Weight Loss Is a Reversible Factor in the Prognosis of Chronic Obstructive Pulmonary Disease

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The objective of the study was to further unravel the prognostic significance of body weight changes in patients with COPD. Two survival analyses were performed: (*1*) a retrospective study, including 400 patients with COPD none of whom had received nutritional therapy; (*2*) a *post hoc* analysis of a prospective study, including 203 patients with COPD who had participated in a randomized placebo-controlled trial. There was no overlap between the patient groups. Baseline characteristics of all patients were collected on admission to a pulmonary rehabilitation center in stable clinical condition. In the prospective randomized placebo-controlled trial, the physiologic effects of nutritional therapy alone ($n = 71$) or in combination with anabolic steroid treatment ($n = 67$) after 8 wk was studied in patients with COPD prestratified into a depleted group and a nondepleted group. Mortality was assessed as overall mortality. The Cox proportional hazards model was used to quantify the relationship between the baseline variables age, sex, spirometry, arterial blood gases, body mass index (BMI), smoking, and subsequent overall mortality. Additionally, the influence of treatment response on mortality was investigated in the prospective study. The retrospective study revealed that low BMI ($p < 0.001$), age ($p < 0.0001$) and low Pa_{O_2} ($p < 0.05$) were significant independent predictors of increased mortality. After stratification of the group into BMI quintiles a threshold value of 25 kg/m^2 was identified below which the mortality risk was clearly increased. In the prospective study, weight gain (> 2 kg/8 wk) in depleted and nondepleted patients with COPD, as well as increase in maximal inspiratory mouth pressure during the 8-wk treatment, were significant predictors of survival. On Cox regression analysis weight change entered as a time-dependent covariate remained an independent predictor of mortality in addition to all variables that were entered in the retrospective study. The combined results of the two survival analyses provide evidence to support the hypothesis that body weight has an independent effect on survival in COPD. Moreover the negative effect of low body weight can be reversed by appropriate therapy in some of the patients with COPD. Schols AMWJ, Slangen J, Volovics L, Wouters EFM. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease.

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Chronic obstructive pulmonary disease (COPD) is an invalidating disorder characterized by aggravating dyspnea, impaired exercise tolerance, and, frequently, weight loss associated with muscle wasting (1). Although weight loss commonly occurs, it is debatable whether this is an epiphenomenon of severe disease or an independent risk factor that should be treated. On the other hand, the relevance of weight loss and muscle wasting for the clinical condition has been clearly demonstrated in recent years by an adverse effect on physical performance (2) and respiratory muscle function (3), independent of the degree of airflow obstruction. Reported prevalence rates of muscle wasting in clinically stable patients range from 20 to 35% (4, 5).

An elevated energy metabolism not adequately met by an increased spontaneous dietary intake underlies weight loss in COPD (6). Several studies have shown that restoration of the energy balance by nutritional support results in a significant increase in body weight, fat-free mass, and respiratory muscle function (7–10), and even in the immune response (11). Long-term results of weight maintenance or weight gain on morbidity and mortality are not yet available. In retrospective survival studies, however, an inverse relationship between weight loss (12) and a low body weight (13, 14) with survival has been reported.

Here we present two survival studies to further unravel the prognostic significance of body weight changes in patients with COPD. Firstly, we performed a study of patients with moderate to severe COPD to investigate retrospectively the relation between body weight and survival, adjusting for the influence of age, sex, lung function, recent weight loss, and smoking. Thereafter, we performed a *post hoc* analysis utilizing data of a recently published placebo-controlled randomized nutritional intervention trial (10) to investigate prospectively the effects of treatment and treatment response (i.e., weight gain and improvement of maximal inspiratory mouth pressure) on survival.

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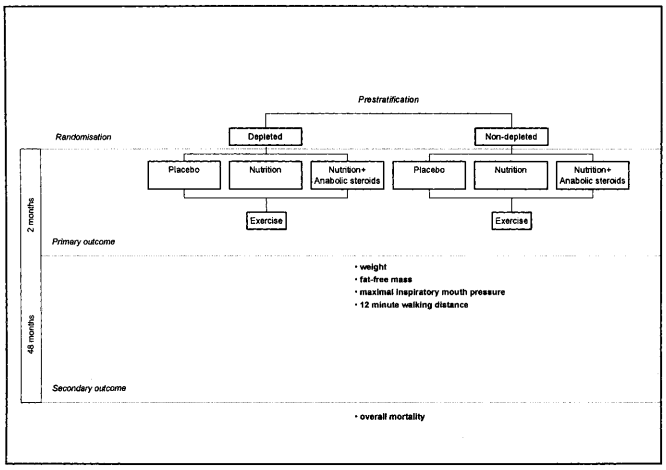

Figure 1. Design of prospective study.

TABLE 1

PATIENT CHARACTERISTICS

	Retrospective Study (*n = 400*)		Prospective Study (*n = 203*)	
	Mean	SEM	Mean	SEM
Age, yr	65	0.5	65	0.6
FEV_1, pre %pred	37	0.7	34	1.1
FEV_1, post %pred	40	0.6	36	1.0
FEV_1, post/pre %	109	0.5	108	0.6
IVC, %pred	74	0.9	68	1.3
Pa_{O_2}, kPa	9.0	0.07	8.7	0.1
Pa_{CO_2}, kPa	5.4	0.05	5.4	0.05
BMI, kg/m^2	24.0	0.2	21.5	0.2

Definition of abbreviations: pre = prebronchodilator; post = postbronchodilator; IVC = inspiratory vital capacity; Pa_{O_2} = resting arterial oxygen tension; Pa_{CO_2} = resting arterial carbon dioxide tension; BMI = body mass index.

METHODS

Study Design

Retrospective study. Data were collected from patients with COPD admitted to a pulmonary rehabilitation center between January 1, 1986 and January 1, 1990. Patients are referred to this center by their pulmonary physician in a stable clinical condition to participate in an inpatient pulmonary rehabilitation program (mean duration, 10 wk). Patients were eligible for the study if they had COPD according to the American Thoracic Society guidelines (1), $FEV_1 < 70\%$ of predicted with an increase in $FEV_1 < 15\%$ of the predicted value after administration of a bronchodilating agonist (400 μg salbutamol). Those with unstable disease or with other confounding disorders such as malignancies, insulin-dependent diabetes mellitus, and thyroid or cardiovascular disease were excluded. None of the patients had received nutritional therapy prior to or during the rehabilitation period.

Prospective study. The prospective study was a *post hoc* analysis of a randomized placebo-controlled trial (10) of 203 patients that was performed between January 1, 1988 and January 1, 1992. In this study the effects of nutritional support, alone or in combination with anabolic steroids, on body weight, body composition (fat mass and fat-free mass), and physiologic function was investigated for 8 wk. In addition to the above-mentioned selection criteria with respect to COPD and confounding disorders, patients with a body mass index (BMI) $> 29\ kg/m^2$ were excluded from the intervention trial. There was no overlap with the patient population that was analyzed in the retrospective study. Patients were prestratified into a depleted and a nondepleted group on the basis of a low body weight and/or a low fat-free mass, such as previously described (10). Nutritional support (n = 71) consisted of a daily high caloric liquid supplement (420 kcal/200 ml: 51% fat, 35% carbohydrate, 14% protein; mixture of Nutridrink, Protifar, Fantomalt [N.V. Nutricia, Zoetermeer, The Netherlands], and oil). Anabolic steroid treatment (n = 67) consisted of four (two-weekly administered) intramuscular injections with nandrolone decanoate (Decadurabolin [N.V. Organon, The Netherlands]; men: 50 mg, women: 25 mg). The placebo group (n = 65) received intramuscular injections with nandrolon decanoate vehicle (arachis oil). Daily nutritional supplementation could not be administered in a double-blind fashion. The study design is schematically displayed in Figure 1.

Measurements

FEV_1 and inspiratory vital capacity (IVC) were measured with a wet spirometer; the highest value of at least three acceptable spirometric maneuvers was used. Prebronchodilator and postbrochodilator FEV_1 and IVC were expressed as a percentage of the reference values (15). Arterial blood gases were drawn by puncture of the brachial artery at rest while the subjects breathed room air. Pa_{O_2} and Pa_{CO_2} were analyzed on a blood gas analyzer (ABL 330; Radiometer, Copenhagen, Denmark). Body height was measured with subjects standing barefoot and determined to the nearest 0.5 cm (Lameris WM 715; Breukelen). Body weight without clothes was measured on a beam scale (SECA, Germany). Respiratory muscle strength was measured as mouth pressure during maximal static inspiratory (PI_{max}) maneuvers from RV using the technique described by Black and Hyatt (16). The best of three reproducible efforts was chosen. Exercise performance was evaluated with a 12-min walk along an indoor corridor 100 m long. All tests were performed in the early afternoon, and no encouragement was given. Walking distance was not evaluated in patients suffering from chronic hypoxemia or with locomotor ailments.

Statistical Analysis

Univariate analysis of survival was performed using the Kaplan-Meier method (17). A log-rank chi-square test for comparing the survival between groups was used to analyze the association of clinical characteristics at entry with survival. Mortality was assessed as overall mortality from all causes. A two-sided value of $p < 0.05$ was considered significant. Patients were stratified into two subgroups by the degree of airflow obstruction ($FEV_1 <$ or $\geq 45\%$), by the presence of chronic hypoxemia ($Pa_{O_2} < 7.3$ kPa) and by the presence of chronic hypercapnia ($Pa_{CO_2} > 6.0$ kPa). Kaplan-Meier survival curves were calculated for four BMI classes based on commonly used criteria of leanness and obesity (< 20: underweight, 20 to 24: normal; 24 to 29: overweight; > 29: obese). Because the patients were unequally distributed among these four groups, an additional stratification into BMI quintiles was performed (I: < 20.5; II: 20.5 to 22.8; III: 22.9 to 25.0; IV: 25.1 to 27.6; V: > 27.6). Patients were further characterized by smoking (current smoking/nonsmoking) and weight history (weight loss > 10% of baseline).

The Cox proportional hazards model was used to quantify the relationship between the baseline variables (age, sex, FEV_1, IVC, Pa_{O_2}, Pa_{CO_2}, BMI, and smoking) and subsequent overall mortality. The relative risk (RR) corresponding to a risk factor in this model is the exponential of the regression coefficient. Data were analyzed using the SPSS for Windows statistical package (SPSS Inc., Chicago, IL) (18).

Prior to the prospective survival study, treatment response was defined as an increase in body weight > 2 kg (3.5% of baseline) during the 8-wk intervention period, based on previous nutritional intervention studies (8–10) and subsequently the influence of the treatment response (significant increase in body weight and improvement of PI_{max} as primary outcome measure) on survival was analyzed in an univariate analysis using the Kaplan-Meier method. Subsequently, weight change was entered as a time-dependent covariate in a Cox proportional hazards model adjusting for change in PI_{max} treatment and other possible contributors to overall mortality that were studied in the retrospective analysis.

RESULTS

Retrospective Study

Patient characteristics are given in Table 1. The study group consisted of 400 patients with COPD with a moderate to se-

vere airflow obstruction, 72% of whom were male. Maintainance medication consisted of beta$_2$-sympathicomimetics (96%), theophyllines (82%), ipratropium bromide (90%), and inhalation corticosteroids (73%); 50% were receiving oral corticosteroids. Mean BMI amounted to 24.0 (4.6) kg/m^2 ranging from 12.9 to 41.7 kg/m^2. No difference in age, IVC, and resting arterial blood gas determinations were seen between the classes, but FEV_1 was significantly lower in the underweight (33 [12]%) and normal weight (36 [11]%) patients compared with the overweight (39 [13]%) and obese patients (45 [14]%). A history of weight loss amounting to $> 10\%$ of habitual body weight was reported by 49% of the underweight group, 29% of the normal weight group, 16% of the overweight group, and 0% of the obese group.

Survival was significantly decreased in both underweight and normal weight patients as compared with overweight and obese patients. (Figure 2, *upper panel*) ($p < 0.0001$). A history of weight loss was also significantly related to decreased survival ($p < 0.005$). Kaplan-Meier plots further indicated a decreased survival in the group with severe airflow obstruction (Figure 2, *lower panel*) ($p = 0.0072$) and in the group suffering from chronic hypoxemia (Figure 3, *upper panel*) ($p < 0.0018$) or chronic hypercapnia (Figure 3, *lower panel*) ($p < 0.001$). The majority of patients were current or ex-smokers. Smoking behavior in this group of patients with severe COPD did not significantly influence survival rates. The results of the Cox proportional hazards model are shown in Table 2. BMI as continuous variable was a significant predictor of survival in addition to age and Pa_{O_2}. In this model IVC as percentage of predicted, FEV_1 as percentage of predicted, Pa_{CO_2}, sex, and smoking were not selected as independent contributors. Cox regression plots were made to compare BMI quintiles. For all other variables mean values were used in this model. A noteworthy pattern in these plots is shown in Figure 4. The three lower quintiles (BMI < 25 kg/m^2) nearly overlapped but were significantly lower than the two upper quintile plots.

Prospective Study

Baseline physical and lung function characteristics were not significantly different between the treatment groups (i.e., placebo, nutrition, nutrition and anabolic steroids). Short-term treatment results have been reported before (10). In summary, nutritional intervention resulted in a significant increase in weight, fat-free mass, and fat-mass, whereas no significant changes in any of these parameters was seen in the placebo group. Relative to a similar body weight gain as the group receiving nutritional support only, the anabolic steroids group showed a larger increase in fat-free mass and maximal inspiratory mouth pressure without causing adverse side effects.

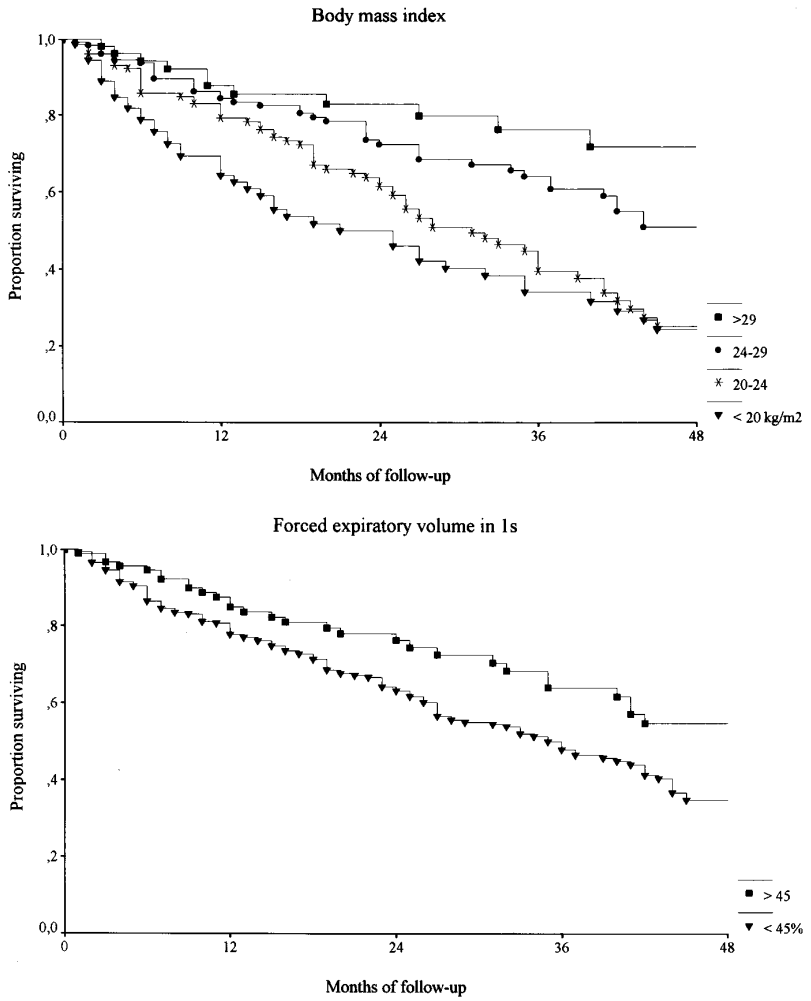

Figure 2. Kaplan-Meier plots of retrospective study. (*Upper panel*) Body mass index (kg/m^2). (*Lower panel*) FEV_1 (%).

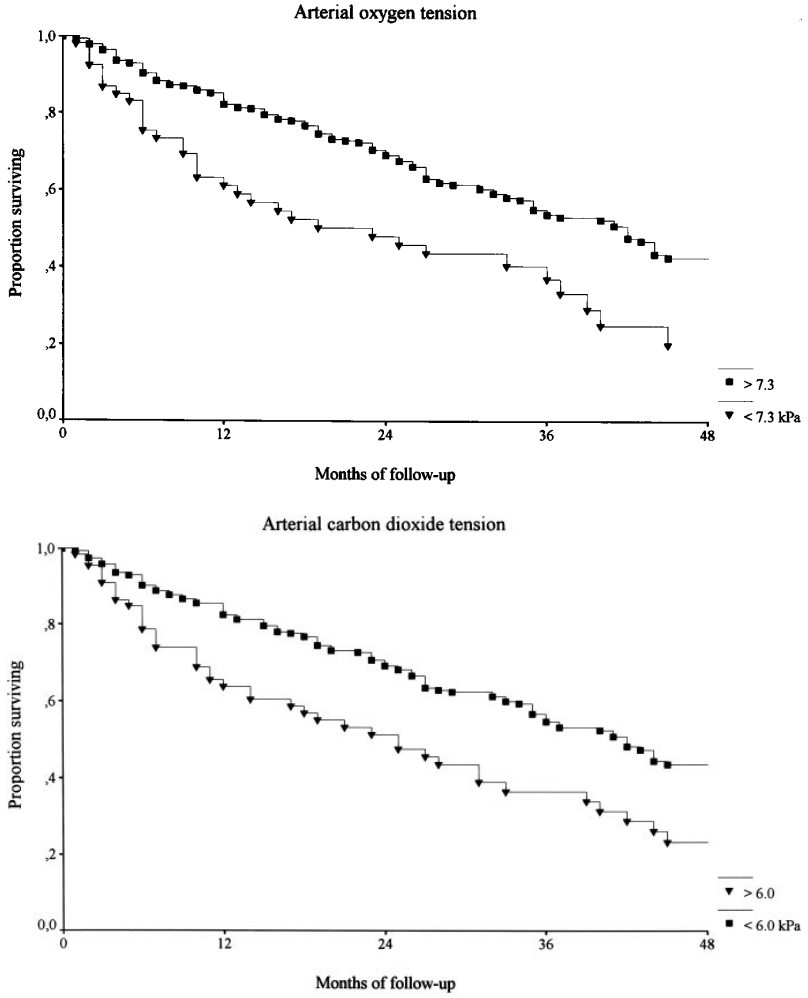

Figure 3. Kaplan-Meier plots of retrospective study. (*Upper panel*) arterial oxygen tension (kPa). (*Lower panel*) arterial carbon dioxide tension (kPa).

No significant difference between the treatments on survival was shown (Table 3). On the basis of body weight change $>$ 2 kg/8 wk, 50% of the treated patients were characterized as responders, including 24% of the placebo group. In 62% of the patients an improvement in $P_{I_{max}}$ was shown. Weight gain in depleted and non-depleted patients with COPD was significantly associated with decreased mortality risk (Figure 5, *upper panel*), and also improvement in $P_{I_{max}}$ during the rehabilitation period was associated with decreased mortality risk (Figure 5, *lower panel*). Survival was not related to baseline 12-min walking distance or to the change in 12-min walking distance obtained during the rehabilitation program. On multivariate analysis weight gain in depleted and non-depleted patients with COPD was an independent predictor of survival in addition to BMI and age.

DISCUSSION

The combined results of the two survival analyses provide further evidence to support the hypothesis that body weight has an independent effect on survival in COPD. Moreover, the negative effect of low body weight can be reversed by appropriate therapy.

Survival data in COPD are limited. Older studies were performed in selected groups of patients and often included too few patients for valid survival analysis (3, 14, 19, 20). Our study was also performed in a selected group of patients, i.e., those eligible for pulmonary rehabilitation, but the setting provided an excellent opportunity to examine our research question with a careful characterization of patients and standardized therapy. Furthermore, the inverse relationship between BMI and survival was found in addition to known single risk factors such as age (20), FEV_1 (14, 20, 21), and Pa_{O_2} (22) and Pa_{CO_2} (21, 22).

TABLE 2

MULTIVARIATE ANALYSIS OF PREDICTORS OF MORTALITY: RETROSPECTIVE STUDY

Variables		RR	95% CI	p Value
BMI, kg/m^2	Linear	0.928	0.894–0.963	$<$ 0.0001
Age, yr	Linear	1.041	1.002–1.062	$<$ 0.0001
Pa_{O_2}, kPa	Linear	0.862	0.752–0.975	$<$ 0.005
Pa_{CO_2}, kPa	Linear	1.129	0.929–1.372	NS
FEV_1, %	Linear	0.999	0.983–1.008	NS
IVC, %	Linear	1.000	0.989–1.011	NS
Men versus women		1.220	0.999–1.490	NS
Smoking versus nonsmoking		1.160	0.886–1.528	NS

Definition of abbreviations: RR = relative risk (Cox proportional hazard model); 95% CI = 95% confidence interval of RR. For other definitions, *see* Table 1.

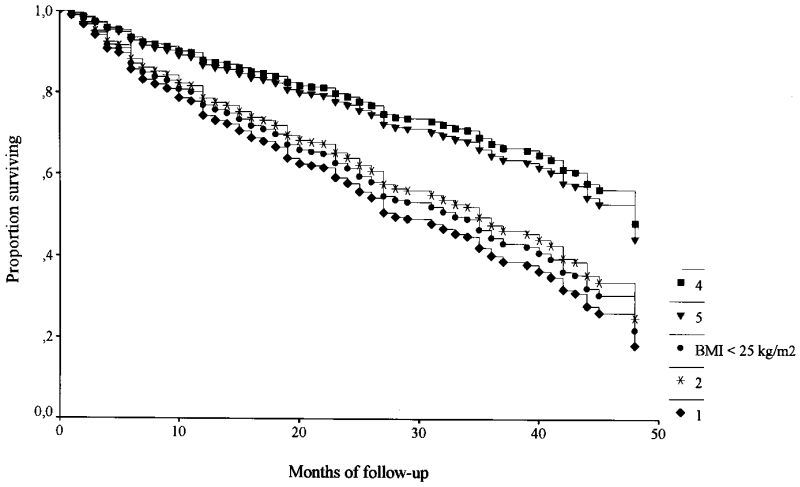

Figure 4. Cox regression plots of retrospective study. Body mass index (BMI) quintiles adjusted for age, sex, FEV_1, IVC, Pa_{O_2}, Pa_{CO_2}, and smoking.

Vandenbergh and coworkers (12) had highlighted already in 1968 a relation between weight loss and mortality in patients with end stage COPD (12). Five-year survival in the weight losing patients was 50% relative to 80% in the weight stable patients. More recently, Wilson and coworkers (13), utilizing data of the National Institutes of Health Intermittent Positive Pressure Breathing Trial (13), studied retrospectively the influence of body weight on survival in 779 male patients with COPD ($Pa_{O_2} > 7.3$ kPa; $FEV_1 < 60\%$). A borderline significant association ($p = 0.055$) was seen between body weight (expressed as a percentage of ideal weight) and survival, in a Cox proportional hazards model, after adjusting for age, postbronchodilator $\%FEV_1$, %TLC, exercise capacity, and heart rate. It is of interest to note that the strongest relation between body weight and survival was found in men with moderate airflow obstruction.

In contrast to the present study the most significant predictor besides age in the IPPB-trial (13) was postbronchodilator FEV_1, which may be related to a higher ratio between post/pre FEV_1 in this study compared with the present study. Furthermore, patients suffering from chronic hypoxemia, which was an independent risk factor in the present study, were excluded from the IPPB trial. More recently, Gray-Donald and coworkers (14) studied the role of the BMI in the prognosis of patients with severe COPD in a cohort of Canadian men and women, including those with hypoxemia, recruited for a clinical trial of negative pressure ventilation. In the total cohort, low BMI and use of home oxygen were independently associated with reduced survival.

When Cox regression plots were drawn to compare BMI quintiles adjusted for age, sex, FEV_1, IVC, Pa_{O_2}, Pa_{CO_2}, and smoking a striking finding in our retrospective analysis was that below the 3th quintile ($BMI < 25.0$ kg/m^2) the relative risk was clearly increased, but that the 3 lower quintiles nearly overlapped. In the study by Wilson and coworkers (13) survival was also remarkably longer in overweight to obese patients with COPD, body weight $> 110\%$ of predicted (ranging from 111 to 210%) compared with the normal weight group (ranging from 90 to 110%). This discrepancy could not be attributed to differences in spirometry or arterial blood gas determinations between the two groups. The present study did not discriminate for the type of disease. In an earlier study, Engelen and coworkers (6) showed a significant relationship between BMI and emphysema based on measurement of $D_{L_{CO}}$. Limited data are available on the prognostic value of $D_{L_{CO}}$ adjusted for spirometry, arterial blood gas measurements, and BMI. In the survival study by Vandenbergh and coworkers (12), no difference in $D_{L_{CO}}$ was shown between weight-stable and weight-losing patients and also no significant drop of $D_{L_{CO}}$ in the follow-up of the weight-losing patients. In a subgroup of hospitalized patients with COPD, Gray-Donald and coworkers found that low diffusing capacity was a significant predictor of respiratory mortality in addition to elevated Pa_{CO_2}, low BMI, and low PI_{max}.

At present the rationale for treatment modalities aimed at an increase in body weight in COPD is based on the observed relationship between weight loss, muscle wasting, and muscle weakness (2, 3) independent of the irreversible FEV_1, as well as the findings that respiratory muscle weakness and dyspnea are closely related. In three randomized controlled nutritional intervention trials (8–10) a clear short-term effect of nutritional supplementation has been shown on body weight, fat-free mass, and respiratory and peripheral skeletal muscle function, and in one of them also on exercise performance. The unique large size of the present study population allowed us to investigate *post hoc* the effects of the treatments as well as the treatment response on survival. As may be expected in view of the short intervention duration (8 wk) and the fact that the placebo group was also encouraged to optimize their

TABLE 3

MULTIVARIATE ANALYSIS OF PREDICTORS OF MORTALITY: PROSPECTIVE STUDY

Variables		RR	95% CI	p Value
Change in weight	Linear*	0.996	0.992–0.999	0.01
Change in PI_{max}	Linear	0.990	0.976–1.004	NS
Treatment	P versus A	0.753	0.447–1.267	NS
	N versus A	0.872	0.530–1.432	NS
BMI	Linear	0.868	0.803–0.939	< 0.001
FEV_1	Linear	0.983	0.962–1.003	NS
IVC	Linear	0.995	0.982–1.008	NS
Pa_{O_2}	Linear	0.877	0.751–1.024	NS
Pa_{CO_2}	Linear	0.977	0.707–1.352	NS
Age, yr	Linear	1.056	1.022–1.090	< 0.001

Definition of abbreviation: PI_{max} = maximal static inspiratory pressure. For other definitions, *see* Tables 1 and 2.

* Entered as time-dependent covariate.

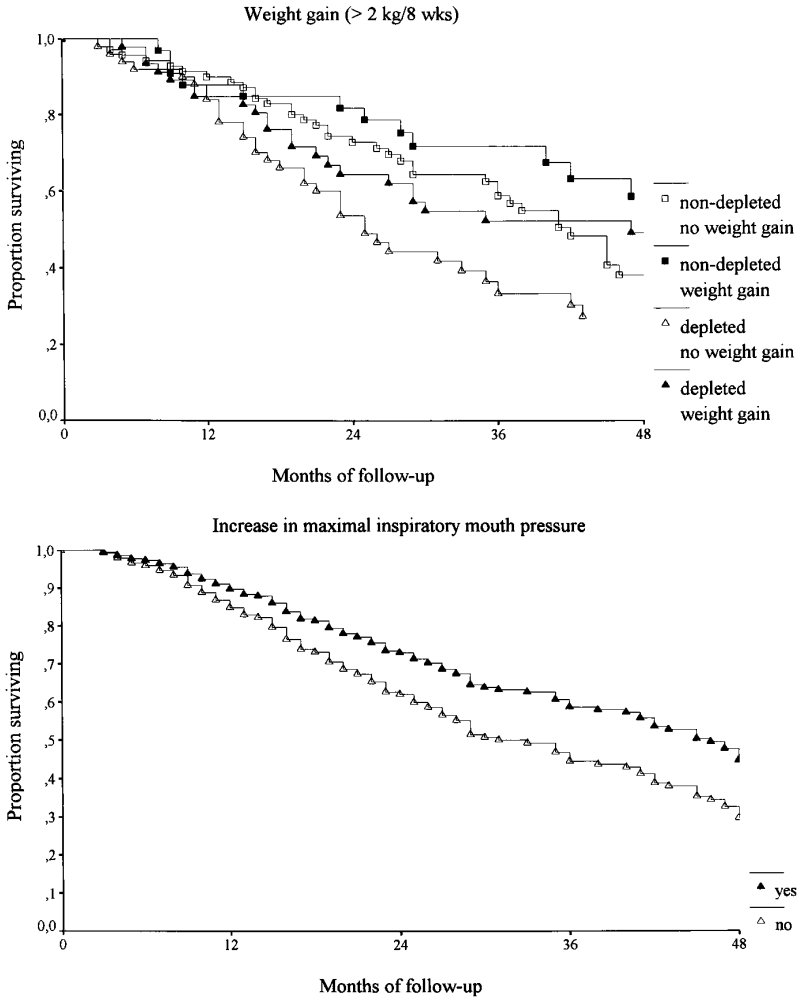

Figure 5. Prospective study. (*Upper panel*) Kaplan-Meier plot: weight gain. (*Lower panel*) Cox regression plot: increase in PI_{max} adjusted for baseline PI_{max}.

diet resulting in 24% "responders," no differential effect of either of the treatments on survival was shown. Treatment response, i.e., both weight gain as well as improvement of respiratory muscle strength, however, were significantly related to survival. After adjusting for the significant influence of BMI on mortality, weight gain remained a significant predictor, but PI_{max} did not. This is not surprising since muscle function is related to muscle mass and muscle metabolism. Independent of muscle mass, we have recently shown alterations in cellular energy metabolism in muscle biopsies of patients with clinically stable COPD in resting condition. Chronic or intermittent hypoxemia could be an important trigger of these metabolic alterations. Although the treatment duration relative to the follow-up period was short, it is conceivable that treatment response could have had longer-lasting implications since during the intervention study, independent of the received treatment, this was the first time that the patients were informed about the role of appropriate nutrition in their disease and how to adapt their dietary habits. Similarly, most patients were for the first time confronted with the beneficial effects of exercise on disability and handicap associated with their disease.

Despite the positive overall results of nutritional support on body weight and body composition in our clinical trial, there was also a high proportion of "nonresponse" similar to that of other studies. Knowledge of the pathogenesis of weight loss and muscle wasting is essential for an optimal implementation and interpretation of nutritional and metabolic therapy. It is clearly established (23) that a substantial proportion of patients with moderate to severe COPD exhibit an elevated resting metabolic rate. Furthermore, Baarends and coworkers (24) recently showed, using the doubly labeled water method, that independent of resting metabolic rate, total energy expenditure is increased in COPD. Careful analysis of the available nutritional intervention studies in view of our recent data on total daily energy expenditure in COPD, suggests that nonresponse to nutritional therapy may have been partly due to inadequate judgment of energy expenditure or patient's inability to ingest the required energy intake. Theoretically, noncompliance of the treatment could also have contributed to nonresponse. However, patients were included in an in-patient pulmonary rehabilitation program allowing good control. The movement therapist monitored the training of the patients and the nurses closely monitored if the patients were eating there daily meals and if and how much they were taking from the daily liquid nutritional supplement.

Another possible explanation could be the presence of alterations in intermediary metabolism superposed on the elevated energy metabolism. Recently, we showed that a subset of patients with COPD with elevated resting metabolic rate

displayed elevated levels of acute phase proteins and soluble TNF-receptors in peripheral blood (25). These patients were further characterized by depletion of fat-free mass, independent of the BMI. In line with these findings, Di Francia and coworkers (26) and de Godoy and coworkers (27) recently reported a significant relation between weight loss and TNF. From the combined results of these previous reports and the present study, it is hypothesized that tissue depletion in patients with COPD may be related in part to a systemic catabolic response induced by inflammation, which cannot completely be reversed by nutritional support only. Further studies are indicated to confirm this hypothesis and to identify further characteristics of nonresponders.

In conclusion, the present survival analyses provide further evidence to support the hypothesis that body weight has an independent effect on survival in COPD. Moreover, the negative effect of low body weight can be reversed by appropriate therapy.

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