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# Analysis of body water compartments in relation to tissue depletion in clinically stable patients with chronic obstructive pulmonary disease<sup>1-3</sup>

Erica M Baarends, Annemie MWJ Schols, Wouter D van Marken Lichtenbelt, and Emiel FM Wouters

**ABSTRACT** Tissue depletion often occurs in patients with chronic obstructive pulmonary disease (COPD), even in those that are weight-stable. Limited data are available, however, about changes in body water compartments in chronic wasting diseases such as COPD. The purpose of this study was to measure body composition in severe COPD patients with special attention to fat-free mass (FFM) depletion and the distribution of body water compartments. Total body water (TBW) and extracellular water (ECW) were measured by deuterium and sodium bromide dilution techniques, respectively, in 38 COPD patients (age:  $65 \pm 9$  y, forced expiratory volume in 1 s:  $38 \pm 14\%$  of predicted) in a stable clinical condition. FFM was calculated by assuming a hydration coefficient of 73%. Underweight patients [body mass index (BMI; in  $\text{kg}/\text{m}^2$ )  $\leq 21$ ] were characterized by a significantly lower percentage fat mass than normal-weight patients, but no significant difference was found in the ratio of ECW to intracellular water (ICW) (BMI  $\leq 21$ :  $0.72 \pm 0.12$ , BMI  $> 21$ :  $0.71 \pm 0.16$ ; NS). When the study population was divided into depleted patients (FFM/height<sup>2</sup>  $\leq 15 \text{ kg}/\text{m}^2$ ) and nondepleted patients (FFM/height<sup>2</sup>  $> 15 \text{ kg}/\text{m}^2$ ), there was no significant difference in the percentage fat mass, but the ECW-ICW ratio was significantly higher in the depleted patients ( $0.78 \pm 0.16$ ) than in the nondepleted patients ( $0.66 \pm 0.12$ ,  $P < 0.05$ ); this was most pronounced in women. In conclusion, it was found that COPD patients with extreme FFM wasting are characterized by an increased ECW-ICW ratio despite a relatively spared fat mass. *Am J Clin Nutr* 1997; 65:88-94.

**KEY WORDS** Body composition, chronic obstructive pulmonary disease, total body water, extracellular water, bromide dilution

## INTRODUCTION

Weight loss and a low body weight often occur in patients with chronic obstructive pulmonary disease (COPD) (1, 2). We showed earlier that weight loss in COPD patients comprises both loss of fat mass (FM) and fat-free mass (FFM). Loss of FFM has even been shown in weight-stable patients (2). The particular relevance of wasting of FFM for the clinical condition of COPD patients was shown in an adverse effect on physical performance (3-7), on respiratory muscle function (8, 9) and even on survival (10, 11).

Body composition can be presented by a simple two-compartment model: FM and FFM. FFM can be measured accurately with deuterium dilution under the assumption of a constant hydration factor of 73% (12). FFM can however be further subdivided into two compartments: the intracellular compartment (also known as body cell mass; BCM), which represents the energy exchanging part, and the extracellular compartment, which represent substances outside the cells (such as collagen, fascia, plasma, and interstitial fluid) and mainly functions as a support and transport tissue. It is not currently possible to measure the intracellular compartment directly (13, 14). Indirect methods to determine BCM by total-body potassium or total-body nitrogen are not readily applicable in clinical practice or require sophisticated equipment. The greatest part of BCM is intracellular water (ICW) and this compartment can be calculated indirectly from total body water (TBW) and extracellular water (ECW). This assessment of ECW and TBW by deuterium and sodium bromide dilution is relatively easy to perform.

A description of body composition by a three-compartment model is especially important in acute wasting diseases (14, 15) or after a catabolic stress such as extreme weight loss (16, 17) or severe trauma. Under these circumstances, the BCM can be decreased, whereas the ECW is absolutely or relatively expanded. Therefore, in cases of fluid shifts, measurement of FFM is an inappropriate measure of the metabolically active tissue mass. Limited data are available about changes in body water compartments in chronic wasting diseases such as COPD, cardiac failure, acquired immunodeficiency syndrome (AIDS), and cystic fibrosis.

The purpose of this study was to measure body composition in severe COPD patients with special attention to FFM depletion and the distribution of the body water compartments.

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## METHODS

### Patients

Thirty-nine patients (24 males, 15 females) with moderate to severe COPD (18) who were participating in a pulmonary rehabilitation program were studied just after entering the program. All patients were referred by a pulmonary physician to the rehabilitation center in a stable clinical condition. None of the patients had a respiratory tract infection or clinically visible signs of severe edema at the time of the study. Patients exhibiting an increase in forced expiratory volume in 1 s ( $FEV_1$ ) > 10% of baseline after inhalation of a  $\beta_2$ -agonist or patients suffering from cancer, unstable pulmonary or cardiac conditions, active gastrointestinal abnormalities, recent surgery, or severe endocrine disorders were excluded from the study. The study was approved by the local ethical committee. Procedures followed were in accord with the Helsinki declaration from 1977 as revised in 1983.

### Nutritional assessment

#### Anthropometry

Body height was determined to the nearest 0.5 cm (WM 715; Lameris, Breukelen, Netherlands) with subjects standing bare-foot. Body weight was measured with a beam scale to the nearest 0.1 kg (SECA, Hamburg, Germany) with subjects bare-foot and in light clothing.

#### Determination of total body water and extracellular water

To measure TBW each patient received a weighed oral dose of deuterium-labeled water (99.84 atom percent excess) of 1 g/L predicted TBW (based on height, weight, age, and sex; 19) mixed into  $\approx 70$  mL water. For the estimation of ECW, 60 mg sodium bromide/L predicted TBW (based on height, weight, age, and sex) was added to the deuterium dose. Patients received this "cocktail" in the late evening at  $\approx 2200$ . Just before and  $\approx 10$  h later venous blood and urine samples were obtained. Urine was analyzed for deuterium with an isotope ratio-mass spectrometer according to the standard Maastricht protocol (12). Deuterium dilution space was calculated from the quantity of administered deuterium and the urine deuterium concentrations after complete equilibration. TBW was calculated from these values by applying a conversion factor of 1.04. This correction accounts for the exchange of labile hydrogen that occurs in humans during the equilibration period (20). FFM was calculated by assuming a hydration factor of 0.73. Bromide concentration in serum ultrafiltrate was determined by HPLC according to the anion-exchange chromatographic method (21). ECW was estimated by the corrected bromide space (CBS) and calculated according to the following formula:

$$CBS = \frac{Br_{\text{dose}} \text{ (mmol)}}{(Br_f - Br_b) \text{ (mmol/L)}} \times 090 \times 0.95 \quad (1)$$

where  $Br_f$  is the final bromide concentration in the serum ultrafiltrate (after 10 h of equilibrium),  $Br_b$  is the background bromide concentration from the initial blood sample, 0.90 is the correction factor for the bromide in the nonextracellular sites, and 0.95 is the correction factor for the Donan equilibrium.

### Blood analysis

From the blood drawn for the analysis of CBS, concentrations of albumin and chloride were also determined by an automated system (Cobas Mira; Hoffmann-La Roche, Basel, Switzerland). Serum sodium and potassium concentration were determined by a flame photometer (243; Instrumentation Laboratory, Ysselstein, Netherlands). Hematocrit was determined after separation of the whole blood.

### Pulmonary function tests

Lung function tests consisted of flow volume measurements [ $FEV_1$  and forced vital capacity (FVC)]. The highest value of at least three measurements was used and expressed as a percentage of the reference value (22).

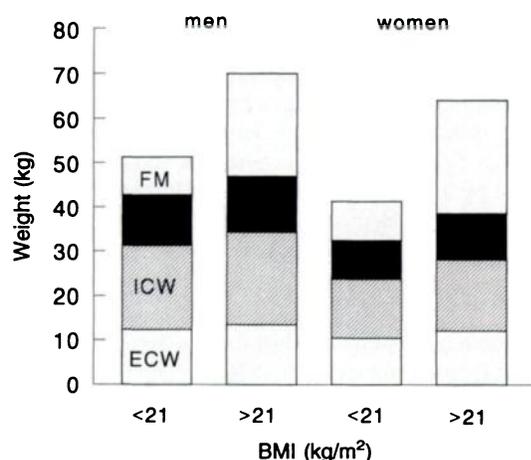
### Data analysis

Results are given as means  $\pm$  SDs. Differences between groups were analyzed with an unpaired Student's *t* test or in the case of small group sizes the Mann-Whitney *U* test. The level of significance was determined as a *P* value  $\leq 0.05$ . The SPSS/PC+ (SPSS Inc, Chicago) computer software program was used for statistical analyses. A body mass index (BMI; in  $kg/m^2$ ) of 21 was used to divide the patient population into underweight and normal-weight groups. In addition, on the basis of the total patient group median FFM index (FFMI;  $FFM/height^2$ , an analog to BMI), 15, the patients were divided into depleted and nondepleted groups.

## RESULTS

There was one patient with a significantly and disproportionately high ECW-TBW ratio of 64.5% (analyzed with the Bonferroni-corrected outlier test). This patient was excluded from further statistical analysis. Of the remaining 38 patients, mean age was  $65 \pm 10$  y for women and  $65 \pm 8$  y for men (NS). Mean  $FEV_1$  was  $40.3 \pm 11.6\%$  of predicted for women and  $36.2 \pm 14.7\%$  of predicted for men. The BMI ranged widely from 13.6 to 31.0; mean BMI was  $22.1 \pm 5.1$  for women and  $22.6 \pm 3.7$  for men (NS). The mean ECW-ICW ratio was significantly different for men ( $0.67 \pm 0.15$ ) and for women ( $0.78 \pm 0.12$ ,  $P < 0.05$ ).

In **Figure 1** the mean body composition values of underweight ( $n = 12$ ) and normal-weight ( $n = 26$ ) men and women are shown. Underweight women ( $n = 5$ ) were characterized by a significantly lower FM ( $8.9 \pm 5.6$  kg or  $21.0 \pm 11.4\%$  of wt compared with  $25.4 \pm 9.8$  kg, or  $38.8 \pm 8.8\%$  of wt,  $P < 0.01$ ), a tendency toward a lower TBW ( $23.6 \pm 3.6$  compared with  $27.9 \pm 2.9$  L,  $P = 0.05$ ), and a similar ECW ( $10.4 \pm 1.8$  compared with  $12.1 \pm 1.1$  L, NS) than the normal-weight women ( $n = 9$ ). No significant difference was found in the ECW-ICW ratio between underweight women ( $0.79 \pm 0.09$ ) and normal-weight women ( $0.78 \pm 0.14$ ). Compared with normal-weight men ( $n = 17$ ), underweight men ( $n = 7$ ) were also characterized by a significantly lower FM ( $8.5 \pm 3.1$  kg or  $16.7 \pm 6.5\%$  of wt compared with  $23.1 \pm 5.1$  kg or  $32.9 \pm 5.8\%$  of wt,  $P < 0.001$ ), a nonsignificantly lower TBW ( $31.2 \pm 3.5$  compared with  $34.1 \pm 3.8$  L, NS), and a similar ECW ( $12.4 \pm 1.2$  L versus  $13.5 \pm 2.4$  L, NS). The ECW-ICW ratio was also not significantly different between underweight men ( $0.68 \pm 0.13$ ) and normal-weight men ( $0.67 \pm 0.16$ ).



**FIGURE 1.** Body composition of patients with a low ( $\leq 21$ ) or normal ( $> 21$ ) BMI.  $n = 24$  men, 14 women. FM, fat mass; ICW, intracellular water; ECW, extracellular water.

On the basis of FFM, the body composition of the study population was divided into depleted patients (FFMI  $\leq 15$ ) and nondepleted patients (FFMI  $> 15$ ); the results are presented in **Table 1**. Patients with wasting of FFM did not have a lower BMI or a significantly different FM (depleted:  $18.4 \pm 9.2$  kg, nondepleted:  $19.7 \pm 9.8$  kg; NS) or percentage FM (depleted:  $31.5 \pm 11.3\%$ , nondepleted:  $28.3 \pm 10.6\%$ ). TBW was significantly lower in the depleted patients ( $26.9 \pm 3.7$  L) than in the nondepleted patients ( $33.9 \pm 3.6$  L,  $P < 0.001$ ). However, ECW was not significantly lower in depleted patients, men ( $12.1 \pm 1.8$  L) or women ( $11.1 \pm 1.52$  L), compared with nondepleted men ( $13.6 \pm 2.2$  L) and women ( $12.4 \pm 1.4$  L). The ECW-ICW ratio was significantly higher in depleted women ( $0.82 \pm 0.12$ ) than in nondepleted women ( $0.70 \pm 0.08$ ,  $P < 0.05$ ). In men the depleted patients also had a higher ECW-ICW ratio ( $0.72 \pm 0.20$ ) than the nondepleted men

( $0.65 \pm 0.13$ ) but the difference was not significant. Serum hematocrit values and concentrations of sodium, potassium, and chloride were not significantly different between depleted and nondepleted patients.

Although there was no relation between ECW-ICW ratio and BMI (**Figure 2**), a weak but significant linear relation was found between ECW:ICW and FFMI ( $r^2 = 0.14$ ,  $P < 0.05$ ). **Figure 2** shows that all patients with an FFMI  $< 14$ , and nearly all patients with an FFMI  $< 15$  had an elevated ECW-ICW ratio. No significant correlation was found between FFMI and FM/height<sup>2</sup> (**Figure 3**).

## DISCUSSION

This study shows that tissue wasting occurred despite a relative sparing of FM in patients with clinically stable COPD. Fluid shifts manifested as a relative increase in ECW can occur in COPD patients with extreme FFM wasting. It is suggested that below an FFMI of 15, body composition is generally characterized by a relatively increased ECW.

Measurement of body composition is important in the clinical evaluation of (chronic) wasting disease and acute metabolic stress. Assessment of the magnitude of the energy exchanging part of the body is important for the interpretation of functional capacity, and the evaluation of nutritional, pharmacologic, and training interventions (24).

Weight loss and tissue wasting may be due to a decreased food intake, disease-related metabolic stress, or a combination of these two. A catabolic state is generally defined as "malnutrition" or "undernutrition," which may be confusing because these terms only refer to the nutritional cause of weight loss. Earlier we mentioned that, especially in wasting disease, it would be more appropriate to call patients depleted instead of malnourished (2). Kinney and Weissman (25) also made a distinction between depletion after a reduced intake ("un-

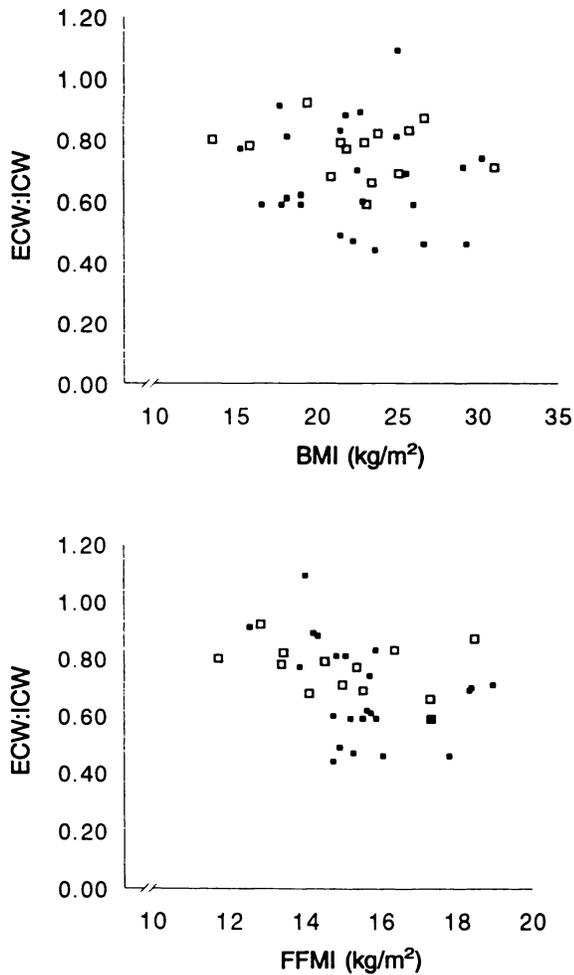
**TABLE 1**

Characteristics of chronic obstructive pulmonary disease in patients with fat-free-mass indexes (FFMI; kg/m<sup>2</sup>)  $\leq$  and  $> 15^1$

Variable	FFMI $\leq 15$			FFMI $> 15$		
	All ( $n = 17$ )	Men ( $n = 7$ )	Women ( $n = 10$ )	All ( $n = 21$ )	Men ( $n = 17$ )	Women ( $n = 4$ )
BMI (kg/m <sup>2</sup> )	21.0 $\pm$ 4.2	21.2 $\pm$ 2.3	20.9 $\pm$ 5.2	23.5 $\pm$ 3.9	23.2 $\pm$ 4.0	25.1 $\pm$ 3.7
FFMI (kg/m <sup>2</sup> )	13.9 $\pm$ 0.9	14.3 $\pm$ 0.8	13.7 $\pm$ 0.9	16.5 $\pm$ 1.3 <sup>2</sup>	16.7 $\pm$ 1.3 <sup>2</sup>	15.9 $\pm$ 0.9 <sup>3</sup>
Fat mass						
(kg)	18.4 $\pm$ 9.2	19.4 $\pm$ 5.8	17.7 $\pm$ 11.3	19.7 $\pm$ 9.8	18.6 $\pm$ 9.1	24.3 $\pm$ 12.9
(% by wt)	31.5 $\pm$ 11.4	31.8 $\pm$ 9.1	31.4 $\pm$ 14.2	28.3 $\pm$ 10.6	26.6 $\pm$ 10.3	35.2 $\pm$ 10.2
TBW (L)	26.9 $\pm$ 3.7	29.7 $\pm$ 2.7	24.9 $\pm$ 3.0	33.9 $\pm$ 3.6 <sup>2</sup>	34.7 $\pm$ 3.3 <sup>3</sup>	30.3 $\pm$ 2.4 <sup>3</sup>
ECW (L)	11.5 $\pm$ 1.7	12.1 $\pm$ 1.8	11.1 $\pm$ 1.5	13.2 $\pm$ 2.1 <sup>3</sup>	13.6 $\pm$ 2.2	12.4 $\pm$ 1.4
ECW:TBW (%)	43.2 $\pm$ 5.4	41.1 $\pm$ 7.2	44.7 $\pm$ 3.3	39.5 $\pm$ 4.4 <sup>4</sup>	39.1 $\pm$ 4.7	40.9 $\pm$ 2.9 <sup>4</sup>
ECW:ICW	0.78 $\pm$ 0.16	0.72 $\pm$ 0.2	0.82 $\pm$ 0.12	0.66 $\pm$ 0.12 <sup>4</sup>	0.65 $\pm$ 0.1	0.69 $\pm$ 0.08 <sup>4</sup>
Albumin (g/L)	36.7 $\pm$ 1.6	35.8 $\pm$ 1.2	37.4 $\pm$ 1.6	37.3 $\pm$ 2.1	37.5 $\pm$ 1.9 <sup>4</sup>	36.7 $\pm$ 2.9
Hematocrit (l)	0.412 $\pm$ 0.033	0.413 $\pm$ 4.6	0.411 $\pm$ 0.023	0.418 $\pm$ 0.028	0.417 $\pm$ 0.028	0.423 $\pm$ 0.029
Serum Na (mmol)	138.1 $\pm$ 2.3	139.3 $\pm$ 1.7	137.3 $\pm$ 2.3	139.0 $\pm$ 3.9	139.6 $\pm$ 3.6	136.5 $\pm$ 5.2
Serum K (mmol)	4.3 $\pm$ 0.5	4.1 $\pm$ 0.5	4.5 $\pm$ 0.5	4.3 $\pm$ 0.5	4.2 $\pm$ 0.4	4.6 $\pm$ 0.8
Serum Cl (mmol)	101.2 $\pm$ 4.5	102.3 $\pm$ 2.9	100.5 $\pm$ 5.3	101.1 $\pm$ 5.1	101.7 $\pm$ 5.1	98.5 $\pm$ 5.1

<sup>1</sup>  $\bar{x} \pm$  SD. TBW, total body water; ECW, extracellular water estimated by corrected bromide space; ECW:TBW, extracellular water as a percentage of TBW.

<sup>2-4</sup> Significantly different from group or subgroup with FFMI  $\leq 15$  (Mann-Whitney  $U$  test for men and women separately, paired  $t$  test for men and women together): <sup>2</sup>  $P < 0.001$ , <sup>3</sup>  $P < 0.01$ , <sup>4</sup>  $P < 0.05$ .



**FIGURE 2.** Relation between the extracellular (ECW)-intracellular water (ICW) ratio and BMI or fat-free-mass index (FFMI) for men (■) and women (□). Upper panel: linear association:  $r^2 = 0.01$ ; NS ( $n = 38$ ). Lower panel: linear association:  $r^2 = 0.14$ ;  $P < 0.05$  ( $n = 38$ ).

stressed” depletion) or associated with a disease condition (“stressed” depletion), in view of different body-composition changes in these conditions (25). Recent studies, however, suggest that body-composition changes also vary between different (acute or chronic) diseases (26–30).

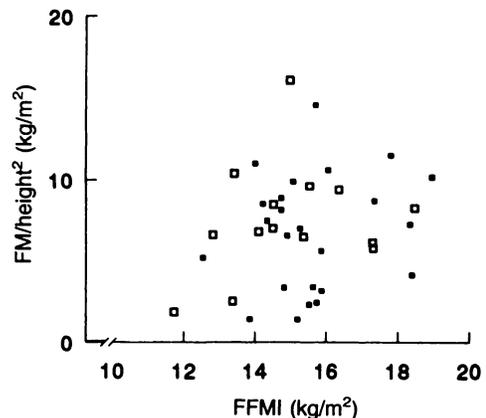
The effects of total starvation on body composition and body water compartments have rarely been studied. In a case report of total starvation associated with acute and rapid weight loss in a normal-weight subject, clinical edema was not observed (31). Several studies of total starvation have been performed in obese subjects (32–34), and they all reported a reduction of FM as well as lean tissue loss, but unfortunately, no measurements of ECW were made. One study in seven obese subjects with an extremely long fasting period (20–48 wk) reported a 25–67-kg loss of weight, 8–20-L loss of TBW resulting from a loss of ICW (5–15 L), as well as a loss of “sodium space” (or ECW) of 0–7 L (35). On the contrary, the effects of chronic partial starvation (50–60% of normal dietary intake) on body composition were thoroughly studied in the historical studies by Keys et al (17) and more recently by Barac-Nieto et al (16). The changes described included a large decrease in FM, a decrease in BCM, no changes in absolute ECW, but because of the

reduced body weight a relative increase in ECW. Partial (relatively short) starvation in obese subjects, however, resulted in an increase in ICW (instead of a decreased BCM), and no change or a decrease in relative ECW (36).

The effects of stressed depletion on body composition have been studied in great detail by Moore et al (15) and Schizgal (14) in hospitalized patients using isotope dilution methods. They described a depleted state after acute metabolic stress that was associated with a decreased FM, a decreased BCM, but an absolutely as well as relatively increased ECW (25).

Recently, more studies have been performed of body (water)-composition changes in chronic wasting diseases. Schizgal (37) found in a subgroup of depleted cancer patients a decrease in BCM, an (absolute and relative) increase in ECW, and a massive reduction of FM. Several studies in lung cancer patients found mainly a reduction of FM instead of FFM in patients losing weight (38, 39), but measurements of ECW were not made in these studies. Another recent study in cancer patients (cancer of the stomach, esophagus, or pancreas) found a decrease in body weight and BCM (measured with  $^{40}\text{K}$ ), but no reduction of BCM as a percentage of body weight, indicating that only in patients with dramatic fat loss would ECW be increased (40). In AIDS, a chronic wasting disease, two studies by Kotler et al (29, 30) showed that there was no evidence for an increased ECW (measured with dilution methods and measurements of BCM with  $^{40}\text{K}$ ). The authors stated that the wasting observed in AIDS was similar to historical reports of semistarvation. These recent studies show different patterns of body composition in chronic diseases that can deviate from body-composition changes assumed to be associated with acute metabolic stress. This was also found in patients with myelomeningocele or spina bifida (depletion of BCM, absolute or relative increases in ECW, but increased relative FM) (41), spinal cord injury (body weight and TBW reduction, but only a relative increase in ECW) (42), and liver cirrhosis (heterogeneous presentation of body-composition changes) (26, 27, 43).

Why is COPD an interesting chronic wasting disease with respect to metabolism? On the one hand, COPD patients represent a homogeneous population with a normal dietary intake (44, 45) and no gastrointestinal abnormalities. On the other hand, a substantial percentage of depleted COPD patients do not manifest the natural metabolic adaptation to weight loss but



**FIGURE 3.** Relation between fat mass (FM)/height<sup>2</sup> and fat-free-mass index (FFMI) for men (■) and women (□). Linear association:  $r^2 = 0.04$ ; NS ( $n = 38$ ).

have an increased resting energy expenditure (46, 47). Furthermore, total daily energy expenditure can be increased in COPD patients, even independently of an increased resting energy expenditure (48). Factors contributing to the elevated resting energy expenditure in these patients can be a chronic inflammatory state (49), medication such as theophylline and  $\beta_2$  agonists (50), and the oxygen cost of breathing (51, 52). Furthermore, COPD is associated with periods of acute disease exacerbations during which energy expenditure is further elevated (53), possibly associated with catabolism.

In an earlier study we observed that body composition in depleted COPD patients was different from the body composition of patients with acute metabolic stress (2). Wasting of FFM appeared to also occur in stable, normal-weight COPD patients. This observation was confirmed in the present study because FFMI was not significantly correlated with percentage FM (or  $\text{FM}/\text{height}^2$ ). Therefore, the patients with severe wasting of FFM still had a percentage FM similar to that of the patients with a normal FFM. Patients with COPD are usually relatively inactive because of their dyspnea and ventilatory and metabolic limitations. Inactivity may affect FFM more than FM, independently of an impaired energy balance. Comparable results were found in patients with myelomeningocele (42). These patients had a depletion of BCM, an absolute as well as relative increase in ECW, but a relatively high percentage FM. The latter was especially evident in the nonambulatory group of patients. FFM in COPD can also be affected by a disturbed intermediate muscle (exercise) metabolism (lower intracellular pH, and ATP depletion), which has been observed in recent studies by using  $^{31}\text{P}$  nuclear magnetic resonance measurements (54, 55). It has been hypothesized that factors like hypoxemia, hypercapnia, and/or medication (corticosteroids) could contribute to the disturbed intermediate muscle metabolism and atrophy of type IIb muscle fibers in COPD patients. Another explanation for the relatively high percentage fat may be the use of corticosteroids prescribed as maintenance medication or during exacerbations. In animal studies corticosteroids were shown to stimulate food intake and the maintenance of body fat despite a reduced body weight (56).

Another deviation in the body composition of depleted COPD patients compared with the general observations associated with acute depletion is the fact that fluid shifts could not be detected by stratification of the group by body weight. BMI was not correlated with the ECW-ICW ratio. Stratification of patients by FFMI, however, showed that the ECW-ICW ratio was significantly higher in the depleted women. In men, the ECW-ICW ratio was not significantly higher in patients with depletion of FFM, but wasting of FFM in men was associated with a significantly lower TBW without a decreased ECW. Indications of a relatively increased ECW in COPD patients were found earlier (57). This observation results in two interesting issues, which, to our knowledge, have not been discussed previously for chronic wasting diseases. Because  $\text{FM}/\text{height}^2$  was not correlated with FFMI, the patients with FFM depletion who had a significantly higher ECW-ICW ratio had a relatively spared FM. Second, the results of this study suggest that below a certain critical point of FFM wasting a relative increase in ECW is more likely to occur. However, note that the variance of the ECW-ICW ratio was high in the patients with a higher FFMI and that in men the relation between depletion and fluid shifts was not as clear as it was in women.

The difference between men and women is difficult to explain, and to our knowledge was not observed and discussed earlier. The increased ECW-ICW ratio in depleted patients might be explained by the theories of Flear and Singh (58). They suggested that the cell membrane function is probably altered in disease ("sick cells"), especially the function regulating osmolarity, causing fluid shifts. This could also mean that the changes in the cell membrane caused bromide leakage to the ICW, and ECW in fact was not increased, but Flear and Singh said that the ECW is likely to increase in the case of "sick cells." Häussinger et al (59) also posited interesting theories concerning cellular hydration state in catabolism and stated that factors like inflammatory state, amino acid starvation, and stress conditions that result in hormonal alterations (low insulin, high glucagon and catecholamines) could favor cell shrinkage (water flow out of the cell). Cell shrinkage would act as a catabolic signal. The chronic inflammatory state in COPD patients, especially in depleted patients or those losing weight (49, 60), could be important with respect to the theories of Häussinger et al. Furthermore, pharmacologic treatment in many COPD patients includes  $\beta_2$ -sympathomimetics, which can influence  $\text{Na}^+ - \text{K}^+ - \text{ATPase}$  activity (61). In the study by Hofford et al (62), increased norepinephrine concentrations were observed in COPD patients. With respect to the theories of Häussinger et al (59) these factors might also be important for fluid shifts.

A relative increase in ECW implies that BCM is overestimated in these patients (by 13–30%) by the measurement of FFM. As a consequence, the increased resting energy expenditure found earlier (48) or total daily energy expenditure (49) despite a low FFM in COPD patients may therefore have even underestimated the metabolic derangements in COPD.

Finally, is the use of a theoretical constant hydration factor to calculate FFM valid in depleted patients? In a study by Beddoe et al (63), the hydration of FFM was studied in protein-depleted patients. The 95 patients who were studied had undergone surgery and were selected for intravenous nutrition. The mean hydration of these patients was 0.719, which was significantly lower than that of the control group (0.741). However, there were still 48 patients with a normal hydration factor despite a 15% loss of body protein. A recent study by Royal et al (64) showed that in malnourished patients (mean BMI < 21) with Crohn disease the hydration of FFM (measured by dual-energy X-ray absorptiometry and isotope dilution) was 71.1%, which was not significantly different from the theoretical value of hydration, 73%, as well as the hydration in healthy humans, 71.9%, studied by Streat et al (65). Furthermore, Streat et al also reported that depleted patients (who underwent surgery) had a hydration of FFM comparable with that of normal volunteers.

In summary, we found that COPD patients with FFM wasting showed an increased ECW-ICW ratio. This was especially evident in those with extreme FFM wasting, many of whom had a relatively spared FM. This study showed that in a chronic disease such as COPD, which is associated with weight loss and/or tissue wasting, body-composition changes may deviate from the usually ascribed (acute) disease-related changes, or those after reduced energy intake. This study stresses the importance of a detailed measurement of body composition in chronic wasting diseases to investigate further the prevalence

of body-water compartment fluid shifts and the possible causes for this phenomenon. 

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