med dagens metodik, visar sig vara av föga värde.

List of original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Slinde F, Grönberg AM, Engström CP, Rossander-Hulthén L, Larsson S. **Body Composition by Bioelectrical Impedance Predicts Mortality in Chronic Obstructive Pulmonary Disease Patients.** *Submitted.*

II. Slinde F, Rossander-Hulthén L. **Bioelectrical impedance: effect of 3 identical meals on diurnal impedance variation and calculation of body composition.** *Am J Clin Nutr 2001;74:474-478.*

III. Slinde F, Bark A, Jansson J, Rossander-Hulthén L. **Bioelectrical impedance variation in healthy subjects during 12 h in the supine position.** *Clin Nutr 2003;22:153-157.*

IV. Slinde F, Ellegård L, Grönberg AM, Larsson S, Rossander-Hulthén L. **Total energy expenditure in underweight patients with severe chronic obstructive pulmonary disease living at home.** *Clin Nutr 2003;22:159-165.*

V. Slinde F, Kvarnhult K, Grönberg AM, Nordenson A, Larsson S, Rossander-Hulthén L. **Energy Expenditure in Underweight Chronic Obstructive Pulmonary Disease Patients before and during a Physiotherapy Program.** *Manuscript.*

Abbreviations

BF %	body fat percentage
BI	bioelectrical impedance
BIA	bioelectrical impedance assessment
BMI	body mass index
BMR	basal metabolic rate
BW	body weight
CI	confidence interval
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CRP	c-reactive protein
CT	computer tomography
DIT	diet-induced thermogenesis
DLW	doubly labelled water
DXA	dual-energy X-ray absorptiometry
EI	energy intake
EU	European Union
F	female
FAO	Food and Agriculture Organization
FEV_1	forced expiratory volume in one second
FFM	fat-free mass
FFMI	fat-free mass index
FM	fat mass
g	gram
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
H	hydrogen
HR	heart rate
IBW	ideal body weight
IL	interleukin
kcal	kilocalories
kg	kilogram
kJ	kilojoule
KOL	kroniskt obstruktiv lungsjukdom
kPa	kilopascale
LBP	lipopolysaccharide binding protein
LCNA	the less complicated nutritional assessment
m	meter
M	male
MJ	megajoule
n	number
NIH	National Institutes of Health
O	oxygen

OLIN	The Obstructive Lung Disease in Northern Sweden Studies
PAL	physical activity level
Pa_{O2}	arterial partial pressure of oxygen
RMR	resting metabolic rate
SD	standard deviation
SDR	age-standardized death rate
TBW	total body water
TDE	total daily energy expenditure
TEF	thermic effect of food
TNF	tumor necrosis factor
UNU	United Nations University
U.S.	United States of America
VO_2	oxygen uptake
WHO	World Health Organization

Subjects, methods and statistics

Subjects

- Healthy university students and coworkers
- Patients with severe COPD (FEV_1 < 50 % predicted)

Methods

- Bioelectrical impedance assessment for estimation of body composition
- Body weight and height
- Doubly labelled water for assessment of total daily energy expenditure
- Dual energy X-ray absorptiometry for assessment of body composition
- Indirect calorimetry for assessment of basal metabolic rate
- Seven-day dietary registration for assessment of energy intake
- Spirometry for assessment of pulmonary function
- Zutphen physical activity questionnaire for assessment of physical activity

Statistics

- Cox proportional hazards model
- Degree of agreement following Bland & Altman
- Descriptive statistics
- Dunett's *t*-test
- Fischer's exact test for comparison of proportions
- Unpaired *t*-test

Definition and diagnosis of COPD

A collaborative project of the World Health Organization (WHO) and the U.S. National Heart, Lung and Blood Institute, called "The Global Initiative for Chronic Obstructive Lung Disease (GOLD)" has defined COPD as (91):

> "A disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with abnormal inflammatory response of the lungs to noxious particles or gases."

Varying combinations of airway disease and emphysema are causing the airflow limitation. Increased wall thickening, increased intraluminal mucus and changes in the lining fluid of the small airways are the main constituents of the airway component (120). Emphysema is defined as "permanent, destructive enlargement of airspaces distal to the terminal bronchioles" (120). Chronic bronchitis is also included in the definition of COPD and is defined as "chronic or recurrent increase in volume of mucoid bronchial secretion (present on most days for a minimum of three months a year, for at least two successive years) sufficient to cause expectoration" (83).

Spirometry is used to confirm the COPD diagnosis. In this thesis, forced expiratory volume in one second (FEV_1) in relation to reference values (FEV_1 % predicted) was used, since this is recommended as the best assessment of airflow limitation in moderate to severe disease (120). The patients included in this thesis (paper I, IV and V) were categorized by COPD severity following The European Respiratory Society (120); mild ($FEV_1 > 69$ % predicted), moderate (FEV_1 50-69 % predicted) and severe COPD ($FEV_1 < 50$ % predicted). All patients included in this thesis had a $FEV_1 < 50$ % predicted, hence diagnosed as severe COPD.

The main risk factor for COPD is inhaled agents, particularly cigarette smoke, but also occupational exposures as cadmium and silica are established risk factors (120). All patients included in the thesis had a cigarette smoke induced COPD.

Prevalence and treatment of COPD

The prevalence of COPD is varying widely between countries, mainly due to differences in prevalence of cigarette smoking. In 1998, The Global Burden of Disease study suggested that COPD will increase from 12th place in 1990 to 5th place in 2020, concerning disease burden *worldwide* (74). In that study the worldwide prevalence of COPD in 1990 was estimated to be 9.34/1,000 in men and 7.33/1,000 in women, i.e. 0.8 %. These numbers include all ages, and therefore underestimate the true prevalence in older adults. This is one reason why prevalence of COPD varies between different sources in the literature. Halbert et al (55) showed in their review article a variation in COPD prevalence from 0.23 to 18.3 %, concluding that the overall mortality appears to lie between 4 and 10 %. Another reason for difference in reported prevalence is the use of different diagnostic criteria. This is shown in the OLIN studies in Northern Sweden where 1,237 subjects (46 years or older) were studied (76). Using the GOLD guidelines (91), the prevalence of COPD was 14.3 % compared to a prevalence of 8.1 % using the more strict diagnosis suggested by the British Thoracic Society (11). 25 % of the subjects were classified as smokers, and 25 % of the smokers were qualifying for a COPD diagnosis, following the GOLD guidelines. 15 % of the ex-smokers and 8 % of the non-smokers were also diagnosed as COPD patients, with the highest COPD prevalence in the oldest sub-group (76-77 years of age) (76).

The European Respiratory Society defines the goals of COPD treatment as (120):

> "To prevent symptoms and recurrent exacerbations and to preserve optimal lung function both in short- and long-term; thus improving activities of daily living and enhancing the quality of life."

Prevention of the onset and progression of COPD could be done by smoking cessation and reduction of total exposure to tobacco smoke, occupational dust, chemicals and air pollutants (91, 120). Pharmacotherapy, mainly different types of bronchodilators, is used to decrease symptoms and complications, since none of the existing medications have been shown to affect the progress of the disease (91). In advanced stages of the disease even long-term oxygen treatment or different kinds of surgery (bullectomy, lung volume reduction surgery, and lung transplantation) are used.

Pulmonary rehabilitation, which was studied in paper I and V in this thesis, is also a treatment recommended in international guidelines (91, 120). The goals of such rehabilitation are to increase exercise capacity and enhance quality of life.

Mortality of COPD

COPD is the fifth leading cause of mortality in North America (69, 78). Differences in mortality rates between countries could be due to varying exposure to risk factors, but could also be due to methodological problems with death certification and coding. In Figure 1, death rates are presented for death in bronchitis, emphysema and asthma, since numbers for COPD can not be distinguished from the WHO database (137). Another reason for the underestimation of mortality in COPD could be that another diagnosis is defined as the main cause of death, while COPD often is characterized only as a contributing cause of death. This is illustrated in paper I (Table 2) where only nine of the 47 deaths had COPD as main cause of death on the death certificate, whilst COPD was mentioned as second or third cause of death on 25 of the death certificates with other main causes of death.

However, Figure 1 tells us that the mortality in bronchitis/emphysema/asthma increased during the 1990's. Age-standardized death rates mean that the death-rates are age-adjusted for a European population, so comparisons can be made between different countries, independent of the age distribution in that specific country. We can also see that Sweden is at the same level as the average in the European Union (EU). Denmark, on the other hand, is an example of a country with high mortality in bronchitis/emphysema/asthma and high prevalence of tobacco smoking. The countries within the EU (before the enlargement of the EU which took place in 2004) with the lowest mortality in bronchitis/ emphysema/asthma are Greece, France and Spain (137). Figure 2 presents mortality numbers from the Swedish Cause of Death Register (70).

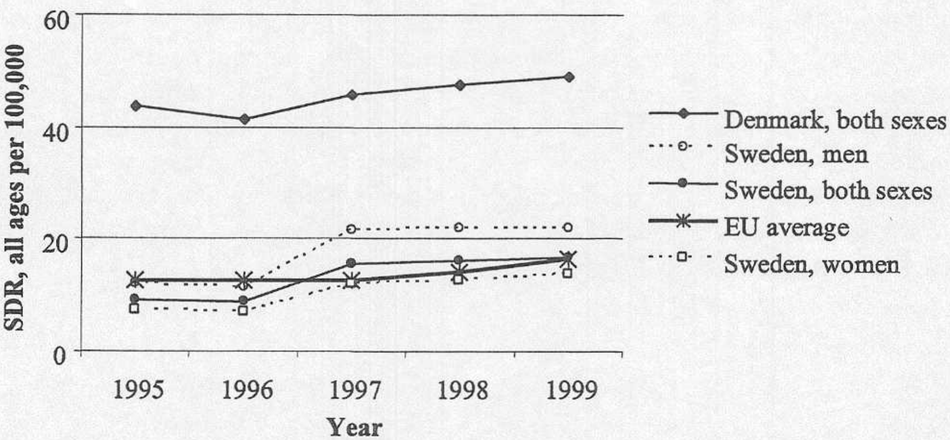

Figure 1. Age-standardized death rates (SDR), bronchitis/emphysema/asthma, all ages per 100,000 for the years 1995-1999 (137).

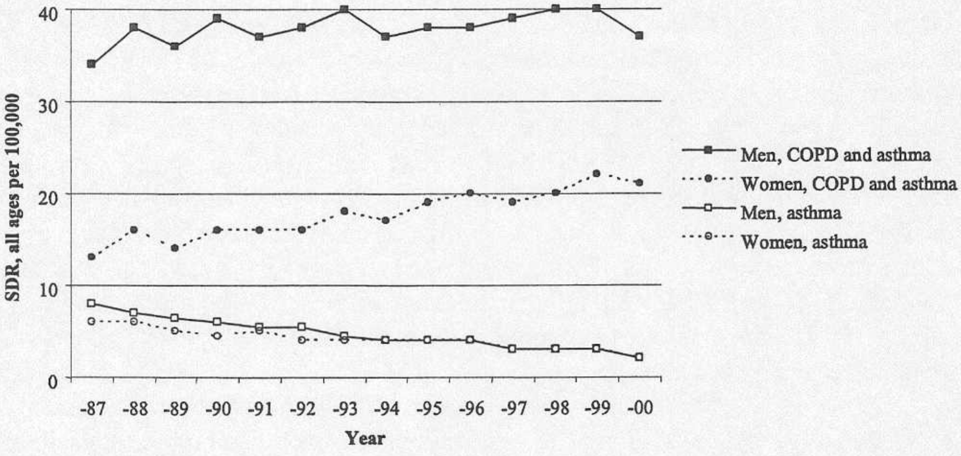

Figure 2. Age-standardized death rates (SDR) in lower respiratory diseases, deaths per 100,000 for the years 1987-2000 in Sweden (70).

Mortality in asthma has decreased, probably due to earlier misclassifications of asthma as COPD deaths. Changes in mortality of lower respiratory diseases (mainly COPD and asthma) are therefore mirroring how COPD mortality has developed with a small increase in mortality for men and about doubled mortality for women. Figure 1 and 2 also show that men have higher mortality in bronchitis/emphysema/asthma compared to women. Paper I confirmed that male patients with severe COPD have a higher mortality, compared to female patients, independent of other possible factors known to affect mortality such as age and disease severity. There are indications from epidemiological studies that women are more susceptible to develop COPD than men (101), but the risk of developing COPD might not be identical with the severity of the disease when it has been established. In addition to paper I, other studies have shown that male patients with established COPD have a higher mortality risk compared to female COPD patients (27, 41, 78, 126).

Summary of paper I

Aim: To study mortality in a sample of patients with severe COPD included in a one-year multidisciplinary rehabilitation program in relation to body composition as evaluated by bioelectrical impedance.

Subjects and methods: Mortality was studied in 86 patients using the Cox proportional hazards model.

Main findings:

- 47 patients (55%) died during the mean follow-up time which was almost six years
- Gender, age, and fat-free mass index (FFMI) were significant predictors of mortality when controlling for other baseline variables in a multivariate analysis

Mortality and nutritional status in COPD patients

In 1967, Vandenberg et al showed that in a group of 100 patients with COPD, weight loss was a risk factor for death (133). Five years later, a new statistical method was presented which was called the Cox proportional hazards model (22). Wilson and coworkers applied this method on 779 male COPD patients and found that mortality was influenced by body weight, using percentage ideal body weight (IBW), independent of FEV_1 (140). The relationship between body weight and mortality was strongest for the patients with FEV_1 between 47 and 60 % predicted. Both these studies had limited possibilities to control for potential confounders. In the total cohort, constituting both hospitalized and non-hospitalized COPD patients, Gray-Donald et al found that low body mass index (BMI) and use of home oxygen were independently associated with reduced survival (51). All these studies can not tell us whether the associations are due to a causal effect, or if body weight is a marker of increasing health problems during disease development. In 1998, Schols et al provided considerable information concerning the causal effect (114). They showed, prospectively, that weight gain of more than 2 kg/8 weeks was an independent predictor of survival in a sample of 203 patients with COPD. In the same publication they also showed, in a retrospective analysis, that low BMI was a significant independent predictor of mortality, and a threshold value of <25 kg/m^2 was identified where the mortality risk was clearly increased. This could be compared to the recently published study in 8,100 "healthy" Dutch women over 50 years of age, where mortality was highest in the highest BMI-quartile (>27.8 kg/m^2) (81).

Marquis et al hypothesized that loss of muscle tissue would have more prognostic implication than the loss of other body compartments (80). They therefore scanned 142 COPD patients with a computer tomography (CT) scan of the midthigh and followed the patients for six years. They found that the midthigh muscle cross-sectional area was a better predictor of mortality than BMI, especially in patients with severe COPD (FEV_1 < 50 % predicted). Mid-thigh circumference and quadriceps skinfold thickness were also measured anthropometrically. These measurements, however, were not sufficiently accurate to give the same predictive effect on mortality as the CT scan. In an editorial following that paper, Mador (77) asked for confirming studies showing that body composition, preferably using simpler and less expensive methods for assessing body composition, predicts mortality better than BMI. This was the origin of paper I in this thesis. The paper is a retrospective analysis of the mortality in a patient group which was included in a one-year multidisciplinary rehabilitation program between March 1992 and June 1998. Body composition was measured in all patients at inclusion using the bioelectrical impedance assessment (BIA) method, which is a simpler and less expensive method compared to CT. The use of bioelectrical impedance (BI) for body composition estimation, is based on the principle that fat mass (FM) and fat-free mass (FFM) have different conductive and dielectric properties due to the fact that FFM contains water and therefore has lower resistance than FM (29). Fat-free mass index (FFMI), assessed by BIA, was found to be an independent predictor of mortality as was also gender and age (paper I). Many considerations had to be made when such a study was done retrospectively. I will now elucidate what the results might have turned out to be if other considerations were made than the one presented in paper I.

We chose to express body composition as FFMI as recommended by VanItallie et al in the well-known Minnesota Study, which gives examples that justify the use of a height normalized value of body composition (134). They showed that two subjects with about the same FFM (61.6 kg vs. 60.7 kg) but who had different height (170.4 cm vs. 185.3 cm) differed in functional status. The highest subject (with a low FFMI (=17.7 kg/m^2)) was "physically weak and felt chronically tired and mentally depressed" compared to the shortest subject (with the higher FFMI (=21.2 kg/m^2)). Compared to the 5,635 healthy subjects described by Kyle et al (67), most of the patients in paper I seem to have an FFMI within the normal range which was described to be between 16.7 to 19.8 kg/m^2 for men and 14.6 to 16.8 kg/m^2 for women. Schols and colleagues have suggested presenting FFM as percentage of IBW (115). In paper I we present the body weight as a percentage of the weight of a normal Swedish elderly population (7) and chose to call it "% reference weight". If we adopt the Schols model of presenting FFM using % reference weight, this would not affect the results presented in paper I; FFMI still is an independent predictor of mortality in the patient sample.

Another decision was to use the original calculations of FFM from the BIA. Manufacturer supplied equations were used, based on comparison with densitometry in a normal population. More than 30 different equations are available where FFM and FM can be calculated based on BIA measurements. Most of them are developed and validated on healthy adults. Currently, two prediction equations are developed on patients with COPD. One is developed from deuterium dilution (117) and the other from dual-energy X-ray absorptiometry (DXA) (66). A homogenous group of 24 male and eight female COPD patients were included in the deuterium dilution study and the best-fitting regression equation to predict FFM comprised $height^2$/resistance and body weight. Kyle et al (66) used a larger group of 75 patients to develop their equation from the DXA, and the best-fitting regression equation to predict FFM included height, weight, resistance, and gender. Table 1, which is comparable to Table 1 in paper I, presents the results from these two equations.

Table 1. FFMI calculated by two different equations and their prediction of mortality in an univariate analysis (mean (SD)), n=86.

	All patients	Survivors (n=39)	Non-survivors (n=47)	p-value*	Hazard ratio	95 % CI	p-value
FFMI, kg/m^2(117)	15.9 (1.9)	16.4 (1.9)	15.5 (1.8)	0.021	0.85	0.72-0.99	0.038
FFMI kg/m^2(66)	15.0 (1.6)	15.1 (1.5)	14.8 (1.6)	0.37	0.94	0.18-1.12	0.48

* Survivors compared to non-survivors

Table 1 tells us that the FFMI calculated from the DXA-derived prediction equation is not a statistical significant predictor of mortality, not even in a univariate analysis, while the equation derived from deuterium dilution qualifies to be included in a multivariate analysis. This might be due to the fact that BIA and deuterium dilution both are based on the same principle of hydration of the FFM, while DXA is independent of body fluids and is based on absorption of X-rays in the body (82). The remaining question is then, what happens with the dilution derived FFMI when entered into a multivariate Cox proportional hazards mode instead of the one used in paper I. Table 2 gives the answer.

Table 2. Baseline predictors of mortality: multivariate analyses, n=86.

	Hazard ratio	95 % CI	p-value
Age, years	1.06	1.00-1.11	0.038
Sex (F/M)	1.93	0.89-4.15	0.094
Hospital days*	1.01	0.99-1.02	0.40
Reference body weight, %	1.01	0.97-1.06	0.59
FFMI (117), kg/m^2	0.80	0.57-1.13	0.21
FEV_1, % pred	0.98	0.94-1.01	0.19
6-min walking distance, m	1.00	0.99-1.00	0.27

*Hospital days the year before inclusion

As shown in Table 2, age – and possibly gender – are independent predictors of mortality in this patient group. Since the equation developed from deuterium dilution on COPD patients is based on a limited, selected and homogenous group of patients, we chose to present the results based on the equations provided by the manufacturer (RJL systems, Akern, Florence, Italy). We have, however, not been able to get information from the manufacturer on what material they have based their equation. This is a trade secret which the manufacturer will not reveal. In any case, the equation is widely used and it has also been shown to give better or as good precision as any other prediction equation (68, 98, 119). However, compared to the DXA method, the precision is lower (54, 142).

Conclusion, paper I:

> ***"Body composition, measured by BI and presented as FFMI, is an independent predictor of mortality in COPD patients."***

Bioelectrical impedance assessment (BIA)

Our understanding of the composition of the human body is based on chemical analysis of six human bodies which were performed between 1945 and 1956. Table 3 is an overview of what was found in those analyses.

Table 3. Overview of findings in chemical human bodies analyses between 1945 and 1956 (42, 43, 84, 138).

Reference	(84)	(138)	(138)	(42)	(43)	(43)
Gender	M	M	F	M	M	M
Age	35	25	42	46	60	48
BMI (kg/m2)	21.1	22.4	15.8	19.0	24.8	21.7
Water (g/kg FFM)	775	728	733	674	704	730
FFMI (kg/m^2)	18.4	19.1	12.1	16.8	-	-

M=male; F=female

Table 3 shows that the mean water content of the human FFM is 724 g per kg FFM, with a considerable variation. Also in 1945, in a study of 50 guinea pigs, Pace and Rathburn showed that the water content in FFM was rather stable and was found to constitute 72.4 % of the fat-free body mass (90). Following this, one can obtain the FFM by using an estimate of total body water (TBW):

$$FFM = \frac{TBW}{0.724}$$

BIA is one method to achieve an estimation of total body water. BIA makes use of the fact that impedance to electrical flow of an injected current is related to the volume of a conductor (the human body) and the square of the conductor's length (height). Impedance is a measure of how electrical current is slowed or stopped as it passes through a material. Impedance has two components: resistance (a measure of the amount of electrical current a substance will stop) and reactance (a measure of a material's ability to slow a current). Thomasset (129) was the first to report a relation between body water and electrical impedance. In the publication from 1965, Thomasset summarize a thesis in which the BI was compared to Br^{82}. In 42 "normal" subjects they found a correlation coefficient of 0.67 between the methods. When they added 20 subjects with edemas the correlation increased to 0.85. Hoffer et al (59) developed the principle and demonstrated that total body water determined by the tritiated water method were strongly correlated ($R = 0.92$) with $height^2$/ impedance in 20 "normal" volunteers and 34 patients with varying diagnosis and hydration status. Since then, numerous validation studies have been published and several prediction equations are available. Combining the search terms "body composition" and "bioelectrical impedance" in the PubMed database resulted in more than 1,000 hits. BIA has become a widely adopted method for body composition assessment, not only for scientific purposes, but also in the clinical setting and nowadays in the society as well, at different training facilities.

In 1997, Sereno Symposia USA Inc organized an invited panel to update the consensus from the 1994 National Institutes of Health (NIH) Technology Assessment Conference on BIA technology for body composition measurement (35). Guidelines for clinical use were established:

> "The optimal method, though not always practical (in a clinical setting), for obtaining impedance measurements involves having the subject (preferably fasting, but not dehydrated) lie supine for at least 10 min."

During the preparations for the publication of the consensus document, Gallagher and coworkers published a study where they showed that intake of a breakfast meal was followed by a significant decrease in impedance (46). Five hours post-prandially, the impedance had begun to return towards fasting level, although still significantly lower compared to the fasting value. At least in Sweden, it is usual to consume another meal within four or five hours. The aim of paper II was therefore to study the effect on BI of three identical meals during 24 hours.

Summary of paper II

Aim: To study the effect on bioelectrical impedance of three identical meals.

Subjects and methods: BI was measured 18 times during 24 hours in 18 healthy subjects. An identical meal was given at breakfast, lunch, and dinner.

Main findings:

- BI decreased after ingestion of a standard meal, the decrease was additive during the day
- Calculated body fat percentage (BF %) varied by 9 % from the highest to the lowest measurement

An additive decrease of the three meals in BI was found during the day and thus a decrease in the calculated percentage of FM. However, the decrease after the first meal was double the increase after meal two and three, which we in the discussion suggested might be due to a combined effect of rising from a lying position and ingesting food and beverages. It is supported by the findings of Gallagher et al (46) that the decrease in segmental BI largely occurred in the limbs. Standing position makes water pass from the intracellular to the extra-cellular compartment, especially in the limbs, where body electric resistance is higher. This had earlier been shown in ten healthy men who were in the supine position for 60 minutes and than five minutes standing (102). A steady and significant increase in resistance was shown during recumbence, which was interrupted during standing, and the resistance decreased significantly. Simultaneously they measured haematocrit; the mean plasma volume increased 10 % during recumbence and decreased 13 % after five minutes in the upright position. Lozano-Nieto and Turner confirmed, in a study of four subjects during a period of 20 minutes, that increasing impedance during supine position was followed by a decrease when standing, (75).

In the clinical setting however, a supine position for more than 20 minutes or even more than one hour is highly possible; leading us to perform the study which is presented in paper III. It was confirmed that being in the supine position leads to an increasing BI for as long as up to 12 hours. The decreasing effect of ingesting a meal was also found to be apparent, though only statistically significant after the first meal.

Summary of paper III

Aim: To examine the bioelectrical impedance variation in healthy subjects during 12 hours in the supine position.

Subjects and methods: BI was measured 16 times during 12 hours in 18 healthy subjects. An identical meal was given at breakfast, lunch, and dinner.

Main findings:

- BI increased significantly from study start to study end
- Calculated body fat content increased from a baseline mean of 21.7 % to 23.9 % body fat at study end

Common for paper II and III is that in both studies major effects were seen on the calculated BF %, using the manufacturer-supplied equations, but also found when calculated from other published prediction equations. In paper II we found an almost mean 10 % decrease in BF %, and in paper III an increase in BF % at the same size, during 12 hours. Individual variation could be as much as 20 %, which made us draw this conclusion:

BIA measurements should be performed in the fasting state after ten minutes in the supine position. This strengthens the guidelines proposed by Ellis et al (35).

The observant reader probably has detected inconsistency between the findings in paper II / III and the use of BIA in paper I. Measurements of impedance in paper I were "performed in the morning after ten minutes rest in the supine position" i.e. the patients were not fasting. As mentioned earlier the study (paper I) was initiated in 1992, i.e. before the NIH conference in 1994. However, the results in paper I are based on the FFMI. Figure 3 shows the results on the FFMI derived from the results presented in paper II and III.

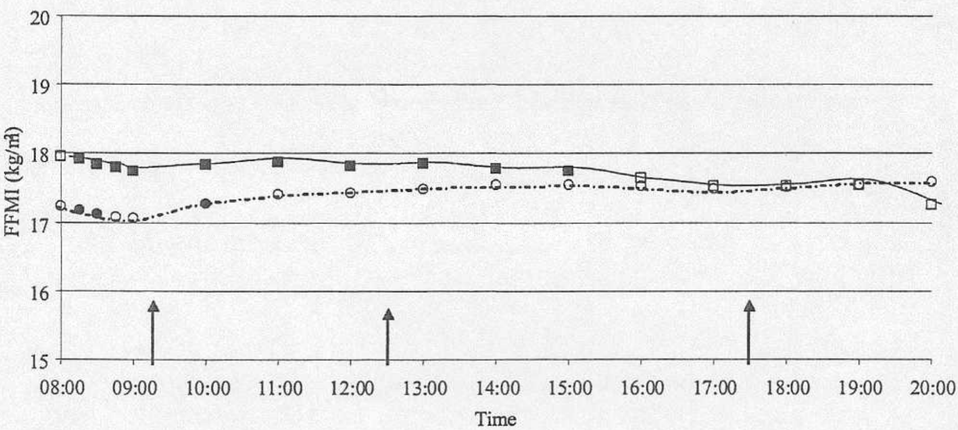

Figure 3. Mean FFMI during 12 hours. Arrows indicate time of meals. Circles = paper II, squares = paper III. Open circles/squares = p<0.05 from baseline, filled circles/squares = n.s. from baseline.

As shown in Figure 3, the FFMI is more stable than the BF %. In paper II there was a difference in FFMI of 2 % between baseline and final measurement and in paper III the difference was 4 %. The largest change in an individual was 8 %. The changes seem to be of limited clinical importance even if some of the changes in FFMI are statistically significant. Why is then FFMI a more stable variable than BF %? BF % includes body weight while FFMI includes body height, which is a more stable variable during 12 hours.

Still most studies report the amount of body fat, often expressed as BF %. Following the measurement guidelines mentioned above, we found a mean BF % in paper II of 22.2 %, calculated with manufacturer supplied equations. However, we also found that it was 20.7 % in the evening. Probably this would have led to other results if it had been a study aiming to investigate body composition and some health aspects. Do we know the true answer concerning the subjects' body composition? Unfortunately we did not use a reference method to measure body composition in these studies, but in the paper II study we actually measured skinfolds at four sites; biceps, triceps, subscapular, and suprailiac and calculated the BF % using the equations of Durnin and Womersley (33). Mean BF % from the skinfolds for the 18 subjects was 22.2 %, which is a weak, maybe speculative, indication of that the guidelines might be even more strengthened by this study.

Malnutrition in COPD patients

Cotes, who followed 235 coalminers from Wales for ten years, starting in 1947, was one of the first to report weight loss in COPD patients (21). In another study, performed in the 1960's, 40 of 86 patients (47 %) with emphysema were defined as underweight and 22 as weight-losers (141). Hunter and coworkers (64) reported in their material of 38 COPD patients, that half of the patients had a body weight less than 90 % of IBW. Openbrier et al (89) reported that 43 % of the 70 emphysema patients studied had an IBW less than 90 %. Two reports from a Dutch research group showed that 15 of 72 COPD out-patients (20 %) and 35 % of those eligible for pulmonary rehabilitation, had depletion of FFM (37, 115). In the latter of those two studies, 79 of the 205 patients (39 %) had an IBW less than 90 %. It seems as if the prevalence of underweight in COPD patients is somewhere between 20 and 50 %. In paper I in this thesis, which was based on a material of consecutively recruited patients with severe COPD, 30 of the 86 patients (35 %) included had a BMI < 21 kg/m^2. Underweight and malnutrition are often used synonymously. This is however not correct. PubMed defines the MeSH-term malnutrition as: "An imbalanced nutritional status resulted from insufficient intake of nutrients to meet normal physiological requirement". The result from an insufficient intake of energy is hence weight loss.

> "**malnutrition** *n.* the condition caused by an improper balance between what an individual eats and what he requires to maintain health. This can result from eating too little (*subnutrition* or *starvation*) but may also imply dietary excess or an incorrect balance of basic foodstuffs such as protein, fat, and carbohydrate. A deficiency (or excess) of one or more minerals, vitamins, or other essential ingredients may arise from **malabsorption** of digested food or metabolic malfunction of one or more parts of the body as well as from an unbalanced diet."
>
> *Concise Medical Dictionary*, Oxford University Press, 2002.

According to the definition of malnutrition quoted above, one should need to measure an individual's nutritional intake and the nutritional requirement to be able to define malnutrition. Ideally, that should be done for both macro- and micronutrients. This is done very seldom, due to methodological problems on both the intake and the requirement side. However, several possible explanations to the development of underweight in COPD patients have been suggested. Most of them are relating to the energy balance scale on the front page of this thesis.

Basal metabolic rate (BMR)

The largest single component of the total daily energy expenditure (TDE) in most individuals is the BMR, which is the energy expended by an individual lying at physical and mental rest in a termoneutral environment, at least 12 hours after the previous meal. Indirect calorimetry is considered to be the standard method for assessing BMR. Browsing the literature gives conflicting messages about the terms used; BMR and resting metabolic rate (RMR). A lack of one of the conditions mentioned above would mean that the term RMR should be used. Turley et al (132) could not find any difference between an inpatient and an outpatient protocol for measuring, what they defined as, RMR. Adriaens et al (1) even showed that differences in physical activity the day before measurement did not affect the measurement of, what they defined as, BMR. We have measured BMR in the patients in paper IV and V, since all of the conditions mentioned above are fulfilled, even if an outpatient protocol was used.

Summary of paper IV

Aim: To assess TDE and describe its components in home-living underweight patients with severe COPD.
Subjects and methods: BMR was measured by indirect calorimetry and estimated by prediction equations, TDE assessed by the doubly labelled water (DLW) method and energy intake assessed by seven-day dietary registration in ten COPD patients with BMI < 21 kg/m^2.
Main findings:

- BMR was not precisely predicted using available prediction equations, the most precise prediction included FFM
- Physical activity level ranged from 1.15 to 1.80

Prediction equations of BMR have been developed since indirect calorimetry is not a widely accessible method. The equations most used and referred to are the ones produced by Harris and Benedict in 1919 from 333 individuals (56), Schofield in 1985 from 7,549 individuals (109), and FAO/WHO/UNU in 1985 from 11,000 individuals (38). In addition to these equations, several other equations have been developed for specific groups; children, adolescents etc. In the late 1980's a prediction equation was developed on COPD patients with moderate to severe obstructive dysfunction (85). The prediction equation was developed from 43 COPD patients, of which only ten were women. In paper IV, we conclude that none of these equations make especially good predictions of BMR in underweight patients with severe COPD and recommend a measurement of BMR with indirect calorimetry before calculating energy requirement for a patient.

Summary of paper V

Aim: To investigate how TDE changes when underweight patients with COPD entered into a physiotherapy program.

Subjects and methods: TDE of ten COPD patients with BMI < 21 kg/m^2 was assessed by the DLW method in a two week control period and during two weeks in a physiotherapy program.

Main findings:

- Physical activity level in the control period varied from 1.21 to 1.88
- Six of the patients had lower TDE during the physiotherapy period, compared to the control period. Median change in TDE was -10 % or -700 kJ/day

Even if two different indirect calorimeters were used in paper IV and V, I have added the patients in paper V in the Bland-Altman plots from paper IV. The results are presented in Figure 4. In seven of the 21 patients, the the BMR predicted from WHO equations was lower than measured BMR, with a mean difference of -0.3 MJ. Prediction of BMR from measured FFM also leads to an underestimation of BMR in seven patients, with a smaller mean difference at -0.11 MJ. The equation developed for COPD patients underestimated BMR in four of the 21 patients, with a mean difference of -0.50 MJ. The question is then if this is of any clinical concern? Imagine that the underestimation of BMR is 500 kJ and the patient has a PAL of 1.5, which was the mean PAL of the 21 patients in paper IV and V. Calculating the energy requirement for this patient would lead to an underestimation of 750 kJ, almost 10 % of the TDE of the patients. An energy deficit of that size is equivalent to a loss of 25 g of body FM per day, or 765 g FM per month. Probably, not only FM would be lost, meaning that the actual weight loss would be even greater than 765 g.

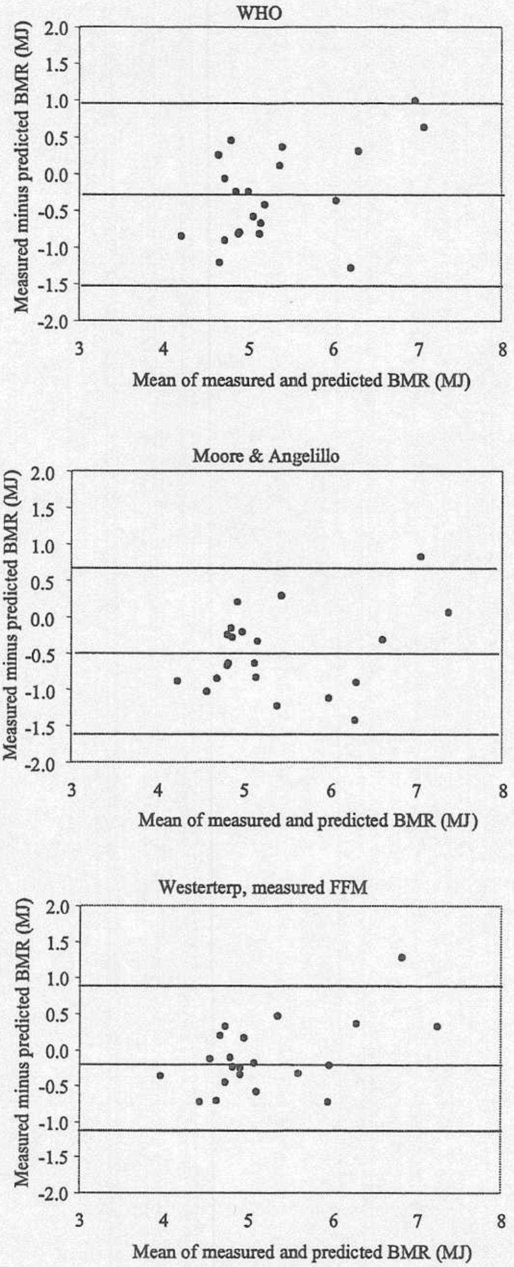

Figure 4. Differences between measured and predicted BMR plotted against mean of measured and predicted BMR predicted from equations from WHO, Moore & Angelillo and Westerterp in the 21 underweight patients with severe COPD presented in paper IV and V. Lines indicate mean difference and +/- 2 SD.

Table 4 is an overview of studies which have measured and reported BMR/RMR in patients with a stable COPD, using indirect calorimetry. Several studies (17, 23, 24, 28, 31, 44, 47, 63, 110, 123) did not report BMR in kJ or kcal. Those studies are not included in Table 4. All studies including a control group have found a higher BMR in COPD patients compared to the control group, except one in which the control group had a significantly higher amount of FFM and lower amounts of body fat compared to the patients (105). It is hard to compare the BMR values, partly because the studies have used different measurement equipment, but most important is that the patient groups differ in body weight and body composition between the studies. Few studies have reported BMR/kg BW or BMR/kg FFM, which makes a more general conclusion from the studies impossible. It is noticeable that paper IV and V seem to report lower BMR compared to most of the studies. Actually the only study having as low BMR as ours is the study made by Tang et al (128). Only women were included in that study and, unlike the other studies, our studies also have a majority of women. Women have lower BMR than men, due to a higher proportion of body fat. That might be the reason for the low BMR in our studies. All patients were included due to a low BMI, which also would lead to a lower BMR, compared to studies including patients with higher BMI.

As the largest component of TDE, an elevated BMR has a major impact on an individual's energy requirement. Most of the studies in Table 4 found an elevated BMR compared to predicted BMR. In a majority of these studies, measured BMR have been compared to the Harris & Benedict equation (56). Figure 5 clearly demonstrates that the Harris & Benedict equation predicted a lower BMR compared to a prediction using the WHO equations in the 21 patients presented in paper IV and V.

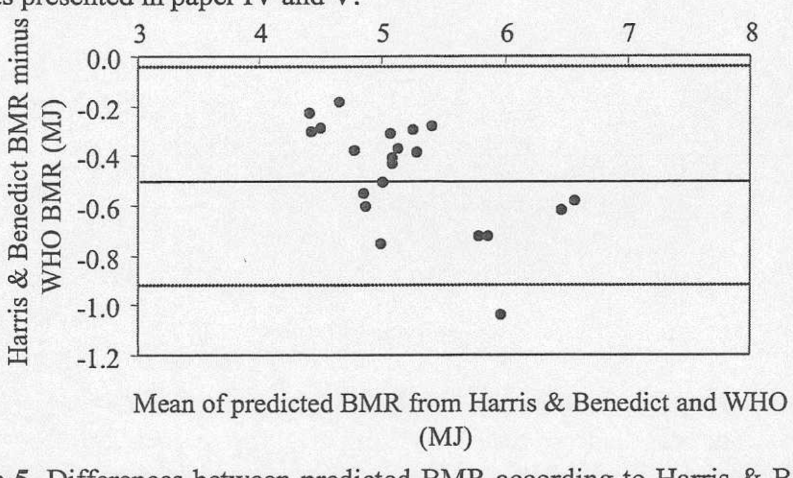

Figure 5. Differences between predicted BMR according to Harris & Benedict (56) and WHO (38) plotted against mean of predicted BMR according to Harris & Benedict and WHO in the 21 underweight patients with severe COPD presented in paper IV and V. Lines indicate mean difference and +/- 2 SD.

Table 4. Overview of studies which have measured and reported BMR/RMR in patients with a stable COPD using indirect calorimetry.

Reference	FEV_1 (% pred)	n (M/F)	BMR (kJ)	BMR/kg BW (kJ/kg)	BMR/kg FFM (kJ/kg)
		COPD-patients			
(139)[1]	31	7 (?/?)	6,029	-	-
(112)[3]	31	34 (27/7)	6,094	-	-
(116)[3]	35	39 (?/?)	6,243	110	146
(79)[1]	-	6 (6/0)	7,079	130	-
(85)	-	43 (33/10)	7,309	-	-
(40)	37	10 (10/0)	7,007	117	137
(52)	31	10 (7/3)	-	110	-
(113)	29	12 (?/?)	5,883	-	-
(113)	34	12 (?/?)	5,920	-	-
(53)	36	6 (3/3)	5,552	102	-
(53)	30	9 (6/3)	6,126	101	-
(61)	34	11 (11/0)	6,145	-	-
(103)	43	10 (5/5)	4,422	92	-
(62)	34	16 (16/0)	6,688	-	-
(4)	36	8 (8/0)	6,155	-	-
(5)	38	10 (10/0)	6,791	-	-
(5)	31	10 (9/1)	5,966	-	-
(3)	37	33 (23/10)	6,372	-	-
(12)	39	13 (10/3)	6,092	-	-
(13)	42	8 (7/1)	-	107	-
(13)	37	8 (7/1)	-	115	-
(136)	37	23 (12/11)	6,196	-	-
(100)	32	12 (12/0)	-	-	140
(88)	-	36 (30/6)	6,477	-	-
(105)	36	9 (9/0)	6,782	-	-
(128)	37	10 (0/10)	4,134	-	-
(127)	35	23 (1/22)	6,017	-	-
(50)	40	20 (11/9)	5,800	-	-
(139)[2]	44	8 (?/?)	6,029	-	-
(112)[4]	39	34 (26/8)	6,295	-	-
(116)[4]	35	41 (?/?)	6,251	95	133
(79)[2]	-	4 (4/0)	7,602	88	-
Mean (sum of n)	***36***	***535 (303/113)***	***6,188***	***106***	***139***
Paper IV	31	10 (5/5)	5,581	102	131
Paper V	37	11 (2/9)	4,766	95	126

Table 4. Continued

Reference	FEV_1 (% pred)	n (M/F)	BMR (kJ)	BMR/kg BW (kJ/kg)	BMR/kg FFM (kJ/kg)
		"Normal" subjects			
(40)	-	10 (10/0)	6,158	90	110
(139)	110	7 (?/?)	6,925	-	-
(112)	-	34 (18/16)	6,114	-	-
(52)	92	6 (5/1)	-	84	-
(53)	100	7 (2/5)	-	91	-
(61)	115	11 (11/0)	6,326	-	-
(62)	108	12 (12/0)	6,808	-	-
(4)	-	8 (8/0)	6,167	-	-
(100)	113	8 (8/0)	-	-	118
(79)	-	5 (5/0)	7,130	100	-
(105)	-	9 (9/0)	7,502	-	-
Mean (sum of n)	***106***	***117 (88/22)***	***6,641***	***91***	***114***

[1]"undernourished", [2]"adequately nourished", [3]"weight losing", [4] "weight stable"

In fact, as shown in Figure 5, the equation from Harris & Benedict under-estimated BMR in 12 of the 21 patients. This means that more patients would have been classified as having an elevated BMR by using this equation compared to the newer equations presented in Figure 4. A conclusion from this is:

It should not be anticipated that all patients with COPD have an elevated BMR. A measurement with indirect calorimetry is recommended when calculating energy requirements for COPD patients.

However, some COPD patients present an elevated BMR. Several possible explanations for this are available in the literature. Since all the factors mentioned below could be found in the COPD patient they should be taken into consideration, which makes a prediction of BMR even harder. This further strengthens the advice of measuring BMR when estimating energy requirement.

Increased energy cost of breathing

This was first studied by the research group led by Cherniack in Winnipeg, Canada. They showed that oxygen (O_2) cost of increased breathing in rest was higher in 17 COPD patients compared to eleven normal subjects (72). Donahoe et al (31) found that COPD patients with IBW < 90 % had an higher O_2 cost of breathing in rest, compared to COPD patients with IBW > 90 % and normal control subjects. Sridhar et al (123) compared six COPD patients to six scoliosis patients, six thoracoplasty patients and six controls. O_2 cost of breathing was four times higher in the patient groups compared to the controls. Mannix et al (79) showed a higher O_2 cost of breathing in ten COPD patients compared to five control subjects and they also found that the six patients with BMI < 18.4 kg/m^2 had a higher O_2 cost of breathing compared to the four patients with higher BMI (mean 26.0 kg/m^2). It should be noted that these studies includes a limited number of subjects, and selected groups of both patients and "normal" subjects.

Inflammation

DiFrancia et al (30) found higher levels of tumor necrosis factor-alpha (TNF-α), which is a pro-inflammatory cytokine, in 16 underweight male COPD patients compared to the 14 normal weight male COPD patients. The latter ones had normal levels of TNF-α. A similar finding was made by de Godoy et al (28), who presented higher TNF-α production after lipopolysaccharide stimulation, in ten weight-losing COPD patients compared to ten weight-stable COPD patients and 13 age-matched healthy controls. Schols et al (110) further elucidated this in their study on 30 COPD patients and 26 healthy age-matched controls. Sixteen of the patients were defined as hypermetabolic, which was defined as a measured BMR > 120 % of the BMR predicted from the Harris & Benedict equation. They found higher levels of C-reactive protein (CRP) and lipopoly-saccharide binding protein (LBP) in the hypermetabolic group. Eight hyper-metabolic patients had elevated CRP, and these patients also had increased levels of soluble TNF receptors 55 and 75 and interleukin-8 (IL-8). These findings have later been confirmed by others (34, 88, 99). The role of cytokines in COPD is probably more complex than the possible effects on BMR and we are probably only in the start pit of understanding the relation between inflammation and malnutrition.

Medication

In a study of 13 stable COPD patients, Burdet et al (12) reported that salbutamol, a β_2 adrenergic bronchodilator, increased BMR with 5 %. This was not the case with ipratropium bromide, an anticholinergic bronchodilator, or placebo. A similar finding was found by Creutzberg et al (23) who found an increase in BMR of 4 % after nebulization of 5 mg salbutamol. Congleton and Muers (20), however, did not find any change in BMR in 17 patients with COPD after eight months of 5 mg salbutamol per day. An abstract, presented by Sridhar et al (122), indicates that the increase in BMR followed by salbutamol, is smaller in COPD patients, compared to controls. This might indicate a blunting of the effect following chronic use of salbutamol. An interesting study, illustrating this point, is a study of BMR after use of fluoxetine in obese women, which is used as medication for depression (8). A significant acute increase in BMR was noted, but after 12 weeks of treatment, no significant change in BMR was seen. Following this, we know that some medications used by COPD patients have acute effects on BMR, but the long-term effect is not yet fully understood. The same applies to the combined effect of several different medications.

Nicotine and caffeine

Collins et al (18) showed that smoking four 0.8 mg nicotine cigarettes increased BMR by 3 % over three hours in ten healthy men. Consumption of 200 mg caffeine increased BMR by 5 %. Ingesting 200 mg caffeine and in addition smoking four cigarettes increased BMR by 8 %. In a recent study, Jessen et al (65) reported the results from a randomized, double-blind placebo-controlled, crossover study using chewing gums with different amounts of nicotine and caffeine in 12 healthy men. BMR was measured before and 2.5 hours after the gum was chewed. The gum with the highest content of nicotine and caffeine, 2 mg and 100 mg respectively, increased BMR by 10 % A number of studies have reported acute effects of nicotine on BMR (2, 19, 92-97), while others (57, 87) showed no effect in heavy smokers. These studies investigated the acute effects on BMR. Hofstetter et al (60) studied eight healthy smokers twice during 24 hours in a metabolic chamber, once without smoking, and once while smoking 24 cigarettes. They found the energy expenditure to be 10 % higher during the smoking day compared to the non-smoking day, but the difference in BMR (105 kJ) was not statistically significant different. To summarize, both nicotine and caffeine have increasing effects on BMR, at least acutely.

Diet-induced thermogenesis (DIT)

DIT, or thermic effect of food (TEF) as it is also called, accounts for approximately 10 % of the TDE. In ten COPD patients, Goldstein et al (47, 48) found that DIT was 30 % higher compared to five control subjects, when following both a fat-based and a carbohydrate-based diet. Green and Muers (52) studied ten COPD patients and six age- and sex-matched controls. They showed that DIT, as a percentage of energy intake, was greater in the COPD patients compared to the controls. However, one year later they reported a study in which they found no difference in DIT between four groups of emphysematous COPD patients, bronchitic COPD patients, asthma patients or a control group (53). Ryan et al (103) reported a DIT of 24 % following a large meal (0.5 x BMR) in ten underweight COPD patients. This was not confirmed by Hugli et al (61) which compared DIT in eleven COPD patients and eleven healthy controls and found no significant difference in DIT between the two groups. Doré et al (32) did not find any difference in DIT between ten malnourished and 16 normally nourished COPD patients, and concluded that "these results suggest that malnutrition is not a consequence of an increased DIT". It is hard to draw any conclusions from these studies. They are performed in small patient groups and selected control groups, with different kind of meals, both in total energy content and in energy constituents.

Total daily energy expenditure (TDE) and physical activity

Even if BMR is the largest component of TDE, physical activity is the main determinant of variation in energy requirement, at least in healthy subjects. In paper IV and V in this thesis, we have used the DLW method to assess physical activity energy expenditure, which we have defined being the difference between TDE and BMR. DLW is well established and validated both in animals and humans (106-108) and is today considered to be the golden standard for assessment of TDE. The assessment is made with high precision without limiting the subjects' daily life. DLW consists of water labelled with the stable isotopes deuterium (^{2}H) and oxygen-18 (^{18}O), which is orally administered to the patient. The principle of the method is that, when ingested, ^{2}H labels the total body water pool and ^{18}O labels the total body water pool *and* the bicarbonate pool. In the urine samples that the patients leave during two weeks, the elimination rates of the two isotopes can be detected. The difference between the elimination rates of the two isotopes gives an estimate of CO_2 production and hence TDE. Accuracy of the method is generally in the order of 1-3 % and precision 2-8 % (86). The use of multi-point regression analysis of isotope elimination rates, which is used in this thesis, seems to offer 2-3 % better precision compared to the two-point (only baseline and final sample) method (86).

As shown in Table 5, only two other studies (4, 5) have reported TDE in COPD patients using the DLW method. Both these studies were performed in patients admitted to a pulmonary rehabilitation unit, hence having a high physical activity, probably accounting for the high physical activity level (PAL) found in those studies. The studies performed in indirect calorimetry chambers (62, 63) on the other hand, have a low level of physical activity. The 21 subjects in paper IV and V had a mean PAL of 1.50, when they were free-living at home. This is the same mean PAL as Fuller et al (45) reported in a study of 23 elderly (> 75 years) British men. Like us, Fuller noted a large range in PAL from 1.2 to 2.0, which is comparable to our values ranging from 1.15 to 1.88. So obviously, using a standard value of 1.5 or any other value to calculate a patient's energy requirement is of limited value. Measuring the physical activity is therefore necessary. In paper IV we used the Zutphen physical activity questionnaire (15), which we concluded can not be used for assessing a PAL-value. One of the problems with self-report physical activity measures, is that the validity is higher for reports of vigorous physical activity than for reports of moderate intensity activities (104). The latter ones are the ones dominating the life of patients with COPD. As we noted in paper IV, self-reports do not provide accurate estimations of the absolute amount of physical activity and we fully agree with Sallis and Saelens, who concluded that objective measurements should be used for this purpose (104).

Table 5. Overview of studies which have measured TDE in patients with stable COPD.

Reference	Method	n	PAL	TDE
		COPD-patients		
(63)	Chamber	13	-	134 kJ/kg BW
(63)	HR	13	-	167 kJ/kg BW
(62)	Chamber	16	1.21	8,096 kJ
(4)	DLW	8	1.7	10,456 kJ
(5)	DLW	10	1.56	10,849 kJ
(5)	DLW	10	1.78	11,000 kJ
(128)	Bicarbonate-urea	10	1.52	6,309 kJ
(50)	Accelerometer	20	1.56	9,100 kJ
Paper IV	DLW	10	1.49	150 kJ/kg BW
Paper V	DLW	11	1.51	140 kJ/kg BW
		"Normal" subjects		
(63)	Chamber	8	-	121 kJ/kg BW
(63)	HR	8	-	172 kJ/kg BW
(62)	Chamber	12	1.26	8,560 kJ
(4)	DLW	8	1.4	8,816 kJ

What objective methods could then be used? Currently, mainly two methods exist from which a PAL value could be estimated; heart rate recording and movement sensors.

A linear relationship exists between oxygen uptake (VO_2) and heart rate (HR), which makes heart rate recording a possible method for energy expenditure estimation. However, at low intensities, factors such as fear, excitement and related emotional stress, as well as mode, duration and type of physical activity cause an elevated HR above the energy expenditure, and the relation is then no more linear. The method demands individual calibrations and has been shown to overestimate energy expenditure compared to DLW (36, 73, 118). With factors as medications, nicotine and anxiety, HR is hardly the method of choice when studying physical activity in COPD patients, and to my knowledge, heart rate recording has not been reported to be used for this purpose in COPD patients.

Various types of motion sensors have been developed such as the pedometer, which is a simple and low-cost device that records the number of steps taken with varying degree of sensitivity between different types of pedometers. Several types of accelerometers are also commercially available. They are able to detect and record the actual magnitude of acceleration. Under controlled conditions the validity is acceptable for assessing energy expenditure (131, 135). Validation studies performed under free-living conditions most often underestimate TDE due to an inability to detect upper body movement, load carriage, or changes in surface or terrain (6, 9, 58, 71, 124). However, accelerometers are currently used as criterion standard measurement (130) and it has also been used in COPD patients (50). It should, however, be emphasized that no calibration or validation study has yet been performed in COPD patients.

Due to the cost of purchase and analyzing, the DLW method is not applicable for large groups and especially not in the daily clinical setting. Questionnaires or interviews are not objective, heart-rate recording might not be appropriate for COPD patients and the validity of the movement sensors is questioned. So obviously, a lot is to be wished for in the future concerning estimation or measurement of physical activity energy expenditure. The importance of such a method is underlined in paper V, where we found that energy expenditure can increase with as much as 10 % during a physiotherapy program included in the pulmonary rehabilitation recommended in international treatment guidelines (120). This increase, however, was not apparent in more than three out of ten patients. In the clinical setting, it is necessary to have this knowledge about the patient to be able to calculate the energy requirement. One should not forget, however, that a long-term deficit in energy intake always results in a reduction in body weight, which of course needs to be monitored, not only by the dietitian.

Energy expenditure during rehabilitation

Multidisciplinary rehabilitation programs, including physiotherapy (mobility training, breathing exercises, and physical exercise), nutritional support, psychotherapy and education are recommended in treatment guidelines for COPD patients (120). We have shown slight, but uniform, indications of positive effects of dietary intervention during multidisciplinary rehabilitation in the patient sample presented in paper I (121). However, we also found that the underweight patients did not increase both in physical performance and body weight, despite an increase in energy intake. This led us to examine how much extra energy that underweight COPD patients expend when entering a rehabilitation program. During our data collection, Tang et al (128) published a study where they compared energy expenditure on one day *without* physical exercise to a day *with* physical exercise in COPD patients. In the ten patients, they reported a small increase in TDE (mean = 250 kJ), which was non-significant and they explained this by a probable reduction in discretionary activities on the exercise day. Goran and Poehlman reported similar results in eleven healthy elderly (49). Mean TDE, measured with DLW, was not different during a period of cycling exercises three times per week compared to a control period. They calculated that this was due to a compensatory decline in physical activity during the remainder of the day. This is also a possible explanation in paper V, where we found a median reduction of 10 % in TDE during physiotherapy compared to the control period. However, we also suggest that the breathing exercises performed may make the patients reduce their oxygen cost of breathing, both during rest and physical activity, which would lead to a reduction in TDE. This remains to be investigated in detail. The conclusion drawn from paper V is therefore:

Inclusion into a physiotherapy program is not necessarily followed by an increase in TDE. This calls for an individual assessment of each patient's energy requirements and the need to develop and validate alternative methods to the DLW method to assess TDE.

Energy intake

On the left side of the energy balance scale on the front page you find the energy intake (EI), constituted by carbohydrate, protein, fat and alcohol. An EI which is lower than the energy expenditure results in weight loss. Table 6 presents studies having estimated EI in COPD patients. Schols et al (116) could not detect any difference in EI between weight stable and weight loosing COPD patients. They found however, that hypoxemic patients (FEV_1 < 35 % and Pao_2 < 7.3 kPa) had a lower EI compared to non-hypoxemic patients. The studies investigating habitual EI showed a mean EI that was sufficient to meet the requirements, hence some of the patients had an insufficient energy intake. Some of the studies in Table 6 studied EI during hospitalization due to an exacerbation of the disease and found a low EI – especially during the first days of admission. So, even if most of the studies report sufficient energy intake, it is obvious that the habitual intake is suboptimal for some patients and for most patients experiencing an exacerbation. As discussed in paper IV, methodological problems may exist in some of these dietary assessment studies.

Table 6. Overview of studies which have estimated EI in patients with stable COPD excluding studies reporting EI during hospital stay only.

Reference	Method	n	EI/BMR	EI/day
(64)	Diet history	36	-	10,606 kJ
(10)	3 day record	60	1.56	-
(116)	Diet history	39	1.41	133 kJ/kg BW
(116)	Diet history	41	1.46	128 kJ/kg BW
(103)	7 day record	10	1.35	5,874 kJ
(136)[1]	Diet history	23	-	7,863 kJ
(136)[2]	Diet record	23	1.45[2]	9,545 kJ
(111)	Diet history	27	-	8,970 kJ
(111)	Diet history	15	-	7,544 kJ
(26)	Diet history	17	-	8,619 kJ
(121)	Diet history	63	1.37	128 kJ/kg BW
(128)	1 day record	10	-	4,816 kJ
(50)	7 day record	20	-	9,100 kJ
(16)[3]	Diet history	24	-	7,088 kJ
(16)[4]	Diet history	79	-	8,171 kJ
Paper IV	7 day record	10	1.39	131 kJ/kg BW
Paper V	7 day record	11	1.44	137 kJ/kg BW

[1]Habitual intake, [2]Discharge from hospital following an acute exacerbation, [3]Malnourished, [4]Adequately nourished

Three years ago, a meta-analysis of 21 studies (39) concluded that nutritional supplementation therapy has no effect on improving anthropometric measures, lung function or functional exercise capacity. However, further studies have been published showing positive effects of nutritional supplementation programs on pulmonary function (14), body weight and FFMI (25), and exercise capacity (though only in patients with BMI > 19 kg/m^2) (125). Goris et al (50) reported a stable BMI in their intervention study in both the control and the intervention group. A stable body weight is a better result than a further decreased body weight. To my knowledge, a study with the aim of preventing normal-weight COPD patients to reduce body weight has not yet been made.

Summing up and suggestions for the future

Body composition, measured by BIA and presented as FFMI, is an independent predictor of mortality in COPD patients.

- This finding has to be confirmed in a prospective study with a larger sample size and preferably also including COPD patients with moderate and mild COPD.

BI should be measured in the fasting state after ten minutes in the supine position.

- This is not only valid for scientists, but should also be followed in the clinical setting and other places were BI measurements are performed.

Energy requirements can not solely be calculated from prediction equations. BMR should be measured and physical activity level assessed. Inclusion into a physiotherapy program is not necessarily followed by an increase in TDE.

- Further insight in which factors that affect BMR in COPD patients should be elucidated and COPD-specific prediction equations for BMR based on a large sample of heterogeneous patients should be developed.

- Methods for assessing energy requirements suitable to use in the clinical setting needs to be developed, tested and validated in COPD patients.

- A study with the aim of preventing normal-weight COPD patients to reduce body weight should be carried out.

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Body Composition by Bioelectrical Impedance Predicts Mortality in Chronic Obstructive Pulmonary Disease Patients

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ABSTRACT

Background: Pulmonary rehabilitation is recommended in international treatment guidelines for chronic obstructive pulmonary disease (COPD). No one has however studied the effect on long-term mortality.

Objective: The aim of the current study was to study the mortality in a sample of patients with severe chronic obstructive pulmonary disease included in a one-year multidisciplinary rehabilitation program.

Design: Body composition was assessed at baseline using bioelectrical impedance. Mortality was studied in 86 patients using the Cox proportional hazards model.

Results: 47 (55 %) of the patients died during the mean follow-up time which was almost six years. Risk of mortality increased with increasing age, increasing number of hospital days the year before inclusion and men had higher mortality risk than women. The mortality risk decreased with increasing % reference body weight, increasing fat-free mass index (FFMI), increasing FEV_1 and increasing 6-min walking distance. Gender, age and FFMI continued to be statistical significant predictors of mortality when controlling for the other baseline variables in a multivariate analysis.

Conclusion: Body composition, measured by bioelectrical impedance and presented as FFMI, is an independent predictor of mortality in COPD patients.

Key words: Mortality, chronic obstructive pulmonary disease, body composition, rehabilitation

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fifth leading cause of death in North America and its prevalence continues to increase, especially in women (9, 12). During the last decade, several studies have investigated factors affecting the mortality risk in COPD patients (3, 10, 13, 14, 16). Common for most of these studies is that a low body weight or a low body mass index (BMI) is found to be a major mortality risk factor. Marquis et al (13) however, in their study on 142 COPD patients, found that body composition, measured as midthigh muscle cross-sectional area obtained by computed tomography (CT) scan, was a better predictor of mortality than BMI. However this finding was not confirmed using body composition assessed by anthropometry. Studies using simpler and less expensive methods than CT to assess predictive effect from body composition were therefore asked for (11).

Thomasset was the first to report a relation between total body water and electrical impedance (22). The use of bioelectrical impedance is based on the principle that fat mass and fat-free mass (FFM) have different conductive and dielectric properties. This is due to the fact that FFM contains water and therefore has a lower resistance than fat mass (5). An electrical current is sent through the human body and the bioelectrical impedance is measured. Relating the impedance to the conductor's (the human body) height gives an assessment of total body water and hence fat mass and FFM can be calculated (17). The aim of the current study was to investigate the mortality in a sample of patients with severe COPD included in a one-year multidisciplinary rehabilitation program in relation to body composition as evaluated by bioelectrical impedance.

METHODS

Patients

The patients in this study were included from two prospective studies of multidisciplinary rehabilitation of COPD patients at the Department of Respiratory Medicine, Sahlgrenska University Hospital, Göteborg, Sweden. The rehabilitation program has been presented previously (6). The first study comprised 50 patients randomized to a rehabilitation group and a control group. Subjects in the control group were given ordinary medical treatment, but no rehabilitation during the control period. All control subjects, however, went through an identical one-year rehabilitation as the cases the year following the control-period. The control subjects were added as cases in the current presentation with defining study start as the day they started the rehabilitation. The second study comprising 36 patients (to be published), compared the effect of the rehabilitation program supplemented by group psychotherapy. In both studies identical inclusion criteria were applied. Patients aged 40-75 with COPD with a forced expiratory volume in one second (FEV_1) < 50 % of predicted and with no demand of oxygen therapy were included. All of the patients were smokers or former smokers with a smoking history of at least ten pack years. Exclusion criteria were other disabling or severe diseases and/or coexistence of other causes of impaired pulmonary function. Patients with a history that indicated asthma were excluded. None of the subjects had an acute exacerbation at the time of inclusion and they were included consecutively. The decision to make the present analysis was however retrospective.

Between March 1992 and June 1998, 86 patients were included in the studies. Patients that survived were followed from date of inclusion to 1 January 2003, and the ones who died from date of inclusion to their date of death. The subjects gave written informed consent to the study and the study was approved by the Ethics Research Committee of Göteborg University.

Study design

Assessment of diet, with the diet history method (19) and measurements of FEV_1, were performed at study start and after 12 months. Anthropometric measurements, bioelectrical impedance assessments, and 6-min walking distance tests were performed every third month. The 6-min walking distance test was performed by the same nurse at each occasion and all patients had one training test before the study started. Individualized dietary advice and follow-up by the dietitian were routinely done at study start and after three, six, nine, and 12 months and additional visits were individualized for each patient when judged needed by the dietitian. The patients trained on a bicycle under the supervision of a physiotherapist. Training also included breathing techniques and arm-training. At study start patients trained twice a week. A home training program was introduced, which by time substituted supervised training. The time for changing from supervised to home-based training was individualized after each patients needs. Further details of the training program is published by Engström et al (6).

Body composition assessment

Height was measured to the nearest 0.5 cm and weight was measured on a Lindelltronic Scale to the nearest 0.1 kg with the subjects in light clothing. In addition to calculating the BMI, the weight of the patients was expressed as a percentage of the weight of a normal Swedish elderly population (1), defined as % reference weight (% IBW). Single-frequency bioelectrical impedance assessment was performed in the morning after 10 min rest in the supine position. Impedance was measured by one single measurement of resistance (in Ohms) and reactance (in Ohms) with a BIA-101 equipment (Akern Florence, Italy). The four electrodes were attached on the dorsal side of the foot and the ankle and on the dorsal side of the hand and the wrist at the right side of the body. FFM was calculated using manufacturer supplied equations, based on comparison with densitometry in a normal population. The fat-free mass index (FFMI) was calculated as FFM in kg divided by body height^2.

Physiological measurements

Routine spirometry was performed with a Vitalograph spirometer (Selefa, Buckingham, Ireland) before and 15 min after inhalation of 1 mg terbutaline to reach optimal standardization. The 6-min walking distance tests were performed following standardized instructions (2).

Nutritional assessment and dietary intervention

A trained dietitian interviewed each patient with a diet history interview that constituted the background for the individual dietary advice given to the patients during the rehabilitation. One of the aims of the dietary advice was to give the patient an adequate intake of energy, in order to give maximal effect of physical training and reducing malnutrition.

Table 1. Patient characteristics at baseline and their prediction of mortality in an univariate analysis (mean (SD)), n = 86

	All patients	Survivors (n=39)	Non-survivors (n=47)	p-value*	Hazard ratio	95 % CI	p value
Age, years	65.9 (6.6)	63.6 (7.0)	67.7 (5.6)	0.0036	1.06	1.01-1.12	0.013
Sex (%F/%M)	49/51	59/41	40/60	0.13	1.64	0.92-2.94	0.096
Smokers (% of group)	29	36	23	0.24	0.85	0.43-1.68	0.65
Hospital days	9 (24)	5 (18)	12 (27)	0.18	1.01	1.00-1.02	0.063
BMI, kg/m^2	22.8 (4.1)	23.5 (3.5)	22.3 (4.4)	0.17	0.95	0.88-1.02	0.17
% IBW	91.4 (16.3)	94.6 (14.1)	88.8 (17.7)	0.10	0.98	0.97-1.00	0.10
FFM, kg	48.6 (9.6)	50.1 (10.7)	47.3 (8.5)	0.18	0.98	0.95-1.01	0.20
FFMI, kg/m^2	16.8 (2.3)	17.3 (2.4)	16.3 (2.2)	0.046	0.88	0.77-1.01	0.061
Body fat, %	25.8 (7.2)	25.9 (6.3)	25.6 (8.0)	0.85	1.00	0.96-1.04	0.87
FEV_1, % pred	35 (11)	39 (11)	31 (10)	0.0013	0.96	0.93-0.99	0.0060
6 MWD, m	329 (82)	354 (71)	307 (85)	0.0087	0.99	0.99-1.00	0.0031

*Survivors compared to non-survivors

M=male; F=female; Hospital days=hospital days the year before inclusion; BMI=body mass index; % IBW=% reference weight; FFM=fat-free mass; FFMI=fat-free mass index; 6 MWD=6-min walking distance; FEV_1=forced expiratory volume in 1 s, as percentage of predicted

The normal weight patients were given dietary advice in order to stabilize the body weight. Overweight and obese patients were given individualized weight reducing advice (reduce energy intake, reduce fat intake, increase intake of fiber). The underweight patients were given advice intended to increase their body weight. They were also offered free availability of nutritional supplements containing energy and micronutrients. Effort was also made to correct imbalances between the energy-providing nutrients; fat, carbohydrates and protein.

Hospital days

The number of hospital days at Sahlgrenska University Hospital during the year before study start was recorded. So was the number of hospital days from study start to time of death or study end (1 January 2003).

Statistical analysis

Descriptive statistics were used to describe the study population at inclusion. Baseline information was used as independent predictors of mortality in a univariate analysis based on the Cox proportional hazards model where survival status at the 1 January 2003 was used as the dependent variable. Baseline variables that were associated with mortality with a $p < 0.15$ were further on included in a multivariate analysis based on the Cox proportional hazards model. To examine differences between survivors and non-survivors, an unpaired t-test was used for continuous variables, and the Fisher's exact test for comparison of proportions. Data were analyzed using the SPSS 11.5 for Windows statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the patients (42 women and 44 men) are presented in table 1. During the rehabilitation year three of the patients died, one patient received oxygen treatment, two patients underwent major surgery and one patient was diagnosed for cancer and they are included in the further analysis. In total there were 47 deaths (55 %) and the causes of death are presented in table 2.

Table 2. Main cause of death, n = 47

Respiratory failure	19
COPD	9
Heart failure	8
Lung cancer	5
Cancer, other than lung	2
Other	4

The causes of death included in "other" were stroke, mediastinitis, pulmonary embolism and drug overdose. Mean follow-up time for the survivors was seven years and two months. For the patients who died, it was four years and three months. The Cox proportional hazards model presented in table 1 and figure 1, shows that the mortality risk increased with increasing age, increasing number of hospital days during the year before inclusion and that men had higher mortality risk than women. The mortality risk

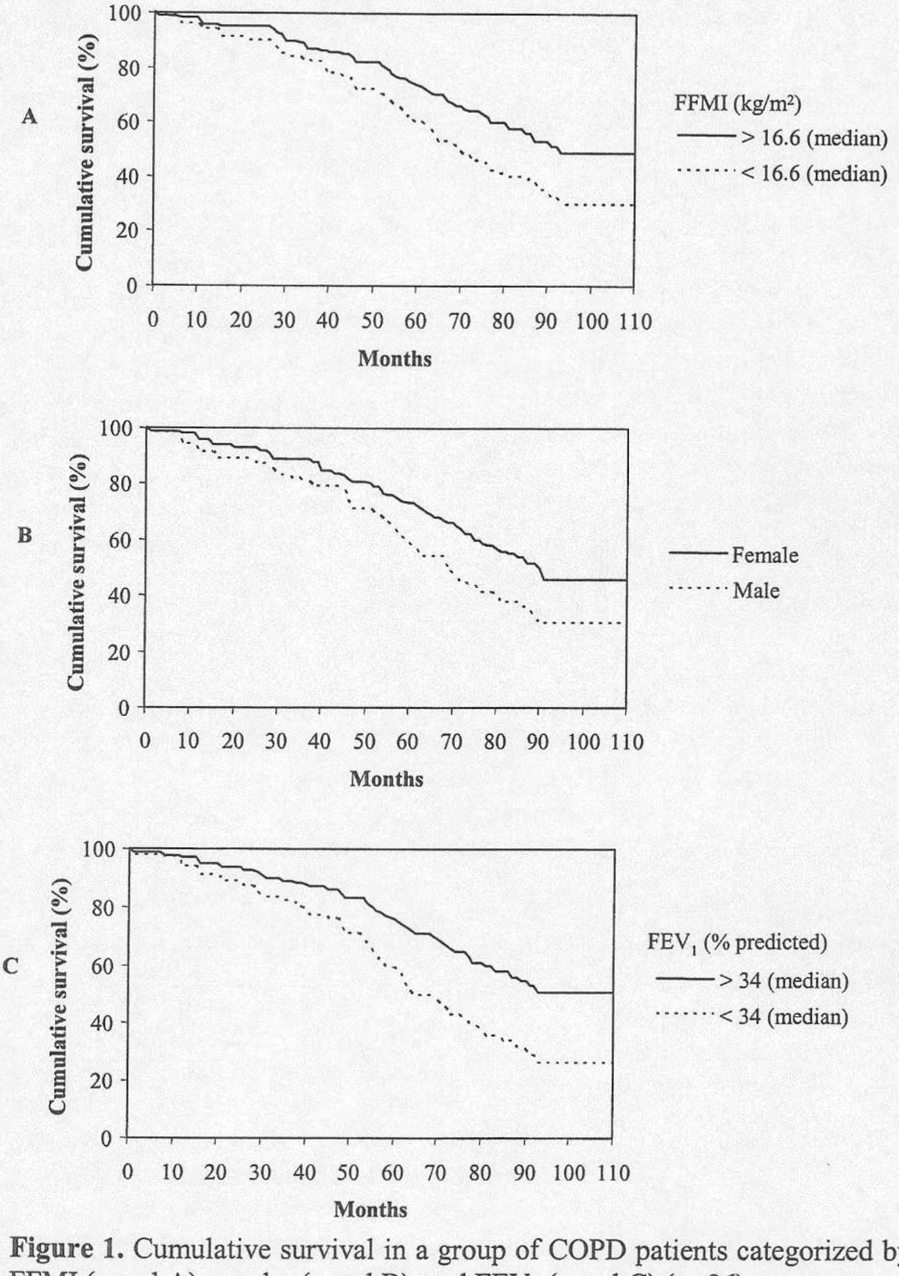

Figure 1. Cumulative survival in a group of COPD patients categorized by FFMI (panel A), gender (panel B), and FEV_1 (panel C) (n=86)

decreased with increasing percentage reference body weight, increasing FFMI, increasing FEV_1 and increasing 6-min walking distance. In addition to gender and age, FFMI continued to be a statistically significant predictor of mortality when controlling for the other baseline variables in the multivariate analysis (table 3).

Changes in some variables from baseline to end of the rehabilitation year are presented in table 4. The results for the total patient group is presented earlier (19) showing slight, but uniform, indications of positive effects of the rehabilitation. A larger proportion of the non-survivors were prescribed nutritional supplements while the survivors had more visits at the physiotherapist.

Table 3. Baseline predictors of mortality: multivariate analyses, n = 86.

	Hazard ratio	95 % CI	p value
Age, years	1.06	1.00-1.12	0.037
Sex (F/M)	3.52	1.27-9.78	0.016
Hospital days	1.01	0.99-1.02	0.30
% IBW	1.05	0.99-1.10	0.11
FFMI, kg/m^2	0.65	0.44-0.96	0.030
FEV_1, % pred	0.98	0.95-1.02	0.28
6 MWD, m	1.00	0.99-1.00	0.54

M=male; F=female; Hospital days=hospital days the year before inclusion; % IBW=% reference weight; FFMI=fat-free mass index; 6 MWD=6-min walking distance; FEV_1=forced expiratory volume in 1 s, as percentage of predicted

DISCUSSION

We have shown that body composition, measured by a non-invasive and relatively simple method, is an independent predictor of mortality in COPD patients. The present study supports the findings of Marquis et al (13) that suggested that body composition would be a significant predictor of mortality in COPD patients.

In this study we used bioelectrical impedance assessment, which is a non-invasive, simple and relatively non-expensive method of body composition assessment. Body composition results were presented as FFMI as recommended by VanItallie et al (23). It is important that techniques for body composition analysis are standardized.

Table 4. Patient characteristics during the rehabilitation year (mean (SD)), n=86

	All patients	Survivors (n=39)	Non-survivors (n=47)	p-value*
Δ BMI, kg/m^2	0.0 (1.2)	+ 0.1 (1.1)	- 0.2 (1.2)	0.25
Δ FFM, kg	- 0.1 (2.3)	0.0 (2.4)	- 0.2 (2.4)	0.69
Δ FFMI, kg/m^2	0.0 (0.8)	0.0 (0.8)	- 0.1 (0.8)	0.61
Δ FEV_1, % pred	+ 3 (8)	+ 3 (8)	+ 3 (8)	0.77
Δ 6 MWD, m	+ 17 (58)	+ 27 (56)	+ 6 (59)	0.12
Cortisone, n	1.9 (2.2)	1.4 (1.5)	2.4 (2.6)	0.069
Dietitian, n	8.5 (5.0)	7.6 (4.7)	9.3 (5.1)	0.10
Nutr suppl (%)	51	36	64	0.017
Physiotherapist, n	25.8 (14.2)	29.2 (13.0)	23.0 (14.7)	0.042

*Survivors compared to non-survivors

BMI=body mass index; FFM=fat-free mass; FFMI=fat-free mass index; FEV_1=forced expiratory volume in 1 s, as percentage of predicted; 6 MWD=6-min walking distance; Cortison=number of cortisone treatments during the year; Dietitian=number of visits at the dietitian during the year; Nutr suppl=proportion of group prescribed nutritional supplements; Physiotherapist=number of visits at the physiotherapist during the year

We have previously shown that measurements of bioelectrical impedance used for body composition assessment need to be highly standardized (18, 20). In the current study, the subjects were measured in the morning after 10 min rest in the supine position.

However, we could not confirm previous findings that BMI or body weight are predictors of mortality (10, 13, 16). This is in consistency with the findings of Marquis et al (13), who found a body composition measure to be a better predictor of mortality than BMI. The lack of this relation in the present study could be due to a limited group size. Except body composition, old age and male gender also were found to be independent predictors of mortality in this study. Age is a natural risk factor for death. The effect of gender is complicated. In the current study, men did not differ from women in disease severity (FEV_1). Even if the men were older than the women ($p < 0.05$), the effect of gender on mortality is shown independently of age. There are indications from epidemiological studies, that women are more susceptible than men to develop COPD (15), but the risk of developing COPD might not be identical with the severity of the disease when it has been established. The results of the present study, however, is in line with other studies investigating the prognosis in groups of patients with established COPD, in which poor prognosis in male patients was shown (4, 7, 12, 21).

The mortality rate in this study is well in line with results from comparable studies of similar patient groups performed the last decade. In this study, 55 % of the patients died during the mean follow up time of 5.6 years, which gives an annual death rate of 9 %. In the study of Marquis et al (13) 18 % of the patients died during the 3.4 years of follow-up, resulting in an annual death rate of 5 %. The patients in that study had however somewhat less severe disease (mean FEV_1 was 42 % predicted compared with 35 % predicted in the current study). In a Canadian study (8) 47 % of the patients died during the follow-up of almost 3 year , giving an annual death rate of 16 %. In that study, mean FEV_1 was 27 % predicted, and they also included patients receiving oxygen treatment, indicating a lower pulmonary function and hence a higher mortality rate would be expected. Thus approximately 50 % of patients with severe COPD included in rehabilitation programs can be expected to die within five years. Thus the prognosis in advanced COPD is worse than for most forms of malignant diseases (24).

In this study we have shown that body composition, measured by bioelectrical impedance and presented as FFMI, is an independent predictor of mortality in COPD patients.

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Bioelectrical impedance: effect of 3 identical meals on diurnal variation and calculation of body composition.
Slinde F and Rossander-Hulthén L.
Am J Clin Nutr 2001;74:474-478

II

Bioelectrical impedance: effect of 3 identical meals on diurnal impedance variation and calculation of body composition[1,2]

Frode Slinde and Lena Rossander-Hulthén

Bioelectrical impedance: effect of 3 identical meals on diurnal impedance variation and calculation of body composition[1,2]

Frode Slinde and Lena Rossander-Hulthén

ABSTRACT

Background: Bioelectrical impedance analysis (BIA) can be used for estimating body composition. Earlier studies showed that the ingestion of meals lowers bioelectrical impedance, but none studied the effect of repeated ingestion of an identical meal in narrow intervals on impedance measurements during 24 h.

Objectives: The objectives were to study the effect on bioelectrical impedance of 3 identical meals and to compare the results from single-frequency BIA measurements with those from multiple-frequency BIA measurements.

Design: Bioelectrical impedance was measured 18 times during 24 h in 18 healthy subjects [10 women and 8 men; $\bar{x} \pm$ SD age: 31.5 ± 11.7 y; body mass index (in kg/m^2): 22.2 ± 2.7]. An identical meal was given at breakfast, lunch, and dinner.

Results: Bioelectrical impedance decreased after ingestion of a standard meal ($P < 0.05$). The decrease in impedance lasted 2–4 h after each meal. The decrease was additive during the day, although it was more pronounced after the first meal because of the combined effect of rising from the supine position and meal ingestion. This is an important consideration when calculating body composition: percentage of body fat varied by 8.8% from the highest to the lowest measurement in women and by 9.9% from the highest to the lowest measurement in men. The bioelectrical impedance at 50 kHz was identical when measured with multiple frequencies or a single frequency.

Conclusion: The ingestion of meals leads to an additive decrease in bioelectrical impedance and thus to a decrease in the calculated percentage of body fat. *Am J Clin Nutr* 2001;74:474–8.

KEY WORDS Multiple-frequency bioelectrical impedance analysis, single-frequency bioelectrical impedance analysis, diurnal variation, body composition, meal ingestion

INTRODUCTION

The term bioelectrical impedance (BI) was introduced ≈50 y ago. Thomasset (1) was the first to report a relation between total body water and electrical impedance. The use of BI to estimate body composition is based on the different conductive and dielectric properties of various biological tissues at various frequencies of current.

Single-frequency bioelectrical impedance analysis (sfBIA) uses a frequency of 50 kHz to measure impedance and calculate body composition. Multiple-frequency BIA (mfBIA) instruments were developed because the frequency necessary to detect the distribution between extracellular water (ECW) and intracellular water (ICW) is probably >50 kHz (2). During the past 10 y, numerous validation studies have been published concerning estimation of body composition with use of mfBIA (2–7). van Marken Lichtenbelt et al (3) showed that results from mfBIA and sfBIA were comparable in their study of 29 adults and that mfBIA appears to provide acceptable values for total body water and extracellular water compared with deuterium and bromide dilution.

BIA is an easily applied method of determining body composition. It is necessary, however, to measure BI under standardized conditions, and the method is sensitive to several physiologic factors. For example, body temperature is important when measuring BI (8–10). Additionally, for female subjects the variation in body fluids during the menstrual cycle affects BI (11). These physiologic factors are important to consider when comparing results between different studies in which BIA was used for body composition assessment or when the aim is to do repeated measurements over time, eg, in patient follow-up.

Several studies showed that the ingestion of a meal decreases BI (11–14). It is, however, natural to consume another meal within 4 h. The effect of several meals on BI, with frequent multiple measurements of impedance, has not been previously studied. A well-known limitation on the accuracy of BI for calculating body composition is the selection of appropriate prediction equations. However, a meal effect will influence calculated body composition regardless of the choice of equation. The purpose of this study was therefore to study the effect on BI of 3 identical meals and to compare the results from sfBIA with those from mfBIA.

SUBJECTS AND METHODS

Eighteen apparently healthy male and female university students and co-workers volunteered to participate in this study. Informed consent was given. The study was performed in accord with the Helsinki Declaration of 1975 as revised in 1983. The women were

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TABLE 1
The nutritional composition of the test meal[1]

Nutritional component	Content per meal
Energy (kJ)	2731 ± 324 (2338–3394)
Fat (% of energy)	34 ± 1 (33–35)
Protein (% of energy)	17 ± 0 (16–17)
Carbohydrate (% of energy)	49 ± 1 (47–51)
Calcium (mg)	155 ± 15 (134–184)
Iron (mg)	4.4 ± 0.5 (4.0–5.3)
Magnesium (mg)	117 ± 13 (99–143)
Sodium (mg)	771 ± 88 (677–955)
Potassium (mg)	1414 ± 170 (1190–1750)
Zinc (mg)	6.1 ± 0.7 (5.5–7.6)
Total fluid (mL)	618 ± 0

[1] $\bar{x}$ ± SD; range in parentheses. $n = 18$.

between day 9 and day 16 of their menstrual cycles. At the 0700 study start the subjects were in a fasting state and were dressed in light clothing. They rested or slept in the supine position for 1 h before the first BI measurement was done. The subjects then remained in a supine position, and impedance measurements were performed every 15 min for an additional 1 h. All the BI measurements were performed with both single- and multiple-frequency instruments at 18 time points during the 24 h studied.

The subjects rose from the supine position and were served a meal at 0915. The meal consisted of a cheeseburger with tomato, orange juice, coffee or tea, and a banana. The energy content in the meal was 27% of the individual predicted total daily energy requirement, and the amount of fluid given was 618 mL for all the subjects. Impedance was measured 30 min after the first meal was completed. The subjects then started their working day at the university. Subjects were served an identical meal at 1230 and at 1730.

Impedance measurements

A BIA-101 (Akern, Florence, Italy) was used for measuring sfBIA. For measuring mfBIA, the UniQuest-SEAC SFB-3 instrument (UniQuest Limited, Brisbane, Australia) was used. Both instruments were used according to the manufacturers' instructions. The electrodes were positioned at the middle of the dorsal surfaces of the hands and feet, respectively, proximally to the metacarpal-phalangeal and metatarsal-phalangeal joints and medially between the distal prominence of the radius and the ulna and between the medial and lateral malleoli at the ankle. Each additional BI measurement was taken after the subject had been in a supine position for 10 min. Manufacturer-supplied equations were used for calculating body composition from sfBIA. For calculating body composition from mfBIA, we used the manufacturer-supplied equation of Hannan et al (15).

Anthropometric measurements

Height was measured to the nearest 0.5 cm before the study started, and weight was measured to the nearest 0.1 kg within 5 min after every impedance measurement.

Statistical methods

All values are presented as means and SDs. Dunnett's t test was used to compare the impedance, ECW, and ICW between baseline and each consecutive measurement. Statistical calculations were performed by using the SPSS for WINDOWS (version 10.0; SPSS Inc, Chicago) software program.

RESULTS

Ten women and 8 men participated in this study. The subjects' mean age was 31.5 ± 11.7 y; their mean weight and height were 68.3 ± 7.7 kg and 1.76 ± 0.1 m, respectively; and their mean body mass index (in kg/m^2) was 22.2 ± 2.7. The nutritional composition of the test meal is presented in **Table 1**.

Impedance

The impedance at 50 kHz measured with mfBIA was identical to that measured with sfBIA. Women had a higher baseline impedance than did men (women, 602 ± 51 Ω; men, 513 ± 40 Ω). The diurnal variation in BI is shown in **Figure 1**. The postprandial decrease in BI lasted 2–4 h after the meals, with an apparent additive effect during the day. The decrease in impedance after the first meal was double the decrease after meals 2 and 3. Impedance returned to baseline values after one night of fasting. For single-frequency impedance, all measurements, except measurements 2, 3, 6, and 18, were significantly different from baseline ($P < 0.05$). The subject with the largest decrease in BI had a decrease of 11%, from 629 Ω at baseline to 557 Ω at measurement no. 17.

Body composition

Measuring BI in the fasting state after 1 h of resting or sleeping (BIA measurement no. 1) gave a calculated body fat percentage from sfBIA of 26.5 ± 6.3% for the women and 16.2 ± 2.8% for the men. With subjects remaining in a supine position, the calculated fat percentage increased to 27.1 ± 6.6% for the women and 17.2 ± 3.1% for the men (BIA measurement no. 5). The lowest calculated percentage of body fat was observed at BIA measurement no. 17 (195 min after dinner) for the women and at BIA measurement no. 11 (125 min after lunch) for the men. The lowest calculated mean body fat percentage was 24.8 ± 5.6% for the women and 15.5 ± 3.3% for the men. The difference between the highest and lowest calculated body fat percentage was 8.5% for the women and 9.9% for the men (2.3 and 1.7 percentage points, respectively). The subject with the largest decrease in percentage of body fat had a decrease of 13%, from 29.7% body fat at baseline to 25.9% body fat at measurement no. 17.

After the subjects rested or slept for 1 h (BIA measurement no. 1), the calculated body fat percentage calculated from mfBIA was 23.6 ± 6.8% for the women and 16.1 ± 3.8% for the men. With subjects remaining in a supine position, the fat percentage increased to 24.0 ± 7.0% for the women and 17.5 ± 4.1% for the men (BIA measurement no. 5). The lowest calculated body fat percentage was observed at BIA measurement no. 17 (195 min after dinner) for the women and at BIA measurement no. 11 (125 min after lunch) for the men. The lowest calculated mean body fat percentage was 21.7 ± 7.0% for the women and 14.9 ± 4.6% for the men. The difference between the highest and lowest calculated body fat percentage was 9.7% for the women and 7.5% for the men (2.3 and 1.2 percentage points, respectively). The subject with the largest decrease in percentage of body fat had a decrease of 23%, from 17.9% body fat at baseline to 13.7% body fat at measurement no. 17. After another night of fasting the calculated body fat percentages returned to baseline values.

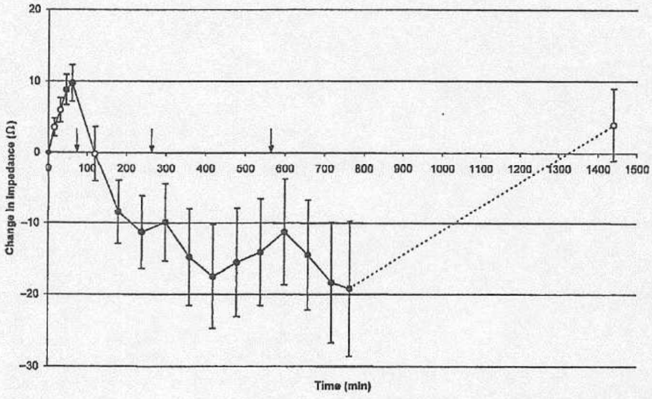

FIGURE 1. Mean changes (and 95% CI) from a baseline value of 563 Ω in single-frequency impedance during 24 h ($n = 18$). Arrows indicate time of meals. ●, significantly different from baseline ($P < 0.05$); ○, NS from baseline.

ECW and ICW calculated from mfBIA are shown in **Figures 2** and **3**.

DISCUSSION

Ingestion of a meal consistently led to a decrease in measured impedance in this study. Impedance decreased consistently for 2 h after the first meal and for 4 h after the second and third meals and then began to increase. The decrease in impedance after the first meal was double the decrease after meals 2 and 3. This was probably due to a combined effect of rising from a lying position and ingesting food and beverages after the first meal. A decrease in impedance produced by ingestion of one meal was also shown by others (11–14). Deurenberg et al (11) reported that BI decreased by 13–17 Ω 2–4 h after intake of a liquid meal of 1941 kJ in 12 adult men. They also showed that BI decreased significantly by 4 ± 4 Ω after intake of beef tea but did not significantly decrease (21 ± 6 Ω) after intake of normal tea, suggesting that the observed effect was due to the intake of electrolytes. Gallagher et al (12) studied 11 males and 18 females and reported that intake of a solid meal (2301 kJ) led to a significant decrease in BI up to 4 h after the meal followed by an increase up to 5 h after the meal regardless of fat content. The authors of both studies concluded that the decrease in BI was probably related to changes in the fluid and electrolyte distribution that follow absorption and digestion of a meal. Rodriguez

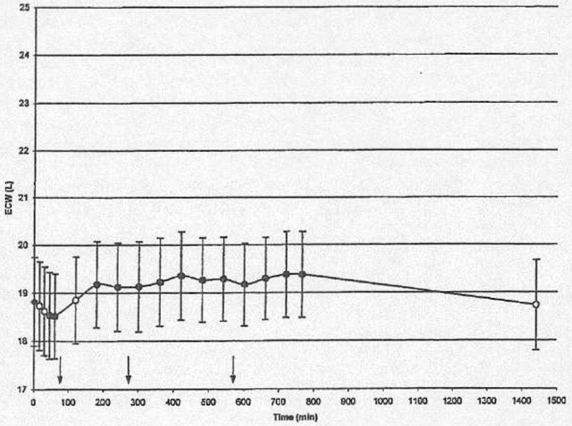

FIGURE 2. Mean extracellular water (ECW) (and 95% CI) calculated from multiple-frequency impedance measurements during 24 h ($n = 18$). Arrows indicate time of meals. ●, significantly different from baseline ($P < 0.05$); ○, NS from baseline.

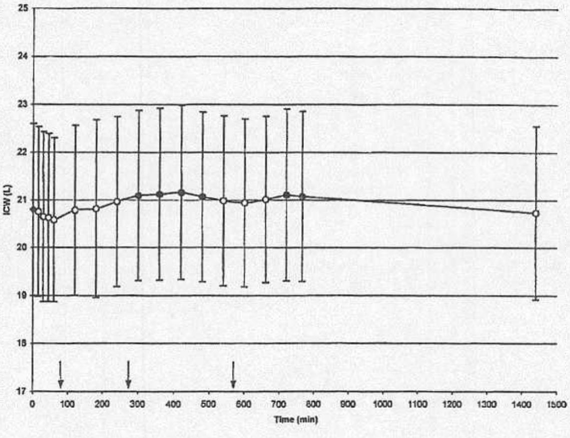

FIGURE 3. Mean intracellular water (ICW) (and 95% CI) calculated from multiple-frequency impedance measurements during 24 h ($n = 18$). Arrows indicate time of meals. ●, significantly different from baseline ($P < 0.05$); ○, NS from baseline.

et al (14) also found a decrease in impedance after food intake in children.

In a study of 12 males, Fogelholm et al (13) showed that resistance decreased significantly (4–6 Ω) 2–4 h after a meal with a high concentration of electrolytes. Resistance also decreased after a meal low in electrolytes (2–3 Ω); however, this decrease was not statistically significant. Resistance tended to return to baseline values after 7 h, which was confirmed by Gallagher et al (12). The meals used in the present study had the same electrolyte concentrations as those in the high-electrolyte meal used by Fogelholm et al (13), except for a lower sodium concentration in the present study.

Because food and beverage intake was identical for the 3 meals in this study, we conclude that the postprandial decrease in impedance was additive, such that the introduction of another meal led to a further decrease in impedance. Thus, we would expect that a subject's BI measured in the evening after normal meal consumption throughout the day would be lower than that subject's BI measured in a fasting state. Time of BI measurement, especially with respect to meals, must be considered in study design and interstudy comparisons.

Rodriguez et al (14) suggest that the decrease in impedance may be consistent with a redistribution of extracellular fluids. The results from the mfBIA (Figures 2 and 3) show that ECW increased immediately after a meal as a result of fluid intake but that ICW was relatively stable during the whole study period. The most marked decrease in impedance was noted after the first meal. This decrease may have been a combined effect of electrolyte intake and redistribution of extracellular fluids, an effect of changing from a supine body position to an ambulatory one. The decrease found after the 2 later meals must have been a result of the meals, because there was no change in body position (ie, all subjects were ambulatory). Because impedance increased 3–4 h after all 3 meals, we conclude that the decrease in postprandial impedance was a direct effect of the ingestion of a meal and was not due to redistribution of the body fluids caused by change in body position.

The BI in the female subjects was higher than that in the male subjects. This difference represents the women's increased resistance due to a lower amount of body water. This result was also found by others (4, 5, 11). The additive, postprandial decrease in impedance was consistent in both sexes.

The difference in calculated body fat percentages between multiple- and single-frequency BI in the female group was due to the different equations used for calculating body composition. There were no obvious differences between the 2 methods in the male group, possibly because men have less body fat than do women and there is therefore a lower possibility of detecting differences. Thus, the choice of equation can influence the results in studies using BIA.

This study showed that measurements of BI must be done in the fasting state. Ingestion of a meal leads to a decrease in BI, and after several meals there is an additive decrease. Thus, the percentage of body fat calculated with use of prediction equations is also decreased.

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Bioelectrical impedance variation in healthy Subjects during 12 h in the supine position.

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ORIGINAL ARTICLE

Bioelectrical impedance variation in healthy subjects during 12 h in the supine position

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Abstract—Background and aim: Bioelectrical impedance analysis is used to assess human body composition. Studies have shown that meal ingestion and change of body posture affects bioelectrical impedance, but none has studied bioelectrical impedance variation in supine subjects. The aim was to examine the bioelectrical impedance variation in healthy subjects during 12 h in the supine position.

Methods: Bioelectrical impedance was measured 16 times during 12 h in 18 healthy subjects. An identical meal was given at breakfast, lunch, and dinner.

Results: Mean (standard deviation) impedance at 50 kHz increased from 558 (87) Ω at study start to 584 (95) Ω at study end ($P < 0.05$). Bioelectrical impedance is reduced after ingestion of the first meal, but not following the meals at 1230 and 1730. Calculated body fat content increased from a baseline mean (SD) of 21.7 (6.1) % body fat to 23.9 (6.7) % body fat at study end ($P < 0.05$).

Conclusions: Bioelectrical impedance increased during 12 h in supine subjects. The increase is probably explained by a shift in body fluids from the extremities to thorax during the day and the importance of strict measurement standardisation both in epidemiological studies and clinical practice is underlined. © 2003 Elsevier Science Ltd. All rights reserved.

Key words: bioelectrical impedance; body composition; body fat; total body water; extracellular water; intracellular water

Introduction

Bioelectrical impedance assessment (BIA) is one of many methods currently used to assess human body composition. BIA is based on the principle that fat mass (FM) and fat-free mass (FFM) have different conductive and dielectric properties due to the fact that the FFM contains water and therefore has lower resistance than FM (1). An electrical current is sent through the human body and the bioelectrical impedance (BI) is measured. Relating the BI to the conductors (the human body) height gives an assessment of total body water (TBW), and hence FM and FFM, can be calculated (2). Single-frequency bioelectrical impedance analysis (sfBIA) uses a frequency of 50 kHz. Only extracellular impedance is measured at this frequency, since such low current does not penetrate the cell membrane (3). Multiple-frequency BIA (mfBIA) measures the impedance at a current usually between 4 and 1024 kHz. In the higher levels of current all body tissues are being penetrated. Measuring impedance at both low and high levels of current makes it possible to separate extracellular and intracellular impedance (4, 5) and hence calculate extracellular and intracellular water (ECW and ICW).

Several factors have been shown to affect BI such as exercise (1), menstrual cycle (6), changes in body fluid balance (7), fasting (8), body posture (9, 10), and intake of food (1, 11, 12). The study by Slinde and Rossander-Hulthén (12) showed that BI decreased after ingestion of a standardised meal and this decrease was additive during the day. In this study, however, the subjects were ambulatory, i.e. they changed their body posture several times during the study day. The objective of the current study was to examine the bioelectrical impedance variation in healthy subjects during 12 h in the supine position.

Subjects and methods

Ten male and eight female university students and co-workers volunteered to participate in this study. Informed consent was given. The study was performed in accord with the Helsinki-Declaration of 1975 as revised in 1983. The subjects' mean (SD) age was 25.9 (4.8) years; their mean (SD) weight and height were 68.9 (10.2) kg and 1.73 (0.1) m, respectively; and their mean (SD) body mass index was 23.0 (2.8) kg/m^2. Mean (SD) body weight at study end was 68.8 (10.3) kg. The women were between day 9 and day 19 of their menstrual cycles.

All subjects slept at home the night before the study day. Mean time of sleep was 7 h with a range from 5 to 9 h. No alcohol or strenuous exercise was allowed the night before study and the subjects were fasting from 2200. The subjects were requested to come to the hospital by car or bus. The duration from the subjects got up from their own bed to they lied down (study start) varied from 45 min to 1 h 45 min, with a mean time of 1 h and 15 min.

They removed all jewellery's, height and weight was measured, and they were requested to go to the toilet. From 0745 the subjects were in a supine position to the study end at 2000 except from toilet visits and weighing. The bed should be horizontal with a maximum of 45° angle at ingestion of meals. Toilet visits were performed at predetermined times, every hour directly after each impedance measurement, starting at 0900. Toilet visits were compulsory for all subjects independent of needs. The first meal was ingested at 0915. The meal consisted of a cheeseburger with tomato, orange juice, coffee or tea, and a banana. The energy content in the meal was 27% of the individual predicted total daily energy requirement, and total fluid ingestion was set to be 618 ml which was identical for all subjects. Subjects were served an identical meal at 1230 and 1730 and they were not allowed to eat or drink anything in addition to the served meals. For nutrient calculation we used the nutrient software program 'Dietist' using the 'Swedish Food Data Base (1992)' from the National Food administration (13). The calculated nutritional composition of the test meal is presented in Table 1.

Impedance measurements

Four electrodes (Conmed® Corporation, NY, USA) were attached to each subject. The electrodes were positioned at the middle of the dorsal surfaces of hands and feet, respectively, proximally to the metacarpal-phalangeal and metatarsal-phalangeal joints and medially between the medial and lateral malleoli at the ankle. The same electrodes were attached to the subjects during the whole study. Single-frequency BI was measured with a BIA-101 (Akern, Florence, Italy) using a current of 50 kHz. For measuring mfBI, the UniQuest-SEAC SFB-3 instrument (UniQuest Limited, Brisbane, Australia) was used. This instrument analyse the impedance at multiple currents between 4 and 1024 kHz. Both instruments were used at all measurements. During the first hour, a BI measurement was performed every 15 min and thereafter every hour.

Manufacturer-supplied equations were used for calculating body composition from the single-frequency BIA. For calculating body composition from multiple-frequency BIA, we used the manufacturer-supplied equations of Hannan et al. (3). Total body water (TBW), intracellular water (ICW), and extracellular water (ECW) were also calculated using the results from the multiple-frequency BIA and equations of Hannan et al. (3).

Anthropometric measurements

Height was measured to the nearest 0.5 cm before the study started, and weight was measured to the nearest 0.1 kg within 5 min after every impedance measurement.

Statistical methods

All values are presented as means and SDs. Dunnett's *t*-test was used to compare the impedance, ECW, and ICW between baseline and each consecutive measurement. Statistical calculations were performed by using the SPSS for WINDOWS (version 10.0; SPSS Inc, Chicago) software program.

Results

Impedance

Bioelectrical impedance measured at 50 kHz was identically measured with the two instruments and increased during the day ($P<0.05$). Mean (SD) impedance at 50 kHz increased from 558 (87) Ω at study start to 584 (95) Ω at study end ($P<0.05$). Figure 1 shows the variation in BI during the day.

Men and women followed the same pattern of impedance variation, although the women had higher levels of BI. BI is reduced after ingestion of the first meal

Table 1 The nutritional composition of the test meal

Nutritional component	Content per meal ($n=18$)		
	Mean	SD	Range
Energy (kJ)	2354	337	1835–2913
Fat (% of total energy)	34	0	
Protein (% of total energy)	18	0	
Carbohydrate (% of total energy)	48	0	
Calcium (mg)	140	17	117–169
Iron (mg)	3.7	0.6	3.0–5.0
Magnesium (mg)	98	13	78–120
Sodium (mg)	839	119	659–1038
Potassium (mg)	1211	173	947–1497
Zinc (mg)	5.4	0.8	4.2–6.7
Total fluid (ml)	618	0	

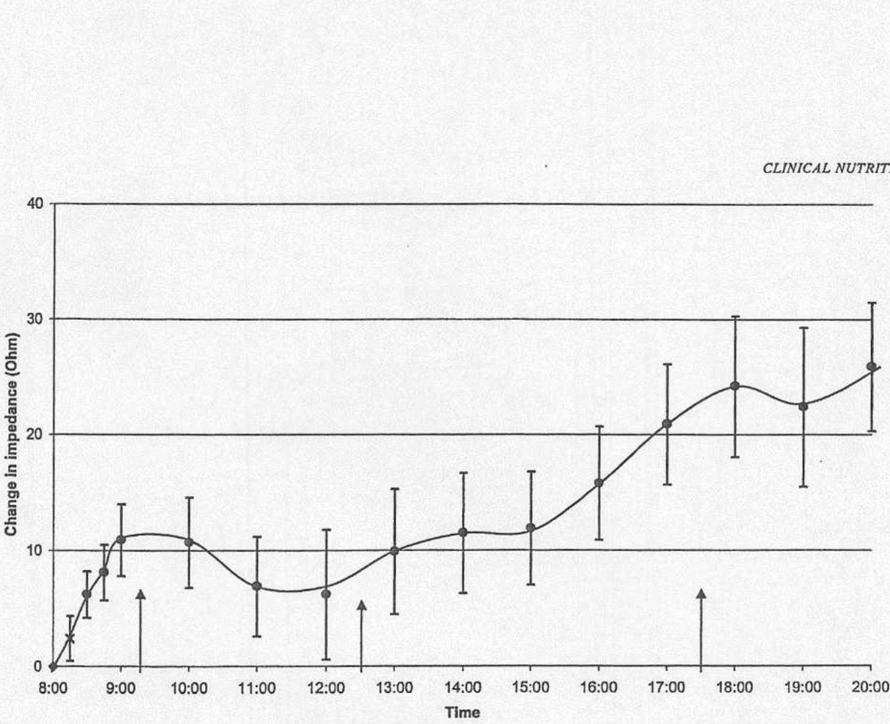

Fig. 1 Mean changes (and 95% CI) from a baseline value of 558 Ω in single-frequency impedance during 12 h ($n = 18$). Arrows indicate time of meals. ●, significantly different from baseline ($P < 0.05$); ×, NS from baseline.

($P < 0.05$), but not following the meals at 1230 and 1730. The subject with the largest increase in impedance had an increase of 9.6%, from 669 Ω at study start to 733 Ω at study end.

Calculated body fat

Calculated body fat content from the sfBI increased by 10.1% from a baseline mean (SD) of 21.7 (6.1)% body fat to 23.9 (6.7)% body fat at study end ($P < 0.05$). There was no difference between men and women (9.8% and 9.9% increase, respectively). Results from the mfBI followed the same pattern. The subject with the largest increase in calculated body fat had an increase of 19.9%, from 32.1% body fat at study start to 38.5% body fat at study end and there was no relation between baseline body fat % and size of change in calculated body fat%.

Calculated body fluids

TBW, calculated from the equation of Hannan et al. (3), decreased during the day, and TBW was statistical significantly lower ($P < 0.05$) at 18.00, 19.00 and 20.00 (Fig. 2) compared with study start. Calculated TBW was 2.5% (1.0 l) lower at study end than at study start ($P < 0.05$). ECW did also decrease during the study, statistically significantly ($P < 0.05$) so already after 45 min (Fig. 3). Calculated ECW was reduced by 4.5% (0.9 l) during the study. Intracellular water, however, was stable during the whole study (data not shown).

Discussion

Bioelectrical impedance, and hence, calculated body fat percentage, increased gradually during 12 h in the supine subjects studied. Calculated body fat percentage increased by 10% during the day ($P < 0.05$). This change is larger than the reduction of 8% in body fat percentage, measured by underwater weighing, found by Kriketos et al. in their 10 week weight loss intervention study in moderately obese subjects (14).

Ingestion of the first meal led to a decrease in BI ($P < 0.05$), which is consistent with what we found in a study of ambulatory subjects (12). In that study, however, BI gradually *decreased* during the first 12 h. The only difference between these two studies is the posture of the subjects. In the current study, we have simulated a patient situation, with the subjects being in a supine position all day. Meal nos. 2 and 3 did not reduce bioelectrical impedance in the current study.

Bioelectrical impedance is determined by the amount of body water. The TBW in the studied subjects appears to have decreased during the day, since we found an increasing BI. This is also revealed in the derived calculations of TBW. Ideally, another method also should have been used to determine TBW in this study. However, there is no reason to believe that a reduction in TBW with a mean of 1.0 l should appear in this study, as we provided the subjects with 1.8 l of fluids during the day and there was no change in body weight from baseline to study end. Other explanations to the increase in BI therefore have to be sought.

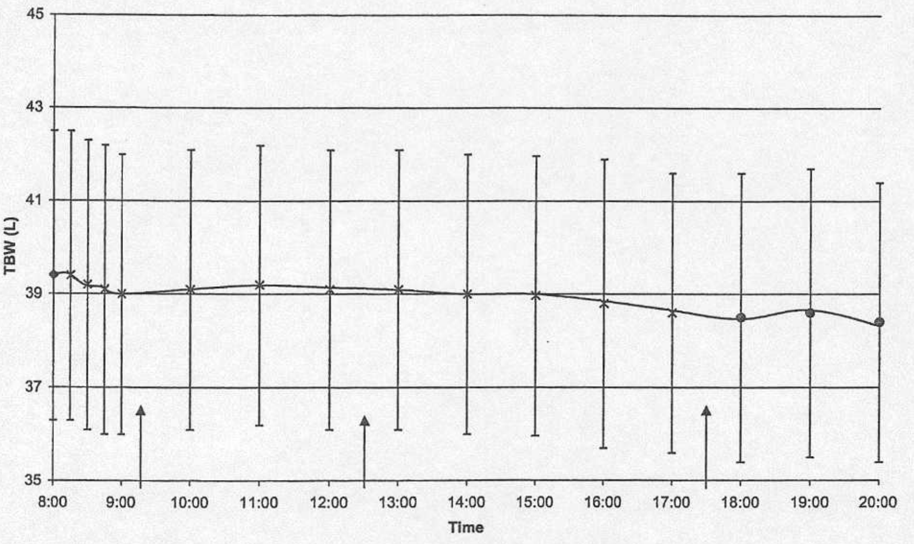

Fig. 2 Mean TBW (and 95% CI) calculated from multiple-frequency impedance measurement during 12 h (n = 18). Arrows indicate time of meals. ●, significantly different from baseline ($P<0.05$); ×, NS from baseline.

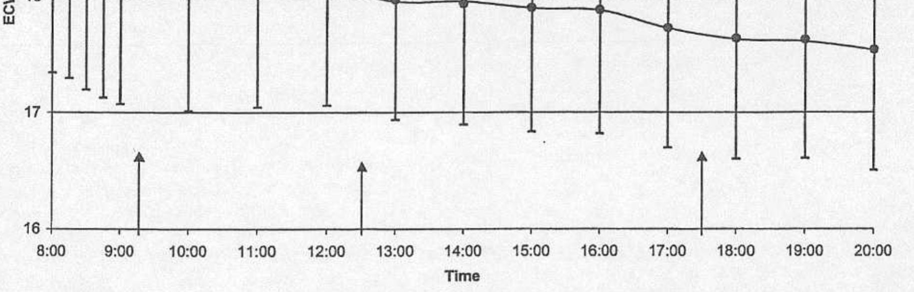

Fig. 3 Mean ECW (and 95% CI) calculated from multiple-frequency impedance measurement during 12 h (n = 18). Arrows indicate time of meals. ●, significantly different from baseline ($P<0.05$); ×, NS from baseline.

Each segments of the human body have their own electrical characteristics determined by their geometrical diameter. A cylinder with a small diameter, i.e. the arm or the leg, will have a higher resistance than a cylinder that has a larger diameter, i.e. thorax or abdomen. Measured BI is thus more affected by the fluid content in the extremities than in the thorax. Studies have shown that as people lie down, body fluids shift from legs and arms to the thorax and abdomen (9, 15). Less fluid in the legs and arms leads to an increasing BI, independent of changes in TBW, due to the determining properties of the extremities. Combined with the fact that the subjects body weights were stable during the day, we suggest that the body fluids shift is the probable explanation to the observed increased bioelectrical impedance in this study. In subjects not being in the supine position, i.e. during a normal working day, we found a statistically significant increase in body weight of 0.5 kg during 12 h ($P < 0.05$), probably due to fluid accumulation during the day (12).

Whatever explanation to the observed increase in BI, the importance of strict measurement standardisation both in epidemiological studies and clinical practice is underlined. Bioelectrical impedance is an easy and validated method of assessing body composition. However, our findings in this study underline the importance of standardisation procedures.

This study strengthens the guidelines proposed by Ellis et al. (16) suggesting that BIA measurement should be performed in the fasting state after 10 min in the supine position, and the current study shows the effects of non-standardised measurements on calculated body composition.

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ORIGINAL ARTICLE

Total energy expenditure in underweight patients with severe chronic obstructive pulmonary disease living at home

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Abstract—Aim: The aim of the study was to assess total daily energy expenditure (TDE), as measured by doubly labelled water (DLW), and describe its components in home-living underweight patients with severe chronic obstructive pulmonary disease (COPD).

Methods: Basal metabolic rate (BMR) was measured prior to the study. Ten patients received DLW, followed by urine analysis by isotope ratio mass spectrometry from 10 standardised occasions during 15 days. Dietary intake was registered by each patient the first 7 days of the study. The patients were also interviewed about their physical activity pattern.

Results: Measured BMR was higher than predicted in five of the 10 patients using equations from WHO. Using disease-specific equations, estimated BMR was higher for male, but not for female COPD patients. The best estimation of BMR resulted from prediction including fat-free mass. TDE varied considerably between 5200 and 11,100 kJ. Physical activity level (PAL) ranged from 1.15 to 1.80. Energy intake varied between 4500 and 9100 kJ. In underweight patients with severe COPD, TDE is highly variable, ranging from 110 to 200 kJ/kg body weight.

Conclusions: This is the first study assessing and describing total energy expenditure in underweight patients with severe COPD living at home. Energy requirement in the patient group cannot solely be calculated from prediction equations. BMR should be measured and physical activity level assessed. © 2003 Elsevier Science Ltd. All rights reserved.

Key words: chronic obstructive pulmonary disease; energy metabolism; doubly labelled water; energy intake; basal metabolic rate.

Introduction

Malnutrition and weight loss are often found in patients with chronic obstructive pulmonary disease (COPD) (1, 2). Malnutrition is associated with loss of muscle mass and impaired muscle function (3), and malnutrition together with a low body weight in COPD is a strong predictor for increased mortality (4). Several factors have been suggested to contribute to the development of malnutrition and weight loss: increased basal metabolic rate (BMR) (5), reduced energy intake from food (5), and/or increased energy cost of physical activity (6). Increased energy expenditure for physical activity have been reported in COPD patients (7, 8) together with increased diet-induced thermogenesis (DIT) compared to healthy controls (8). Total daily energy (TDE) can be measured using doubly labelled water (DLW) and this method is considered to be the golden standard method for TDE assessments. In COPD patients, TDE assessed by DLW has only been reported by one study group, and only in patients performing daily exercises at a hospital pulmonary rehabilitation unit (7).

Since most patients with COPD are living at home, the aim of the present study was to assess the TDE as measured by DLW, and describe its components in home-living underweight patients with severe COPD.

Subjects and methods

Subjects

Ten patients (five men and five women) with severe and stable COPD, diagnosed as forced expiratory volume in 1 s (FEV_1) <50 % predicted, as determined by criteria from The European Respiratory Society (9) were included in this study. All patients were recruited consecutively from the outpatient COPD unit at the Department of Respiratory Medicine, Sahlgrenska University Hospital, Göteborg, Sweden. Of the 15 patients asked to attend, five declined to take part in the study. Exclusion criteria were body mass index (BMI) $>20\,kg/m^2$, active smoking, having external help at home, oxygen treatment, cancer, diabetes mellitus, hypothyroidism or other major diseases. All patients lived at home and none of the patients were involved in any rehabilitation activities during the study period. The patients were informed of the nature and purpose of the study and gave informed consent. Procedures followed were in accord with the Helsinki declaration from 1977 as revised in 1983. The study was approved by the Ethics Committee of Göteborg University.

Study design

The investigation took place over two consecutive weeks for each patient. Prior to the study a measurement of BMR and pulmonary function tests were performed. At day 1, patients received the dose of DLW, underwent body composition measurement, and were interviewed about habitual diet. A visit at home was performed by the dietitian at day 3, to discuss the food diary, check the use of medications, and complete a questionnaire about physical activity. The last day of the study, day 15, the patient delivered the urine samples to the hospital and body weight was measured.

Body composition

Body weight was measured with a calibrated scale (August Saufer, Albstadt, Germany) with patients bare footed in light clothing and was determined to the nearest 0.1 kg at day 1 and day 15. Height was measured with the subject standing bare foot and was determined to the nearest centimeter using a horizontal headboard with an attached wall-mounted metric rule at day 1. BMI was calculated as weight (kg) divided by height^2 (m). Body composition was measured with dual energy X-ray absorptiometry (Lunar Prodigy, GE Lunar Corp, Madison, USA). Fat-free mass (FFM) was also estimated from sex, age, height, and body weight using the equations of Westerterp et al. (10).

Pulmonary function tests

Spirometry was performed with a Vitalograph spirometer (Selefa, Buckingham, Ireland) before and 15 min after inhalation of 1 mg terbutaline to reach optimal standardisation. Arterial blood gases (partial pressure of oxygen (PO_2) and partial pressure of carbon dioxide (PCO_2)) and diffusion capacity of carbon monoxide (DL_{CO}) were measured in all patients.

Basal metabolic rate (BMR)

BMR was measured by indirect calorimetry using a ventilated-hood system. The equipment used was a Medical Graphics Corporation cardio pulmonary exercise system CPX (Medical Graphics Corporation, Minneapolis, USA). The equipment was calibrated before each measurement with gas mixtures with known O_2 and CO_2 contents according to the manufacturer's instructions. All patients were measured after an overnight fast and they arrived from their home by car, hence we measured resting energy expenditure (REE). Since there is only a small difference between REE and BMR, we present the data as BMR. After a 30 min rest, BMR was measured for 20 min when the patients were awake in the supine position and in an environmental temperature between 22°C–23°C. BMR was also calculated using the equations from WHO (11), equations developed especially for COPD patients (12) and from measured and predicted FFM (10).

Total daily energy expenditure–DLW

TDE was determined by the DLW technique. All patients came to the laboratory in the morning at day 1, after voiding, and after a normal breakfast. Prior to dosing, a second voiding was collected for determination of background isotope enrichment.

The subjects drank a mixture of deuteriated and oxygenated water, corresponding to 0.05 g of deuteriumdioxide (^2H_2O) and 0.10 g of oxygen-18-water ($H_2^{18}O$) per kilogram bodyweight. The dose was flushed down the throat with a glass of tap water. The exact time of dosing was recorded, and the subjects were equipped with 30 screw-capped glass vials to be filled 8 and 12 h after dosing, and with the second voiding from day 2, 3, 4, 5, 10, 13, 14, and 15 respectively. Exact voiding times were registered, and the urine samples were stored in freezer before delivery to the laboratory. Measurements of tap water, diluted administered dose, background enrichment and urine samples were performed in triplicates on a Finnigan MAT Delta Plus Isotope-Ratio Mass Spectrometer (ThermoFinnigan, Uppsala, Sweden). Five millilitres urine were introduced into 25 ml glass bottles, and equilibrated together with platinum-coated small rods as catalysts under hydrogen or carbon dioxide at 18°C in a controlled waterbath under agitating, for 2 h for deuterium and for 6 h for oxygen. Isotope ratios of the samples, expressed as delta values per mill, were compared to the isotope ratio of the standard gas, which in turn was compared to internal laboratory standards of water, and also in turn compared to known standards, as Vienna Standard Mean Ocean Water (SMOW), and Standard Light Precipitate (SLAP), purchased from The International Atomic Energy Agency (IAEA, Vienna, Austria). Variation in internal laboratory standard triplicates expressed by standard deviation (SD) in delta per mill was 0.47 for deuterium and 0.16 for oxygen. Variation in triplicates of urine samples expressed by SD in delta per mill was 0.40 for deuterium and 0.14 for oxygen, respectively. TDE was calculated by the multipoint method by linear regression from the difference between elimination constants of deuterium and oxygen-18, with the assumptions for fractionating as suggested by IAEA (13). All elimination curves were checked for major or diverging residuals. The coefficient of variation (CV) for the elimination constants were on average 3.4% for hydrogen and 2.9% for oxygen. We used the relationship between pool size deuterium (N_D) and pool size oxygen[18] (N_O) as a quality measurement of the DLW. The energy equivalence of the CO_2 excreted was calculated from the macronutrient intake using estimated food quotient (FQ) from the 7-day dietary registration (14).

Dietary intake

At day 1 the patients were interviewed about their habitual dietary intake. The patients were also interviewed about eventually former dietary counselling and use of nutritional supplements. During the first 7 days of the study, the patients registered food- and beverage-intake with the help of household measures. On the home visit at day 3, the dietitian checked the food diary and weighed the patients usual glasses, cups, pieces of bread, etc. in order to calculate energy intake as accurate as possible. At the same time a list of drugs they used was collected for each patient. At the end of the study (day 15), the patient and the dietitian discussed the registered dietary intake, to ensure a food diary as accurate as possible. For nutrient calculation, we used the nutrient program MATs (Rudans Lättdata, Västerås, Sweden) using the 'Swedish Food Data Base' (1997) from the National Food Administration (15). Data on the nutrient content of dietary supplements were added to the database.

Physical activity assessment

All patients completed the Zutphen physical activity questionnaire (ZPAC) (16) during the home visit at day 3. The questionnaire include questions about several standard activities (walking, cycling, gardening, jobs around the house, household activities, sport activities, hobbies, and walking stairs) and patients were also asked how long these activities were performed the last week. Patients were also interviewed about their outside home working situation, if present.

Data analysis

Results are described individually and as median and range. The statistical method described by Bland and Altman (17) was used to assess the degree of agreement between estimated and measured BMR.

Results

All patients completed the study. Patient characteristics, lung function data and body composition of the patients are shown in Table 1 for the male patients and Table 2 for the female patients. All patients met the diagnostic criteria for severe COPD. One patient (pat no. 4) had a BMI at 20.6 kg/m^2. In the recruitment process the patient had a BMI under 20 kg/m^2, but his body weight had increased at inclusion to the study. We chose to include this patient anyway, as we still consider him representative of the patients with underweight and severe COPD. Data on measured BMR for each patient

Table 1 Patient characteristics, lung function and body composition in five underweight male patients with severe COPD living at home

Pat no.	Age (year)	Weight (kg)	Height (cm)	BMI (kg/m^2)	FEV$_1$ (% pred)	PO_2 (kPa)	PCO_2 (kPa)	DL_{CO} (%)	FFM_{DXA} (kg)
1	69	58.2	180	18.0	44	8.3	4.5	32	47.1
2	57	55.1	173	18.4	41	10.1	4.8	39	49.3
3	47	62.9	178	19.9	24	8.8	5.6	60	48.3
4	70	69.8	184	20.6	26	8.7	5.3	66	55.8
5	66	53.3	166	19.3	33	10.2	6.2	73	44.2
Median	66	58.2	178	19.3	33	8.8	5.3	60	48.3
Range	47–70	53.3–69.8	166–184	18.0–20.6	24–44	8.8–10.2	4.5–6.2	32 –73	44.2–55.8

Definition of abbreviations: FEV$_1$ = forced expiratory volume in 1 s, as percentage of predicted; PO_2 = arterial partial pressure of oxygen; PCO_2 = arterial partial pressure of carbon dioxide; DL_{CO} = diffusion capacity of carbon monoxide; FFM_{DXA} = fat-free mass measured by DXA.

Table 2 Patient characteristics, lung function and body composition in five underweight female patients with severe COPD living at home

Pat no.	Age (year)	Weight (kg)	Height (cm)	BMI (kg/m^2)	FEV$_1$ (% pred)	PO_2 (kPa)	PCO_2 (kPa)	DL_{CO} (%)	FFM_{DXA} (kg)
6	67	48.4	164	18.0	36	5.6	6.0	61	34.5
7	55	50.6	160	19.8	46	13.3	4.8	42	35.4
8	66	42.9	160	16.8	19	8.0	5.3	18	27.7
9	61	53.1	167	19.0	20	8.8	4.7	39	36.4
10	72	49.7	168	17.6	19	11.3	4.8	*	30.6
Median	66	49.7	164	18.0	20	8.8	4.8	41	34.5
Range	55–72	42.9–53.1	160–168	16.8–19.8	19–46	5.6–13.3	4.8–6.0	18–61	27.7–36.4

*Could not perform the diffusion capacity test.
Definition of abbreviations: FEV$_1$ = forced expiratory volume in 1 s, as percentage of predicted; PO_2 = arterial partial pressure of oxygen; PCO_2 = arterial partial pressure of carbon dioxide; DL_{CO} = diffusion capacity of carbon monoxide; FFM_{DXA} = fat-free mass measured by DXA.

are presented in Tables 3 and 4. The median (range) measured BMR, predicted BMR from WHO, Moore and Angelillo, measured FFM and predicted FFM for the men were 6500 (5400–7400) kJ 6500 (5300–6900) kJ, 6800 (6500–7300) kJ, 6200 (5800–7100) kJ, and 6400 (5800–7000) kJ, respectively. For the women, the median (range) measured BMR were 4700 (3800–5600) kJ, predicted from WHO 5100 (4700–5300) kJ, predicted from Moore and Angelillo 5100 (4700–5300) kJ, predicted from FFM 4800 (4200–5100) kJ, and predicted from estimated FFM 5100 (4700–5300) kJ. Figure 1 is a plot showing the agreement between measured BMR and BMR predicted from the four different equations. If a perfect agreement was the case, all the values would have been zero. A positive value means that the prediction underestimate BMR, compared with the measured value. In five of the patients (four men and one woman), the measured BMR was higher than the BMR predicted from WHO equations (11). Compared with predicted BMR from the COPD-patient-specific equations of Moore and Angelillo (12), three of the patients (two men and one woman) had a higher measured BMR. Predicting BMR from measured FFM (10) leads to an underestimation of BMR in five patients (two women and three men), and using an estimated FFM in the prediction of BMR (10) leads to an underestimated BMR in three men and one woman.

Total daily energy expenditure as measured by DLW varied considerably from 5200 to 11,100 kJ (Tables 3 and 4). Expressed as kilojoule per kg body weight energy expenditure varied from 110 to 200 kJ/kg. The relation between TDE and measured BMR varied from 1.15 to 1.80. The quality measurement of the DLW analysis expressed as the relationship between N_D and N_O is presented in Tables 3 and 4. Our results fell well into the accepted range between 1.015 and 1.060 as proposed by IAEA.

All patients, except one (pat no. 9) drank coffee regularly, two patients (pat nos. 1 and 3) used nicotine supplements, three patients (pat nos. 6, 9 and 10) used theophylline-containing drugs, all patients except one (pat no. 10) used β_2 agonists, and two patients (pat nos. 5 and 6) used selective serotonin reuptake inhibitors (SSRI). Three patients (pat no 2, 6 and 10) regularly used liquid nutritional supplements in their diet. The results from the dietary record showed good agreement with the results from the dietary interview concerning food choices and meal pattern (data not shown). Energy intake (EI) as assessed by the 7-day dietary registration varied from 5300 to 9100 kJ, as shown in Tables 3 and 4. The relation between EI and measured BMR (PAL_{EI}) varied between 0.95 and 1.70.

Physical activity pattern measured by the ZPAC (16) is presented in Table 5. Data are presented both as types of physical activity and levels of intensity. Most of the activities performed were gardening or light-to-moderate intensive hobbies. Three patients (pat nos. 1, 8 and 10) reported no or almost no activity at all. Six patients lived in their own house with a garden, and the other four (pat nos. 3, 7, 8 and 10) lived in apartments. Patient 10 used a wheelchair for transportation outside the home, all other patients were ambulatory. Two patients were in the active workforce (pat no. 1 was a taxi driver

Table 3 BMR measured with indirect calorimetry, TDE assessed by DLW and energy intake from 7 day dietary registration in five underweight male patients with severe COPD living at home

Pat no.	BMR–IC (kJ)	TDE (kJ)	N_D/N_O	TDE/Body weight (kJ/kg)	EI (kJ)	TDE/BMR-IC	EI/BMR-IC
1	6500	9000	1.037	150	8600	1.39	1.33
2	7500	11100	1.031	200	9100	1.48	1.22
3	5600	8600	1.038	140	7900	1.54	1.42
4	7400	10900	1.044	160	7800	1.47	1.05
5	5400	8600	1.039	160	7500	1.59	1.38
Median	6500	9000	1.038	150	7900	1.48	1.33
Range	5400–7500	8600–11100	1.031–1.044	140–200	7500–9100	1.39–1.59	1.05–1.42

Definition of abbreviations: TDE = total daily energy expenditure; N_D = pool size deuterium; N_O = pool size oxygen[18]; EI = energy intake; BMR-IC = BMR measured with indirect calorimetry.

Table 4 BMR measured with indirect calorimetry, TDE assessed by DLW and energy intake from 7 day dietary registration in five underweight female patients with severe COPD living at home

Pat no.	BMR-IC (kJ)	TDE (kJ)	N_D/N_O	TDE/body weight (kJ/kg)	EI (kJ)	TDE/BMR-IC	EI/BMR-IC
6	4700	7000	1.038	140	8000	1.49	1.68
7	4500	8100	1.032	160	4500	1.80	1.00
8	3800	5200	1.034	120	6400	1.37	1.70
9	5600	8900	1.028	170	5300	1.59	0.95
10	4900	5600	1.040	110	5700	1.15	1.18
Median	4700	7000	1.034	140	5700	1.49	1.18
Range	3800–5600	5200–8900	1.028–1.040	110–170	5300–8000	1.15–1.80	0.95–1.70

Definition of abbreviations: TDE = total daily energy expenditure; N_D = pool size deuterium; N_O = pool size oxygen[18]; EI = energy intake; BMR-IC = BMR measured with indirect calorimetry.

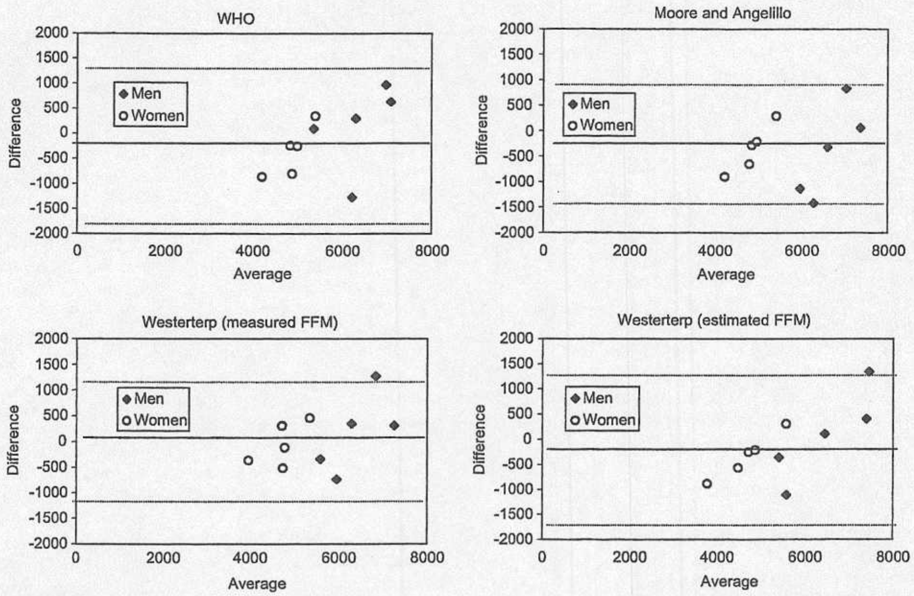

Fig. 1. Differences between measured and predicted BMR plotted against average of measured and predicted BMR predicted from equations from WHO (11), Moore and Angelillo (12), and Westerterp et al. (10) in 10 underweight patients with severe COPD living at home.

Table 5 Time (minutes/week) spent in three levels of physical activity intensity and selected types of physical activity in 10 patients with severe COPD

Pat no.	LA	MA	HA	Walking	Bicycling	Gardening	Hobbies
1	0	0	20	0	20	0	0
2	0	150	660	0	0	660	150*
3	600	0	0	0	0	0	600**
4	0	30	930	30	0	930	0
5	0	135	210	135	0	210	0
6	0	0	315	0	0	315	0
7	420	34	0	34	0	0	420#
8	0	3	0	3	0	0	0
9	0	20	30	20	0	30	0
10	0	0	0	0	0	0	0
Median	0	20	30	3	0	30	0
Range	0–600	0–150	0–930	0–135	0–20	0–930	0–600

*Tinkering with the car.
**Chessplaying.
#Embroidery.
Physical activity levels were adopted from Caspersen et al. (16).
Definition of abbreviations: LA = light activity, MA = moderate activity, HA = heavy activity.

and pat no. 7 a secretary), while the remaining eight were all on a disability pension.

Discussion

Predicting BMR using the equation of WHO underestimated the BMR in half of the patients. Using the disease-specific equation of Moore and Angelillo, BMR was underestimated in three of the 10 patients. This may be due to the fact that the equation of Moore and Angelillo is developed on a relatively small group of COPD patients (n=43) out of which only 10 were women. The FFM is the most important determinant of BMR. Even if the equation with the measured FFM underestimate BMR in five of the patients, this is the prediction with the narrowest limits of agreement. Predicting FFM from sex, age, height and body weight, however, does not improve the prediction compared with the equations from WHO or Moore and Angelillo.

Since none of the used equations gave an acceptable prediction of BMR, we therefore suggest that a *measurement* of BMR always should be performed in underweight patients with severe COPD, to provide a basis for estimating energy requirement. The second best is to predict the BMR from FFM measured by a reliable method.

All patients ingested either caffeine, nicotine or drugs, factors known to influence BMR. Studies have shown acute effects of salbutamol on BMR (18), but the knowledge is limited concerning long-term effects of bronchodilators and the other confounding factors in patients with severe COPD (19). The possible effects on BMR by each single factor in the present study is impossible to account for.

This study shows that underweight COPD patients, both male and female, living at home have a wide variation in TDE, from 5200 to 11,000 kJ, and energy intake, from 5300 to 9100 kJ, measured by DLW and a 7-day dietary registration. TDE varied from 110 to 200 kJ/kg body weight. In dietary counselling an energy requirement of 125 kJ/kg is often used as a guideline. Using this guideline would not have met the energy requirements in eight out of 10 patients in this study.

Baarends et al. (8) reported a mean TDE of 11,000 kJ in 20 COPD patients (19 men and 1 woman), but unfortunately without reporting body weight, so excluding the possibility to compare energy expenditure expressed by kilogram body weight. However, the median TDE (9000 kJ) for *men* in the present study was lower compared to the mean of 11,000 kJ in the study by Baarends et al. (8). Hugli et al. (6) studied 16 male COPD patients in a respiration chamber and found a mean TDE of 130 kJ/kg body weight. These patients though, had a low level of physical activity, with a group mean physical activity level (PAL) of 1.21. In another study of Baarends et al. (7), eight male COPD patients had a TDE of 170 kJ/kg body weight (body weight calculated from FFM and percentage body fat), with a mean PAL of 1.70. Only one of the male patients in the present study exceeded 170 kJ/kg body weight in TDE, but the other four were fairly close (140–160 kJ/kg body weight). The median TDE of 150 kJ/kg body weight and the median PAL of 1.48, in the five male patients in the present study, is halfway between the results from the rehabilitation studies by Baarends et al. and the inactivity study by Hugli et al. This is possibly due to the fact that the patients in those studies were in artificial environments; i.e. a pulmonary rehabilitation unit with training and in a respiratory chamber. The results found in the current study is in consistency with the results recently presented by Tang et al. (20), although they used the bicarbonate–urea method.

All patients had a stable weight during the study (data not shown). Therefore, one would expect the energy intake to equal the TDE. We are aware of the fact that a 7-day dietary registration may not be representative for an individual habitual dietary intake. This may be the fact for patient no. 7, who clearly underestimated her intake of foods and beverages. Her registration shows an energy deficit of 3600 kJ per day. If this was the truth she would have been expected to loose 1.7 kg of body weight, assuming that only fat mass is lost. Five patients (pat nos. 2, 4, 5, 7 and 9) reported an energy intake below 90% of the TDE and two subjects (pat nos. 6 and 8) reported an energy intake above 110% of TDE as measured by DLW. Using the Goldberg cutoff for energy intake (21) calculated with each patient PAL_{DLW}, two patients (pat nos. 7 and 9) were identified as under-reporters, i.e. their reported energy intake cannot be a true measure of their habitual diet.

Median PAL using the TDE analysed by DLW (PAL_{DLW}) was 1.49, ranging from 1.15 to 1.80. The subject with a PAL of 1.15 used a wheelchair for transportation—thereby possibly accounting the low physical activity. A PAL of 1.49 is somewhat lower than Baarends et al. found in their study on eight male COPD patients admitted to a pulmonary rehabilitation unit (7). The large variation in PAL_{DLW} represents the highly variable level of physical activity that can be seen in underweight patients with severe COPD living at home. Median PAL determined from the energy intake (PAL_{EI}) was 1.29 with a range from 0.95 to 1.70. Dividing the patient group into halves of PAL_{DLW} and PAL_{EI} as much as four patients out of 10 are classified in the opposite half, i.e. a misclassification of PAL calculation using energy intake data. So even if we did put a lot of effort in determining the energy intake by dietary registration in this study, this is not very likely a method which should be used to determine total energy requirement. Thus it seems important to determine the amount of physical activity so as to predict the total daily energy requirement. Since the patients in this study had rather low physical activity, a questionnaire like the ZPAC only involves a short amount of the patients total time in activity. In this study, it only accounted for a median of 6 h of the total week (168 h). We have therefore not calculated PAL from the ZPAC, but used it to describe the small amounts of detectable physical activity in COPD patients living at home. A great variation in physical activity was however detected (from 0 h/week (pat no 10) to 16 h/week (pat no. 4)) as presented in Table 5. In this study we lacked a tool to determine the energy expenditure derived by physical activity. Accelerometers have been suggested as a tool to be used, but validation studies against DLW has not shown convincing results (22), and in COPD patients no validation study has been done against DLW.

Since the patients in this study were underweight, a treatment goal with dietary intervention should be to increase body weight. An underestimation of PAL and BMR (using prediction equations) to determine energy requirements would result in dietary advice at a suboptimal energy level and increase rather than decrease the risk of further weight loss.

Among underweight patients with COPD living at home, there is great variation in total energy expenditure, physical activity, energy intake and BMR. There are very few data concerning energy expenditure in female patients with COPD and this is the first time TDE in women with COPD are described. Clearly, more research in energy expenditure in female COPD patients are needed. Estimating the energy requirement of patients with COPD demands a measurement of BMR (indirect calorimetry) and an estimation of the PAL.

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Energy Expenditure in Underweight Chronic Obstructive Pulmonary Disease Patients before and during a Physiotherapy Program

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ABSTRACT

Background: Rehabilitation programs, including physiotherapy, nutritional support, psychotherapy and education are recommended in international treatment guidelines for chronic obstructive pulmonary disease (COPD) patients. For underweight COPD patients however, it is crucial to fulfill energy requirements and little is known concerning the effect on energy expenditure when entering into a physiotherapy program including aerobic exercise and peripheral muscle strength training.

Objective: To investigate how total daily energy expenditure (TDE) changes when underweight patients with COPD enter into a physiotherapy program.

Design: TDE was assessed by the doubly labelled water method in a two week control period and during two weeks in a physiotherapy program. Ten patients with severe COPD and with a body mass index < 21 kg/m^2 completed the whole study. Energy intake was assessed using seven-day dietary registration during control and physiotherapy period.

Results: Median TDE during the control period was 7,300 kJ/day and median ratio between TDE and basal metabolic rate was 1.49. Six of the patients had lower TDE during the physiotherapy period compared to the control period. Median change in TDE was -10 % or -700 kJ/day. Median energy intake during the control period was 6,900 kJ and increased by 5 % or 300 kJ in the physiotherapy period.

Conclusion: Inclusion into a physiotherapy program is not necessarily followed by an increase in TDE. Underweight patients with COPD may show a stable, increased or decreased TDE compared to a control period. This calls for an individual assessment of each patient's energy requirements and the need to develop and validate alternative methods to the doubly labelled water method to assess TDE.

Key words: Chronic obstructive pulmonary disease, energy expenditure, doubly labelled water, underweight, energy intake, rehabilitation, physiotherapy

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease of complex nature, especially in the moderate to severe stages of the disease. In addition to the primary impairment of the lungs and the airways, physiological abnormalities in the structure and metabolism of the skeletal muscles have been shown (3, 14). Rehabilitation programs, including physiotherapy (mobility training, breathing exercises and physical exercise), nutritional support, psychotherapy and education are recommended in international treatment guidelines for COPD patients (18). Lacasse et al (13) concluded in a Cochrane review that rehabilitation relieves dyspnea and fatigue, increases exercise capacity and improves quality of life. Physical exercise comprises activities aiming at maintaining and improving physical and psychological functions and restoring the physiologic balance in the skeletal muscles. Both aerobic exercise and peripheral muscle training are recommended for COPD patients (4). Aerobic exercise could be walking, stair climbing and cycling while peripheral muscle training could contain exercising with weights, pulleys, and/or elastic rubber bands (11).

We have shown slight, but uniform, indications of positive effects of dietary intervention during multidisciplinary rehabilitation in a group of patients with severe COPD (20). However, in the underweight patients, where one of the goals is to increase body weight, we found that the extra amount of energy eaten by the patients was not sufficient to provide both an increase in physical performance and a gain in body weight. This fact raised the question about how much extra energy that is expended during a rehabilitation program. To our knowledge, only one study has examined this thoroughly. Tang et al (22) compared one single day without rehabilitation exercise to one day including exercise using the bicarbonate-urea method. In the ten patients studied, the total daily energy expenditure (TDE) increased from a mean of 1,508 kcal/day to 1,568 kcal/day (ns). A limitation of that study, as the authors' state, was the short measurement time, mainly dependent of the principles of the bicarbonate-urea method.

The doubly labelled water (DLW) method has made it possible to determine the TDE in free-living subjects. The technique is well established and validated both in animals and humans (16, 17) and is today considered to be the golden standard for assessment of TDE . The assessment is made with high precision without limiting the subjects' way of life. The result represents energy expenditure for a relatively long period of time, in contrast to short-term measurements with major limitations in way of life using direct calorimetry. Baarends et al studied ten male COPD patients admitted to a pulmonary rehabilitation center, using the DLW method, and found that the ratio between TDE and basal metabolic rate (BMR) ranged from 1.5 to 2.0 compared to a range from 1.3 to 1.6 in healthy free-living control subjects (1). However, nobody has studied the effect on energy expenditure in the same patients before and during rehabilitation in COPD patients, which is the only way to answer the question. The lack of a controlled study may be due to the complexity of the appropriate study design. Such a study has to be done over a relatively long period of time, including a risk that the patients will experience an exacerbation of their disease. The need for individualization of the physiotherapy program makes standardization of the study design hard to achieve.

The aim of this study was to investigate how TDE changes when underweight patients with COPD enter into a physiotherapy program.

METHODS

Study design

Prior to the study, pulmonary function tests were performed. A control period preceded the physiotherapy period as shown in figure 1. The time between the two measurement periods was set to four weeks to ensure total elimination of the first dose of DLW.

Control period

At day 1, patients underwent measurements of body composition, and BMR. They received the first dose of DLW and were also instructed to register dietary intake during seven days. A visit at home was performed by a dietitian (FS) at day eight, to discuss and collect the food diary and to check the use of medications and nicotine. On day 15, the patient delivered the urine samples to the hospital and their body weight was measured.

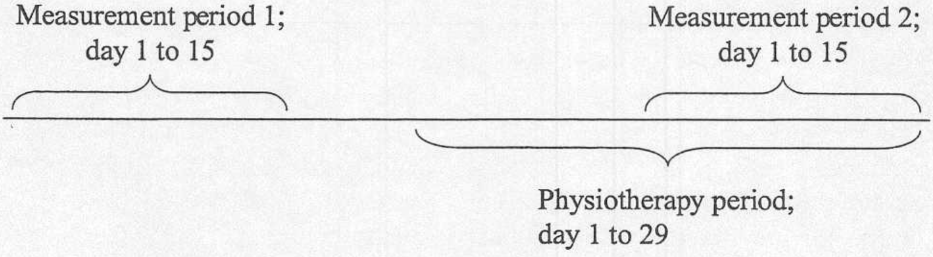

Figure 1. Study design

Physiotherapy period

After two weeks of physiotherapy, i.e. at day one of the measurement period, the patients received the second dose of DLW. They were instructed to register dietary intake during seven days. A visit at home was performed by a dietitian at day eight, to discuss and collect the food diary. On day 15, patients underwent measurements of body weight and they delivered the urine samples.

Patients

Eleven patients (two men and nine women) with severe and stable COPD, diagnosed as forced expiratory volume in one second (FEV_1) < 50 % predicted, as determined by criteria from The European Respiratory Society (18) were included in this study. All patients were recruited consecutively from the outpatient COPD-unit at the Department of Respiratory Medicine, Sahlgrenska University Hospital, Göteborg, Sweden. Inclusion criteria was body mass index (BMI) < 21 kg/m^2 and exclusion criteria were earlier performed rehabilitation, oxygen treatment, cancer, diabetes mellitus, hypothyreoidism, heart failure and angina pectoris during exercise test or other major diseases. The patients were informed of the nature and purpose of the study and gave written informed consent. The study was approved by the Ethics Research Committee of the Göteborg University.

Pulmonary function tests

Spirometry was performed with a Vitalograph spirometer (Selefa, Buckingham, Ireland) before and 15 min after inhalation of 1 mg terbutaline to reach optimal standardization. Arterial blood gases (partial pressure of oxygen (PO_2) and partial pressure of carbon dioxide (PCO_2)) were measured in all patients.

BMR

BMR was measured by indirect calorimetry using a ventilated-hood system. The equipment used was a Deltatrac™ II Metabolic Monitor (Datex, Helsinki, Finland). Before each measurement, the equipment was calibrated with gas mixtures of known O_2 and CO_2 contents according to the manufacturer's instructions. All subjects were measured after an overnight fast and they arrived from their home by car or public transport hence we measured resting energy expenditure (REE). Since there is only a small difference between REE and BMR, we present the data as BMR. The subjects were instructed to limit their physical activity the evening before the measurement. After a 30 min rest in the supine position, BMR was measured during 30 min when the subjects were awake in the supine position. The measurements were performed in an environmental temperature between 22-23°C. The presented mean BMR for each patient is based on the last 25 min of the measurement.

Body composition

Body weight was measured, with subjects wearing light clothing without shoes, to the nearest 0.1 kg. Height was measured and determined to the nearest centimeter using a horizontal headboard with an attached wall-mounted metric rule. BMI was calculated as weight (kg) divided by height^2 (m). Body composition was measured with dual energy X-ray absorptiometry (Lunar Prodigy, GE Lunar Corp, Madison, USA) and fat free mass index (FFMI) was calculated as fat free mass (FFM) (kg) divided by height^2 (m).

DLW

TDE was determined by the DLW technique. TDE from the DLW method was measured over two 14 day periods (measurement period 1 and 2). Sample analysis and calculation procedures have been described elsewhere (19). Prior to dosing, a voiding was collected for determination of background isotope enrichment. The patients ingested a weighed mixture of deuteriated and oxygen-18 enriched water, corresponding to 0.05 g of deuterium oxide (^2H_2O) and 0.10 g of oxygen-18-water ($H_2{}^{18}O$) per kg body weight. The dose was flushed down the throat with a glass of tap water. The exact time of dosing was recorded and the subjects were equipped with 21 screw-capped glass vials to be filled with the second voiding from day two, three, four, eight, 13, 14 and 15. Exact voiding times were registered, and the urine samples were stored in a freezer before delivery to the laboratory. Samples were analysed in triplicates on a Finnigan MAT Delta Plus Isotope-Ratio Mass Spectrometer (ThermoFinnigan, Uppsala, Sweden). TDE was calculated by the multi-point method by linear regression from the difference between elimination constants of deuterium and oxygen-18, with the assumptions for fractionating as suggested by IAEA (12). The energy equivalence of the CO_2 excreted was calculated from the macronutrient intake using estimated food quotient (FQ) from the 7-day dietary registration (2). The relationship between pool size deuterium (N_D) and pool size oxygen-18 (N_O) was used as a quality measurement of the DLW analysis as proposed by IAEA (12).

Dietary intake

During the first seven days of each measurement period, the patients registered food- and beverage-intake with the help of household measures. On the home visit at day eight, a dietitian checked the food diary and weighed the patients' usual glasses, cups, pieces of bread etc. in order to calculate energy intake as accurate as possible. At the same time a list of drugs which each patient used was collected. For nutrient calculation we used the nutrient program Dietist (Kost och Näringsdata AB, Bromma, Sweden) using the "Swedish Food Data Base" (1997) from the Swedish National Food Administration (21). Data on the nutrient content of dietary supplements was added to the database.

The physiotherapy program

The physiotherapy program took place at the Department of Physiotherapy, Sahlgrenska University Hospital. It comprised eight individual 90-min sessions (twice a week) of education and physical exercise plus a home-exercise program. Education included some elements of basic anatomy, respiratory physiology and pathophysiology of COPD. Moreover, instructions on disease management and practical coping skills were given. Physical exercises composed of mobility training, aerobic exercise on a treadmill and peripheral muscle training.

All patients were managed by the same physiotherapist (KK). Practical coping skills focused on managing breathlessness by breathing exercises and sputum removal techniques. Breathing exercises included the pursed-lip-breathing technique, breathing exercises with positive expiratory pressure (PEP) using a BA-tube and postural drainage.

Table 1. Patient characteristics, lung function and body composition in eleven underweight COPD patients

Patient	Sex	Age (years)	BW (kg)	Height (m)	BMI (kg/m^2)	FEV_1 (%pred)	PO_2 (kPa)	PCO_2 (kPa)	FFMI (kg/m^2)
1	F	53	53.8	1.68	19.2	45	11.2	4.7	13.8
2	F	60	49.8	1.60	19.5	49	8.2	5.7	13.7
3	F	55	50.8	1.58	20.5	40	9.1	4.5	13.1
4	F	63	47.0	1.58	18.8	24	12.6	5.3	15.2
5	M	62	41.9	1.76	13.5	21	9.2	5.3	13.1
6	F	54	57.7	1.70	20.0	46	11.0	5.2	12.6
7	M	57	57.8	1.82	17.4	35	9.5	4.5	14.8
8	F	58	56.0	1.67	20.1	42	8.1	6.0	14.7
9	F	73	45.2	1.54	19.1	35	9.2	4.7	15.8
10	F	74	47.1	1.49	21.2	43	8.2	5.5	15.0
11	F	74	50.2	1.69	17.6	27	8.4	4.8	13.1
Median		62	50.2	1.67	19.2	40	9.2	5.2	13.8
Range		53-74	41.9-57.8	1.49-1.82	13.5-21.2	21-49	8.1-12.6	4.5-6.0	12.6-15.8

BW=body weight; M=male; F=female; BMI= body mass index; FEV_1=forced expiratory volume in 1 s, as percentage of predicted; PO_2=arterial partial pressure of oxygen; PCO_2=arterial partial pressure of carbon dioxide; FFMI=fat-free mass index

Instructions on coughing techniques were also given. Mobility training consisted of mobility exercises for the thoracic-, shoulder girdle- and neck muscles. Aerobic exercise was conducted on a treadmill (Power Jog, Sport Engineering Ltd., UK). Intensity and duration of exercise was based upon symptom scores, arterial oxygen saturation (SaO_2) and the history of exercise. Degree of perceived breathlessness was assessed by the modified Borg-scale, scores 0-10. The degree of perceived fatigue was assessed by the Borg-scale, scores 6-20. A level of 2-4 on breathlessness and 12-13 on fatigue was considered suitable. SaO_2 was to be equal to or above 90 %. If the SaO_2 fell below 90 %, supplemental oxygen was given. The speed and duration of the aerobic exercise was each session based upon symptom scores, SaO_2 and the history of exercise. In peripheral muscle training muscle endurance was emphasized. Exercises were focused on the lower extremities and were related to functional activities. The intensity was set to 40-80 % of the repetition maximum. The 6-min walking distance test with assessment of perceived breathlessness and SaO_2 every minute was performed at the first and last appointment with the physiotherapist and all patients had one training test before the study started.

Table 2. Basal metabolic rate, total daily energy expenditure and energy intake in eleven underweight COPD patients during control period

Patient	BMR (kJ)	TDE (kJ)	EI (kJ)	TDE/BMR	EI/BMR	TDE/BW (kJ/kg)
1	5,000	8,100	8,100	1.62	1.62	150
2	4,100	7,600	7,300	1.85	1.78	150
3	4,500	6,700	6,400	1.49	1.42	130
4	4,700	6,900	5,800	1.47	1.23	150
5	4,800	6,700	9,000	1.40	1.88	160
6	4,700	7,400	5,800	1.57	1.23	130
7	5,900	8,100	8,100	1.37	1.37	140
8	4,800	8,300	5,600	1.73	1.17	150
9	5,000	7,200	7,500	1.44	1.50	160
10	4,800	6,600	5,500	1.38	1.15	140
11	4,300	5,200	6,100	1.21	1.44	100
Median	4,800	7,200	6,400	1.48	1.42	140
Range	4,100-5,900	5,200-8,300	5,500-9,000	1.21-1.85	1.15-1.88	100-160

BMR=basal metabolic rate; TDE=total daily energy expenditure; EI= energy intake; BW= body weight

RESULTS

Ten patients (two men and eight women) completed the whole study. One patient (patient 10) decided to drop out after one week of physiotherapy. She had one hour travel by bus to the hospital and found it to strenuous to travel this distance twice a week. As described in table 1, one patient (patient 10) had a BMI of 21.2 kg/m^2. In the recruitment process the patient had a BMI < 21 kg/m^2, but her body weight had increased at inclusion to the study. We still considered her to be representative of the patients with underweight and severe COPD. The results from the control period are presented in table 2. Median time between day 15 in the control period and day one in the physiotherapy period was 21 days. Due to an exacerbation, patient 4 had a period of seven months between control and physiotherapy period. Except her, the time between control and physiotherapy was six to 74 days. Seven of the ten patients completing the physiotherapy program attended more than seven of the eight appointments with the physiotherapist. Patient 5 attended four and patient 3 and 6 six of the eight appointments. All patients, except patient 5, performed an individualized home-exercise program at least twice a week, but most of them several times a week. All patients, except patient 5, performed both 6-min walking distance tests with a median result of 360 meters. No clinically relevant change in median distance was detected between the first and second test. There was however, an improvement in median perceived breathlessness assessed by the modified Borg-scale from three to two. SaO_2 was also improved from a median of 89 % in the first test and 90 % in the second test. As shown in figure 2, patient 4 was the patient with the largest change in body weight (an increase of 7 % or 3 kg). The other patients had a rather stabile body weight during the study. Six of the patients had lower TDE during two weeks of physiotherapy compared to the control period. Median difference in TDE between the periods was -10 % or -700 kJ per day. This was not connected to changes in body weight, the median change in TDE/kg BW was also a 10 % reduction (15 kJ/kg). Energy intake was higher during physiotherapy compared to the control period in six patients and the median difference was 5 % (300 kJ).

DISCUSSION

In this study we have found ambiguous results concerning change in TDE when COPD patients were engaged in a physiotherapy program. Some patients expended more energy, but most of them had a lower TDE during the physiotherapy, compared to a control period. In a study in eleven *healthy* elderly (mean age 66 years), Goran and Poehlman (9) found similar findings as in the current study. Mean TDE was not higher during a period of cycling exercises three times per week compared to a control period. They calculated that this was due to a compensatory decline in physical activity during the remainder of the

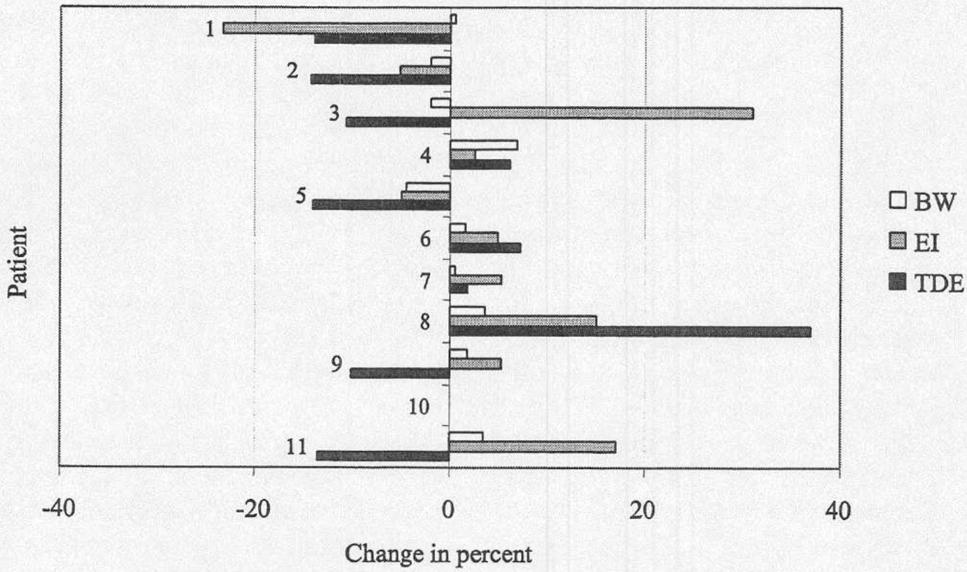

Figure 2. Change (%) in body weight (BW), energy intake (EI) and total daily energy expenditure (TDE) from control to physiotherapy period in ten underweight COPD patients

day. Our finding is also consistent with the findings of Tang et al (22), even if they only studied one day. Tang et al also suggested that lack of increase in TDE during rehabilitation in COPD patients may be caused by a decrease in the patients' normal activity pattern. That means that the training sessions make the patients so feeble that they do not have the energy to perform their usual activities. That might be one of the explanations also in the current study. In the current study another explanation is also possible. One part of the physiotherapy is breathing exercises. The patients do exercises aiming at reducing breathlessness and learn techniques to cope with the experienced dyspnea. Oxygen cost of breathing have been shown to be elevated in COPD patients, especially underweight patients (6, 15). It is possible that when underweight COPD patients do breathing exercises this reduces the elevated oxygen cost of breathing. This might limit the increase in energy expenditure one would expect to occur during a period of increased load of physical exercise. One could also argue that some of the patients did not fulfill all of the appointments with the physiotherapist, reducing the possibility to detect an increase in TDE. There was however no relation between compliance of physiotherapy and change in TDE between the periods.

TDE measured by DLW does not give information about day-to-day variation in TDE or time and intensity of physical activities performed. However it is a more long-term result compared to measures like the bicarbonate-urea method only giving results from one day. Due to the design of this study, we can not exclude the possibility that the patients have changed their activity pattern from the control period to the physiotherapy period. We have to bear in mind though, that most of the patients, having a severe COPD, were sedentary in both periods. 64 % of the patients had a ratio between TDE and BMR lower than 1.5, indicating a lower level of physical activity than the mean in a sample of healthy elderly (> 75 y old) men (8). In the current study with a rather homogenous patient group, we found a large variation in the relation between TDE and BMR ranging from 1.21 to 1.85 in the control period preceding the period including physiotherapy. This is however in consistency with earlier findings of similar patient groups (10, 19).

Even though a lot of effort was made to get as good measure of energy intake as possible in this study, the energy balance equation is not reasonable for most of the patients. Patient no 3 illustrates as a good example. Her energy expenditure was 11 % lower in the physiotherapy period compared to the control period while her energy intake was 30 % higher. If this was the truth, her body weight could not possibly have been reduced by 2 % (1 kg). One of the explanations to this might be that the measurement of energy intake was performed during the first half of the DLW period. We considered a 14 days registration of dietary intake to be a too large burden for the patients. Precision and accuracy of the DLW method using the multipoint method have been shown to be 3.6 % (coefficient of variation (CV)) (5). A use of the method suggested by Elia et al (7) indicated that the precision in our energy balance assessment was about 1,000 kJ/d. This was mainly due to the large CV in the energy intake assessment. As we have shown earlier, a measurement of energy intake can not replace a measurement of energy expenditure (19). The cost of purchasing and analyzing DLW indicates that this is not an applicable method to use in the clinical setting. So clearly, there is a need for a valid method that can estimate changes in energy expenditure to be able to estimate energy requirements in patients that enter into a physiotherapy program.

This study also clearly demonstrates that underweight patients with COPD should not be treated as a group. Earlier studies have made conclusions on groups of COPD patients (1, 10, 22). We have earlier shown that this is not applicable for BMR (19) and the current study shows that this also goes for changes in energy requirements when patients start doing exercise.

To conclude, inclusion into a physiotherapy program is not neces-sarily followed by an increase in TDE. Underweight patients with COPD may show a stable, increased or even decreased TDE compared to a control period. This calls for individ-ual assessment of each patient's energy requirements and the need to develop alternative valid methods to the DLW method to assess TDE.

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