

## Weight Gain in Cachectic COPD Patients Receiving Noninvasive Positive-Pressure Ventilation

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**BACKGROUND:** In chronic obstructive pulmonary disease (COPD), body mass index (BMI) is an important predictor of survival. Little is known about the prevalence of malnutrition or longitudinal changes of BMI in patients undergoing noninvasive positive-pressure ventilation (NPPV). **METHODS:** In a cohort study of 141 patients with COPD and severe chronic respiratory failure (mean forced expiratory volume in the first second [FEV<sub>1</sub>] 0.80 ± 0.27 L, mean P<sub>a</sub>CO<sub>2</sub> 55.6 ± 8.8 mm Hg), we investigated nutritional status in relation to respiratory impairment. Changes in BMI were evaluated at 6 and 12 months after initiation of NPPV. **RESULTS:** Malnutrition, indicated by a BMI of < 20 kg/m<sup>2</sup>, was found in 20.6% of the patients. BMI was significantly correlated with the severity of respiratory impairment, especially with hyperinflation (residual volume divided by total lung capacity,  $r = -0.55$ ,  $p < 0.001$ ). In malnourished patients (BMI < 20 kg/m<sup>2</sup>) there was a significant increase in body weight after 6 months (6.2 ± 12.5%,  $p < 0.05$ ) and 12 months (12.8 ± 16.0%,  $p < 0.01$ ), whereas there were no significant changes in the overall study population. Furthermore, there was no correlation between changes in BMI and changes in blood-gas values, lung function, or inspiratory muscle function, either in the entire patient group or in the subgroup of malnourished patients. **CONCLUSIONS:** In COPD with chronic respiratory failure, malnutrition is common and strongly related to hyperinflation. After initiation of NPPV, a significant weight gain is observed in malnourished COPD patients. *Key words:* chronic obstructive pulmonary disease, COPD, malnutrition, body mass index, noninvasive positive-pressure ventilation, chronic respiratory failure. [Respir Care 2006;51(2):126–132. © 2006 Daedalus Enterprises]

### Introduction

In recent years there has been growing evidence that in patients with chronic obstructive pulmonary disease (COPD), malnutrition, low body weight, and weight loss are independent and negative risk factors for survival.<sup>1–7</sup> However, the underlying pathogenic mechanisms leading to negative energy balance are poorly understood and may be quite varied in origin.<sup>8–10</sup> In contrast to other chronic wasting diseases, COPD patients often have elevated activity-induced energy expenditure and resting energy requirements as well.<sup>11,12</sup> Weight loss is particularly pro-

nounced in advanced and emphysematous COPD with severe hyperinflation and airway obstruction.<sup>13–15</sup> This may indicate that the elevated cost of breathing and increased respiratory muscle activity play at least one important role for increased energy metabolism.<sup>9,15,16</sup> However, as indicated in a recently published meta-analysis, merely a high caloric enhancement and nutritional supplementation were not particularly successful in improving nutritional status in COPD.<sup>17–19</sup>

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Noninvasive positive-pressure ventilation (NPPV) is a well-known treatment option in severe COPD with symp-

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tomatic chronic respiratory failure, and malnutrition seems to be highly prevalent in these patients.<sup>20</sup> The pathogenesis of chronic respiratory failure and the mechanisms by which it can be reversed by NPPV are still under discussion.<sup>21</sup> Some investigators have demonstrated that NPPV can reduce respiratory muscle activity<sup>22,23</sup> or, more recently, lung hyperinflation.<sup>24,25</sup> Both effects could probably lead to decreased energy requirements. Surprisingly, the long-term effects of NPPV on nutritional status have not yet been investigated. Thus, we performed the present analysis to investigate whether initiation of NPPV results in an alteration in body weight, particularly in malnourished patients, up to 12 months after initiation of treatment, and whether there is a link to changes in functional variables.

## Methods

### Selection Criteria

Patients with COPD discharged with NPPV from February 1995 to June 2004 were eligible for the study. With these patients we initiated NPPV based on clinical symptoms (dyspnea, fatigue, morning headache),  $P_{aCO_2}$  ( $> 45$  mm Hg while breathing room air), impaired pulmonary function, and signs of cor pulmonale. We included only patients who were in a stable state of the disease, which was defined by the absence of acidosis ( $pH > 7.35$ ) and the absence of signs of pulmonary infection or systemic inflammation (C-reactive protein  $< 20$  mg/dL). Patients who had been intubated or tracheostomized prior to NPPV were excluded from this analysis. Furthermore, patients who had severe obesity (body mass index [BMI]  $\geq 40$  kg/m<sup>2</sup>) were not accepted. None of the patients had been treated with NPPV before. All patients had received  $\beta$  agonists, anticholinergic agents, inhaled steroids, and (occasionally) systemic steroids; most had also received theophylline.

### Measurements

Before initiation of NPPV, blood-gas measurements (Rapidlab, Bayer, East Walpole, Massachusetts) were taken from the hyperemic earlobe, during the daytime, during spontaneous breathing of room air or the patient's usual oxygen flow. To minimize the bias from different oxygen flows, we primarily used the blood-gas samples while the patient was not inhaling supplemental oxygen, if they were available. Otherwise, the samples were taken while the patient breathed his or her usual resting oxygen flow. However, values closest to the initiation time of NPPV and showing best oxygenation (arterial oxygen saturation  $> 90\%$  or  $P_{aO_2} > 60$  mm Hg) were considered the baseline values. Whole-body plethysmography was performed per the guidelines of the American Thoracic Society.<sup>26</sup> The

reference values were those of the European Community for Steel and Coal.<sup>27</sup> Inspiratory mouth-occlusion pressure at 100 ms ( $P_{0.1}$ ) and maximum static inspiratory mouth pressure were measured as previously described.<sup>28</sup> The best of 3 reproducible efforts was usually chosen.

Weight was measured during each hospital stay, with the patient wearing indoor clothes, and using a digital scale. We measured height to the nearest 1.0 cm, with the patient standing barefoot. BMI was then calculated as  $\text{weight/height}^2$  (kg/m<sup>2</sup>).

Patients were routinely reviewed after 3 months and/or 6 months and 12 months for follow-up investigation. Ventilation was then determined with capillary blood-gas values, measured twice at night during ventilation, and in the daytime during spontaneous breathing 4–6 hours after nocturnal NPPV. Ventilation parameters were adjusted to optimize capillary gas values and nocturnal oxygen saturation. Whole-body plethysmography, inspiratory muscle tests, and BMI were reassessed at the follow-up investigations.

### NPPV Technique and Setting

Upon initiation of NPPV, the ventilator was set in the spontaneous-timed (assist-control) mode, with low inspiratory pressure and back-up respiratory frequency. After a period of adaptation, the ventilation parameters were set to the patient's comfort level, but targeting a tidal volume of 7–10 mL/kg. Oxygen was supplemented to achieve an oxygen saturation of  $> 90\%$ . The beneficial effect of the ventilation and oxygen supplementation was then assessed by repeated measurements of capillary blood-gas values during the night. In the case of persistent hypercapnia, we adjusted the ventilation parameters to achieve more effective ventilation. In this analysis, 10 different home respirators were in use, although most of our patients were ventilated with the Onyx Plus (Nellcor Puritan Bennett, Courtaboeuf Cedex, France) or the Bipap Synchrony ST (Respironics, Murrysville, Pennsylvania). A humidification system was installed if dry mucous membranes developed.

NPPV was delivered to 127 patients via nasal mask (nasal mask Gold or Special, Respironics, Murrysville, Pennsylvania, or NV Ultra Mirage nasal mask, ResMed, North Ryde, Australia), and to 5 patients via full-face mask (Ultra Mirage, ResMed, North Ryde, Australia) of various sizes and types. In 9 patients, an individually manufactured mask was applied. Upon discharge from the hospital, patients were ventilated with a mean expiratory positive airway pressure of  $3.9 \pm 1.6$  cm H<sub>2</sub>O, a mean inspiratory positive airway pressure of  $19.8 \pm 4.2$  cm H<sub>2</sub>O, and a mean respiratory frequency of  $20.1 \pm 4.2$  breaths/min.

Table 1. Follow-Up Data

	Patients (n)		
	Baseline	6 Months	12 Months
Deceased	NA	7	22
Withdrew*	NA	5	9
Missing control†	NA	4	7
Available	141	125	103

\* Patients discontinued noninvasive positive-pressure ventilation  
† Patients did not come to routine follow-up investigation  
NA = not applicable

### Statistical Analysis

Initial BMI was compared to the values at 6 months and 12 months. If the patient missed the 6-month follow-up visit, the values from the 3-month follow-up visit were accepted. Changes in BMI, blood-gas values, and lung/inspiratory muscle function were analyzed with the Wilcoxon test for dependent variables. Relationships between body weight, lung function, and blood-gas values were assessed with a linear regression model (Pearson). Results are shown as mean  $\pm$  SD. Differences were considered statistically significant when  $p < 0.05$ . Calculations were made with SPSS version 10.0 (SPSS, Chicago Illinois).

## Results

### Patient Sample

Using a protocol approved by the institutional review board, we enrolled 308 patients with COPD in whom NPPV was initiated. Sixty-four patients (20.8%) were excluded because they were primarily intubated due to acute-on-chronic respiratory failure or switched from tracheotomy to NPPV. Ninety-three patients (30.2%) had pH  $< 7.35$ , suffered from severe pulmonary infection, or had signs of systemic inflammation (C-reactive protein  $> 20$  mg/dL). Ten patients (3.2%) were excluded because of severe obesity. Thus, data from 141 patients were available for analysis at baseline. Table 1 shows the number of available data entries and the reasons for missing values at 6 months and 12 months.

### Patient Characteristics at Baseline

Median age at baseline was  $65.0 \pm 8.4$  years (range 41.7–80.0 y). The female patients were significantly younger ( $60.6 \pm 9.7$  y,  $n = 35$ ) than the male patients ( $66.4 \pm 7.4$  y,  $n = 106$ ) ( $p < 0.05$ ). The population was characterized by a severe form of COPD, corresponding to

the Global Initiative for Obstructive Lung Disease's (GOLD) stage IV. Their median daytime  $P_{aCO_2}$  was  $55.6 \pm 8.8$  mm Hg during spontaneous breathing ( $1.2 \pm 1.1$  L), and FEV<sub>1</sub> was  $0.80 \pm 0.27$  L, which was  $29.7 \pm 9.1\%$  of predicted. Table 2 shows the baseline data and changes 1 year after initiation of NPPV.

### Distribution of BMI and Prevalence of Malnutrition

In general, the patients had mild obesity, with a median BMI of  $26.0 \pm 6.1$  kg/m<sup>2</sup>. Figure 1 shows the distribution of BMI related to sex. The prevalence of malnutrition, as indicated by a BMI of  $< 20$  kg/m<sup>2</sup>, was 20.6%. Malnutrition was more pronounced among the female patients (28.6%) than among the male patients (17.9%).

### Relationship of Nutritional Status to Functional Variables

Considering baseline values, we found that nutritional status was correlated to the severity of the disease (Table 3). However, the strongest correlation was between BMI and hyperinflation (residual volume divided by total lung capacity) ( $r = -0.55$ ,  $p < 0.001$ ).

### Changes in BMI After Initiation of NPPV

Figure 2 shows the changes in BMI at 6 months and 1 year of nocturnal NPPV treatment. After 1 year, there was a slight overall trend toward weight gain. In malnourished patients (BMI  $< 20$  kg/m<sup>2</sup>) we found significant increases in body weight after 6 months ( $6.2 \pm 12.5\%$ ,  $p < 0.05$ ) and 1 year ( $12.8 \pm 16.0\%$ ,  $p < 0.01$ ).

### Changes in Pulmonary Function and Correlation to Changes in BMI

After 1 year of NPPV treatment, no significant correlation could be seen between changes in BMI and changes in blood-gas values, lung function, or inspiratory muscle function among the studied patients, including the malnourished-patient subgroup.

## Discussion

The aim of this study was to evaluate the prevalence of malnutrition and the longitudinal changes in nutritional status in COPD patients with severe chronic respiratory failure undergoing NPPV. Malnutrition, defined by a BMI of  $< 20$  kg/m<sup>2</sup>, was frequent and related to respiratory impairment, particularly hyperinflation and hypercapnia. After initiation of NPPV there was significant weight gain among the malnourished patients, but this weight gain was

## WEIGHT GAIN AFTER INITIATION OF NPPV

Table 2. Changes in Respiratory Variables After 1 Year of NPPV

Variable	Baseline (mean ± SD)	Value After 1 Year (mean ± SD)	n*	p†
RV/TLC (%)	74.0 ± 8.5	69.1 ± 9.8	97	< 0.001
FEV <sub>1</sub> (L)	0.80 ± 0.27	0.94 ± 0.36	97	< 0.001
P <sub>0.1</sub> (cm H <sub>2</sub> O)	5.2 ± 2.2	5.4 ± 2.0	86	0.94
PIP (cm H <sub>2</sub> O)	39.8 ± 17.4	47.0 ± 20.4	86	0.03
P <sub>0.1</sub> /PIP	0.16 ± 0.12	0.14 ± 0.09	86	0.28
P <sub>aCO<sub>2</sub></sub> (mm Hg)	55.6 ± 8.8	45.2 ± 7.7	101	< 0.001
P <sub>aO<sub>2</sub></sub> (mm Hg)	58.3 ± 18.0	63.9 ± 13.9	101	< 0.001
O <sub>2</sub> flow (L)	1.2 ± 1.1	1.2 ± 1.3	101	0.91
BE (mmol/L)	8.6 ± 4.4	4.7 ± 3.7	101	< 0.001
pH	7.41 ± 0.04	7.43 ± 0.04	101	< 0.001
Hb (g/dL)	14.6 ± 2.1	13.9 ± 1.5	103	< 0.001

\* Number of patients with data available at baseline and at 1 year

† Via Wilcoxon test for dependent variables

NPPV = noninvasive positive-pressure ventilation

RV = residual volume

TLC = total lung capacity

FEV<sub>1</sub> = forced expiratory volume in the first second

P<sub>0.1</sub> = airway occlusion pressure 0.1 s after the onset of inspiratory effort

PIP = peak inspiratory pressure

BE = base excess

Hb = hemoglobin

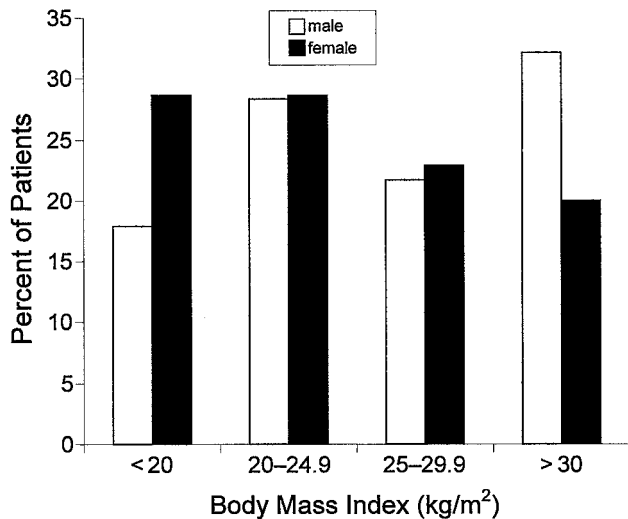


Fig. 1. Distribution of body mass index related to sex.

not correlated to the improvements in blood-gas values or lung function.

### Impact and Prevalence of Malnutrition in COPD

In recent years, evidence has been growing that COPD does not exclusively involve the lungs, but also leads to extrapulmonary abnormalities, or so-called systemic effects of COPD. Among these, malnutrition is a central feature and predictor of survival.<sup>1-7,10,29</sup> A particularly short

Table 3. Correlation of Respiratory Variables With BMI at Baseline

Variable	n	Correlation With BMI (r)	p*
FEV <sub>1</sub>	140	0.47	< 0.001
TLC	140	-0.40	< 0.001
RV/TLC	140	-0.55	< 0.001
P <sub>0.1</sub>	111	-0.20	< 0.05
PIP	111	0.24	< 0.01
P <sub>0.1</sub> /PIP	111	-0.11	0.26
P <sub>aCO<sub>2</sub></sub>	141	-0.26	< 0.01
P <sub>aO<sub>2</sub></sub>	141	-0.07	0.42
BE	141	-0.34	< 0.001

\* Via Wilcoxon test for dependent variables

BMI = body mass index

FEV<sub>1</sub> = forced expiratory volume in the first second

TLC = total lung capacity

RV = residual volume

P<sub>0.1</sub> = airway occlusion pressure 0.1 s after the onset of inspiratory effort

PIP = peak inspiratory pressure

BE = base excess

life expectancy is reported in patients with severe COPD and chronic respiratory failure who are treated with long-term oxygen therapy and/or home mechanical ventilation.<sup>1</sup> However, no study has yet exclusively investigated nutritional status of patients with severe hypercapnic COPD in a large population treated with NPPV, although also hypercapnia—to a lesser extent than other factors—was described several years ago as a prognostic factor of

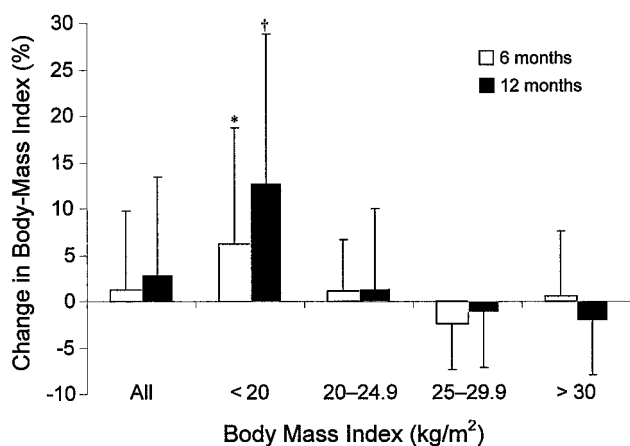


Fig. 2. Change in body mass index after 6 months and 12 months of noninvasive positive-pressure ventilation, compared to baseline values. \*  $p < 0.05$ . †  $p < 0.01$ .

COPD.<sup>30,31</sup> In our analysis of chronic stable COPD patients, malnutrition was present in 20.6% of patients, which is comparable to the prevalence that Gray-Donald et al observed among patients recruited for a study of negative-pressure ventilation.<sup>2</sup> However, other investigators who analyzed COPD patients with LTOT<sup>5</sup> and/or home mechanical ventilation<sup>20</sup> found their patients even more nutritionally depleted, although those patients' FEV<sub>1</sub> percent of predicted ranged over 30% in those studies. This clearly indicates that FEV<sub>1</sub> alone, as a traditional marker of the severity of COPD, is not sufficient to explain nutritional depletion in severe COPD.

### Malnutrition and Respiratory Impairment

Many studies have attempted to establish a relationship between malnutrition and respiratory variables, but most have only analyzed different degrees of severity or small patient samples.<sup>13,20,32-34</sup> In our analysis of a large and homogenous population of severely hypercapnic COPD patients, nutritional depletion was particularly correlated to lung-function impairment. Previous investigators have reported a relationship between airflow obstruction (FEV<sub>1</sub>), diffusing capacity of the lung for carbon monoxide, and body weight.<sup>13,14,20,35</sup> In our study, the factor most strongly correlated with BMI was hyperinflation, or, more specifically, residual volume divided by total lung capacity. This relationship may indicate that respiratory mechanics are involved in cachexia of severe COPD (GOLD stage IV), as previously proposed.<sup>9,15,16,36</sup> In accordance with Fiacadori et al, we also found a significant inverse correlation between hypercapnia and BMI.<sup>34</sup> Moreover, we observed that BMI was significantly correlated to base excess, which in particular reflects the chronic status of respiratory failure. These results could imply that chronic hypercapnia

plays an important role in the development of malnutrition.

### Effects of NPPV on Body Weight

Although the mechanisms of malnutrition in COPD remain unclear, weight gain results in an improved prognosis in COPD.<sup>37</sup> Nevertheless, an adequate strategy for the long-term treatment of cachexia is not available.<sup>12</sup> In the current study we found significant weight gain in malnourished patients after initiation of NPPV. However, although some variables have been found to be correlated to malnutrition, the improvement in those variables, particularly the highly significant reduction in hyperinflation or hypercapnia, were not related to weight gain. These results are in line with those of studies that investigated the effects of lung-volume-reduction surgery, which resulted in similar weight gain and were correlated to changes in diffusing capacity of the lung for carbon monoxide, but not to changes in total lung capacity or residual volume.<sup>38,39</sup> Therefore, it is unlikely that the observed weight gain is simply a consequence of improved respiratory mechanics due to reduced lung volumes.

Since the exact mechanisms of weight loss in COPD are unknown, we can only speculate about the mechanisms by which NPPV reverses weight loss. Patients with COPD have an increased resting energy expenditure, which can be partly explained by increased work of breathing.<sup>9,10,15,16,35</sup> NPPV could, at least theoretically, reduce energy requirements by nocturnal resting of inspiratory muscles. To our knowledge, only one small study, with 6 patients, has directly measured (via indirect calorimetry) changes in energy requirements during NPPV, and that study found only a slight decrease in oxygen consumption.<sup>40</sup> Although some authors have proposed that NPPV primarily acts by unloading ventilatory muscles,<sup>22,23,41</sup> this theory is not generally accepted. Indeed, in our analysis we did not detect any significant changes in inspiratory load (P<sub>0.1</sub>). One of the most important effects of NPPV, shown in numerous studies and the current analysis as well, is that NPPV improves blood-gas values, in particular by reducing hypercapnia and improving hypoxemia.<sup>41-45</sup> It has been postulated that tissue hypoxia may cause cellular bioenergetic alterations, leading to increased metabolic rate and depressed protein synthesis.<sup>10,46</sup> Moreover, hypercapnia and acidosis are thought to be involved in functional and structural changes in skeletal muscle.<sup>47,48</sup> In our study, hypercapnia was correlated with BMI at baseline, but the reduction of P<sub>aCO<sub>2</sub></sub> was not correlated to the increase in BMI, so other mechanisms have to be considered.

Circulating cytokines, such as tumor necrosis factor alpha, are thought to have a causal relationship to nutritional depletion and are particularly expressed in underweight

COPD patients.<sup>49–54</sup> However, fewer episodes of acute-on-chronic respiratory failure caused by progression of the disease, combined with fewer intensive-care-unit admissions after initiation of NPPV, have been reported.<sup>42,55</sup> Thus, although the exact mechanisms cannot yet be explained, one hypothesis is that NPPV influences systemic inflammation by stabilizing the chronic disease.

Finally, NPPV has been shown to reduce dyspnea and respiratory frequency.<sup>23,24,40,56</sup> Since a rapid shallow breathing pattern and arterial oxygen desaturation are thought to limit food intake,<sup>9,33</sup> NPPV therapy could enable patients to attain adequate caloric intake, resulting in significant weight gain.

### Study Limitations

Exacerbation of COPD is accompanied by an impaired energy balance that is due to decreased dietary intake and augmented resting energy requirements.<sup>57</sup> However, to investigate the effects of NPPV on BMI only in stable COPD, we applied strict exclusion criteria to a population of more than 300 patients. Nevertheless, because of the lack of a control group, our results have to be verified in a prospective controlled trial.

### Conclusions

We found that malnutrition is common in severely hypercapnic COPD patients. Moreover, BMI is related to respiratory impairment, particularly lung hyperinflation and hypercapnia. Initiation of NPPV did result in significant weight gain in malnourished patients, which could support the concept of NPPV in the treatment of stable hypercapnic COPD.

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