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Predictors of Survival in COPD Patients With Chronic Hypercapnic Respiratory Failure Receiving Noninvasive Home Ventilation*

Stephan Budweiser, MD; Rudolf A. Jörges, PhD; Theresa Riedl; Frank Heinemann, MD; André P. Hitzl; Wolfram Windisch, MD; and Michael Pfeifer, MD

Background: Patients with COPD and chronic hypercapnic respiratory failure (CHRF) are at high risk, and noninvasive ventilation at home is increasingly being used. Knowledge of prognostic parameters under these conditions is limited but may be clinically helpful and highlight the role of noninvasive ventilation.

Methods: In 188 patients with COPD (mean ± SD FEV₁, 31.0 ± 9.6% of predicted; PaCO₂, 56.3 ± 9.4 mm Hg) discharged from the hospital receiving NIV between July 1994 and July 2004, the prognostic value of body mass index (BMI), lung function, laboratory parameters, and blood gas levels was assessed by univariate and multivariate Cox regression analyses. Moreover, the impact of changes in risk factors on mortality assessed 6.7 ± 2.8 months after the initiation of noninvasive ventilation was evaluated.

Results: Overall, the mortality rate during follow-up (duration, 32.2 ± 24.3 months) was 44.7%, with 1-year, 2-year, and 5-year survival rates of 84.0%, 65.3%, and 26.4%. Deaths resulted predominantly from respiratory causes (73.8%). Univariate regression analyses revealed age, BMI, hemoglobin, FEV₁, specific airway resistance, residual volume (RV)/total lung capacity (TLC), pH, and base excess (BE) to be associated with prognosis (p < 0.01 each), whereas multivariate analysis identified only age, BMI, RV/TLC, and BE as independent predictors (p < 0.05). In patients at risk (BMI < 25 kg/m², RV/TLC > 73%, or BE > 9 mmol/L), changes in these predictors were also associated with survival.

Conclusions: In patients with COPD and CHRF, nutritional status, hyperinflation, and BE, which turned out to be reliable and consistent markers in CHRF, were independent prognostic factors for mortality. These data favor a multidimensional approach in these patients, including the use of noninvasive ventilation.

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Key words: chronic respiratory failure; COPD; mortality; noninvasive ventilation; prognostic factors

COOPD is increasing worldwide and is associated with a growing socioeconomic burden due to morbidity and mortality.1 A number of factors determining the course of COPD have been explored,2,3 with the result that markers such as FEV₁ and hypoxemia cannot fully account for the complexity of the disease due to extrapulmonary, systemic abnormalities beyond the respiratory system.6 Accordingly, a low body mass index (BMI) and fat-free mass have been identified as risk factors for mortality7,8 and a multidimensional grading system has been proposed.8 Patients with chronic hypercapnic respiratory failure (CHRF) have a particularly poor prognosis, although the role of hypercapnia per se is not clear.4,9,10 as most data refer to patients with mild-to-moderate hypercapnia during long-term oxygen-
therapy (LTOT).11–13 In addition to PaCO₂, which is subject to short-term effects, base excess (BE), i.e., the deviation of normal buffer base, could also be well suited for the assessment of CHRF.14

Over time, COPD with concomitant CHRF has become one major indication for domiciliary noninvasive positive pressure ventilation (NPPV).15 Indeed, many authors16–21 have reported positive effects on blood gas levels, particularly a reduction of hypercapnia. Although the role of NPPV on long-term survival in CHRF is still a topic of controversy,24 there is agreement that these patients are at high risk for repeated hospitalization and death.25,26 Surprisingly, prognostic factors have not been explored under the conditions of CHRF and NPPV, although they could be helpful for monitoring and making therapeutic decisions.

Based on these considerations, the present study focuses on predictors of mortality in patients with chronic hypercapnic COPD receiving NPPV. To elucidate the role of NPPV and the plausibility of cross-sectional associations, the impact of changes in baseline characteristics, including a reduction in hypercapnia after initiation of NPPV, was additionally evaluated.

For editorial comment see page 1622

MATERIALS AND METHODS

Study Population

We evaluated data from consecutive patients with COPD discharged receiving NPPV from July 1994 to December 2001. From January 2002 to July 2004, the study was performed prospectively. Only subjects with an event-free observation time ≥ 12 months were included. Diagnosis was based on history, symptoms, and airway obstruction (FEV₁/vital capacity [VC] < 70% of predicted after bronchodilator inhalation). The decision to initiate NPPV involved symptoms and persistently elevated PaCO₂ (> 50 mm Hg). To ensure patient safety, NPPV was also initiated at lower PaCO₂ (45 to 50 mm Hg) if repeated episodes of hypercapnic respiratory failure, very severe lung function impairment, or dyspnea at rest occurred. Exacerbations were identified via increased dyspnea, cough, and sputum production requiring treatment by antibiotics and/or oral steroids.27 None of the patients had been previously treated with home NPPV. Those who required intubation were excluded, as baseline values prior to ventilator therapy were often not available. The study was approved by the local ethics committee.

Assessments

Prior to NPPV, blood gas levels were analyzed from the hyperemic earlobe during daytime and spontaneous breathing. If available, values in the absence of oxygen supplementation were used; otherwise, values obtained at the usual oxygen flow. Spirometry and body plethysmography followed American Thoracic Society guidelines using European Respiratory Society reference values.28,29 In patients with exacerbation, lung function was determined after the clinical state had stabilized. Blood count and C-reactive protein (CRP) [Micros 60-CT; ABX; Montpellier, France; and Dimension Xpand; Dade Behring; Schwabach, Germany] as well as BMI (weight/height squared) were assessed on the first day in the hospital.

NPPV Technique and Settings

NPPV was usually started in the pressure-support mode and after an adaptation phase switched to a pressure-cycled assist-control mode. Inspiratory positive airway pressure (IPAP) was gradually increased, using tidal volumes of approximately 10 mL/kg (ideal body weight), while targeting at a reduction in PaCO₂ ≥ 20%. Low expiratory positive airway pressure (EPAP) was set to counterbalance intrinsic positive end-expiratory pressure.30 Oxygen was supplemented to maintain arterial oxygen saturation > 90%. Usually, nasal masks of different sizes and types were used; if leakage occurred despite a chin band, full facemasks or individually adapted nasal masks were applied. Ten different home respirators were used: in most patients, Onyx plus (Nellcor Puritan Bennett; Courtaboeuf Cedex, France), BIPAP synchrony ST (Respironics; Murrysville, PA), or Twin Air (Airos; Pau, France).

Follow-up

To evaluate treatment efficacy, patients were reassessed approximately 6 months after initiation of nocturnal NPPV. Measurements were performed as before, and ventilation parameters were adjusted according to blood gas levels and nocturnal oxygen saturation. For survival analyses, patients were followed up until death, the end of the study period, or rejection of NPPV. Information on respiratory and all-cause mortality was obtained from relatives or family doctors.

Statistical Analysis

Mean values ± SD and medians were computed. Shapiro-Wilk tests were performed to test for normal distribution. For comparison of baseline characteristics between groups and of baseline with follow-up values, unpaired and paired t tests or the nonparametric Mann-Whitney U test and Wilcoxon rank test were used wherever appropriate. Survival was calculated by the Kaplan-Meier method from initiation of NPPV to the closing date of July 31, 2004. Cutoff values were derived from rounded median values. The predictive value of each single variable for mortality from respiratory causes was analyzed by univariate
regression analyses using the log-rank test. Significant variables in univariate analyses were fed into a stepwise multivariate Cox regression analysis to identify independent predictors, using an entry level of < 0.05 and a removal level of 0.10. For all tests, a p < 0.05 was considered statistically significant. Statistical analyses were performed using statistical software (SPSS version 11.0; SPSS: Chicago, IL).

### RESULTS

#### Study Population and Baseline Characteristics

NPPV was initiated in 305 patients with COPD; 65 patients were excluded because of intubation, and 52 patients were excluded because of event-free observation time < 12 months. Thus, 188 patients remained for analysis (Table 1). Fifty-nine patients (31.4%) had an exacerbation at hospital admission. These patients showed higher BE (p < 0.05), leukocyte counts, and CRP (p < 0.001 each), but lower hemoglobin (p = 0.002) and BMI (p < 0.05) than those without exacerbation (n = 129), while lung function did not differ significantly.

On discharge, mean EPAP was 4.0 ± 1.7 cm H₂O, IPAP was 19.5 ± 4.4 cm H₂O, and respiratory frequency was 20.3 ± 4.1 breaths/min. Comorbidities comprised hypertension (43.6%), diabetes (23.4%), coronary heart disease, or left-heart failure (36.2%) and atrial fibrillation (10.1%). Antibiotic therapy on discharge included β-agonists in all patients, anticholinergics (73%), inhaled/systemic corticosteroids (56%), and theophylline (68%). Due to clinical signs of cor pulmonale, 74% of patients received diuretics.

### Changes at the Follow-up Visit

To evaluate the predominant role of NPPV, changes of baseline values were only assessed in patients without exacerbation (n = 129). Twelve of these patients died, and 1 patient was unavailable for follow-up before readmission. Thus, 116 patients were reassessed 6.7 ± 2.8 months after initiation of NPPV. Improvements (p < 0.05 each) occurred in lung function and blood gas levels (Table 2). Adherence to NPPV, which could be assessed by counter readings (n = 98; 84.5%), was 6.5 ± 2.5 h/d.

#### Survival and Prognostic Value of Baseline Parameters

Considering all patients (n = 188), the mean observation time between initiation of NPPV and the end of study or until patients died or rejected NPPV was 23.2 ± 24.3 months. Within this period, 13 patients (6.9%) rejected NPPV and 2 patients (1.1%) were unavailable for follow-up. Overall mortality was 44.7% (n = 84), with 1-year, 2-year, and 5-year survival rates of 84.0% (n = 158 of 188 patients; 95% confidence interval [CI], 69.3 to 96.3%), 65.3% (n = 98 of 150 patients; 95% CI, 49.5 to 82.8%); and 26.4% (n = 28 of 106 patients; 95% CI, 16.5 to 42.2%), respectively. Deaths resulted predominantly from respiratory causes (n = 62; 73.8%), including respiratory or right-heart failure, pulmonary embolism, or pneumothorax. Nonrespiratory causes (n = 22) comprised sudden cardiac death or myocardial infarction (n = 8), cancer (n = 5), stroke, acute abdomen, GI bleeding, renal failure, sepsis, suicide

### Table 1—Baseline Characteristics and Their Prognostic Value for Survival According to Univariate Analyses

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients, No.</th>
<th>Data</th>
<th>Median</th>
<th>Cutoff</th>
<th>p Value†</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>188</td>
<td>64.5 ± 8.0</td>
<td>65.0</td>
<td>65</td>
<td>0.0004</td>
<td>0.4172</td>
<td>0.2307–0.6550</td>
</tr>
<tr>
<td>BMI, kg/m²‡</td>
<td>188</td>
<td>27.2 ± 6.9</td>
<td>27.2</td>
<td>27</td>
<td>&lt; 0.0001</td>
<td>5.0776</td>
<td>2.9280–8.2037</td>
</tr>
<tr>
<td>Female/male gender</td>
<td>188</td>
<td>41/147</td>
<td></td>
<td></td>
<td>0.3357</td>
<td>1.3717</td>
<td>0.7377–2.4394</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>188</td>
<td>14.7 ± 2.1</td>
<td>14.8</td>
<td>15</td>
<td>0.0063</td>
<td>2.0270</td>
<td>1.2199–3.5479</td>
</tr>
<tr>
<td>Leukocytes, ×10³/µL</td>
<td>188</td>
<td>9.6 ± 3.6</td>
<td>9.1</td>
<td>9</td>
<td>0.1620</td>
<td>0.7018</td>
<td>0.4235–1.1546</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>182</td>
<td>23.5 ± 46.1</td>
<td>5.3</td>
<td>5</td>
<td>0.8991</td>
<td>1.0327</td>
<td>0.6147–1.7399</td>
</tr>
<tr>
<td>sRaw, kPa/s</td>
<td>185</td>
<td>5.2 ± 3.0</td>
<td>4.5</td>
<td>4.5</td>
<td>0.0016</td>
<td>0.4408</td>
<td>0.2604–0.7303</td>
</tr>
<tr>
<td>PC/TLC, %</td>
<td>185</td>
<td>19.9 ± 8.1</td>
<td>18.5</td>
<td>19</td>
<td>&lt; 0.0001</td>
<td>3.9319</td>
<td>2.1703–6.0765</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>185</td>
<td>72.0 ± 15.5</td>
<td>73.3</td>
<td>73</td>
<td>&lt; 0.0001</td>
<td>0.3170</td>
<td>0.1831–0.5213</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>185</td>
<td>0.85 ± 0.31</td>
<td>0.78</td>
<td>0.8</td>
<td>0.0061</td>
<td>2.0395</td>
<td>1.2247–3.9327</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>185</td>
<td>31.0 ± 9.6</td>
<td>30.0</td>
<td>30.0</td>
<td>0.0028</td>
<td>1.7457</td>
<td>1.0550–2.9059</td>
</tr>
<tr>
<td>FEV₁/NC, %</td>
<td>185</td>
<td>46.7 ± 11.1</td>
<td>46.0</td>
<td>46</td>
<td>0.1197</td>
<td>1.4969</td>
<td>0.9005–2.4888</td>
</tr>
<tr>
<td>pH</td>
<td>177</td>
<td>7.40 ± 0.04</td>
<td>7.40</td>
<td>7.40</td>
<td>0.0002</td>
<td>0.3881</td>
<td>0.2055–0.6102</td>
</tr>
<tr>
<td>PacO₂, mm Hg</td>
<td>177</td>
<td>58.2 ± 16.6</td>
<td>56.0</td>
<td>56</td>
<td>0.7373</td>
<td>0.9164</td>
<td>0.5441–1.5355</td>
</tr>
<tr>
<td>PacO₂, mm Hg</td>
<td>177</td>
<td>56.3 ± 9.3</td>
<td>56.0</td>
<td>56</td>
<td>0.5588</td>
<td>0.7568</td>
<td>0.4674–1.3172</td>
</tr>
<tr>
<td>BE, mmol/L</td>
<td>177</td>
<td>8.8 ± 0.5</td>
<td>8.6</td>
<td>9</td>
<td>0.0004</td>
<td>0.3986</td>
<td>0.2923–0.6581</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. unless otherwise indicated. Blood gas tensions were obtained with a mean oxygen flow of 1.3 ± 1.2 L in 50 patients (26.6%) without oxygen supplementation.

†According to Kaplan-Meier analysis (based on log-rank value) and referring to the cutoff values indicated that were derived from rounded median values if not otherwise indicated.

‡Using the cutoff value of Chailleux et al and Schols et al.
(1 each), or unknown causes (n = 3). Fifty-three patients (63.1%) died in the hospital. Information on the cause of death was obtained from the home doctor/hospital (n = 70; 83.4%) or relatives (n = 14; 16.6%).

In univariate analyses significant determinants of survival were age, BMI, hemoglobin, specific airway resistance (sRaw), residual volume (RV)/total lung capacity (TLC) ratio, inspiratory capacity (IC)/TLC ratio, FEV1, % predicted, FEV1/VC, %, pH, and BE (Table 1). An exacerbation of BE by ≥ 4.0% (median decrease, 3.9%) resulted in improved survival (n = 94, p = 0.024; Fig 2, bottom, C) or ≥ 42% (33rd percentile) showed improved survival if baseline BE was ≥ 9 mmol/L (n = 75, p = 0.0150 and p = 0.0059, respectively). In addition, multivariate analysis, with RV/TLC and BMI as covariates, revealed a reduction of BE by ≥ 42% as an independent predictor in patients showing BE ≥ 9 mmol/L (n = 84, p = 0.011).

### Discussion

This study evaluated prognostic markers of long-term survival in patients with severe COPD and CHRF undergoing NPPV. Nutritional status, hyperinflation, and BE turned out to be independent

### Table 2—Changes of Baseline Values in Patients Without Exacerbation (n = 116)*

<table>
<thead>
<tr>
<th>Variables†</th>
<th>Baseline</th>
<th>Follow-up‡</th>
<th>Patients, No.§</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>28.3 ± 7.1</td>
<td>28.1 ± 6.7</td>
<td>114</td>
<td>0.243</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>15.1 ± 2.1</td>
<td>13.8 ± 1.7</td>
<td>116</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Leukocytes, ×10⁵/µL</td>
<td>8.6 ± 2.5</td>
<td>8.9 ± 2.9</td>
<td>116</td>
<td>0.263</td>
</tr>
<tr>
<td>sRaw, kPa/s</td>
<td>5.0 ± 2.6</td>
<td>4.6 ± 2.8</td>
<td>110</td>
<td>0.025</td>
</tr>
<tr>
<td>IC/TLC, %</td>
<td>20.1 ± 8.3</td>
<td>21.9 ± 9.2</td>
<td>110</td>
<td>0.031</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>71.1 ± 9.4</td>
<td>68.2 ± 10.5</td>
<td>110</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>0.89 ± 0.34</td>
<td>1.04 ± 0.44</td>
<td>110</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>31.7 ± 10.2</td>
<td>37.7 ± 14.6</td>
<td>110</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV1/VC, %</td>
<td>46.9 ± 11.5</td>
<td>47.5 ± 10.3</td>
<td>110</td>
<td>0.511</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.04</td>
<td>7.42 ± 0.03</td>
<td>105</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PacO₂, mm Hg</td>
<td>57.7 ± 17.4</td>
<td>60.5 ± 11.8</td>
<td>105</td>
<td>0.021</td>
</tr>
<tr>
<td>PacO₂, mm Hg</td>
<td>56.1 ± 8.7</td>
<td>45.4 ± 6.9</td>
<td>105</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BE, mmol/L</td>
<td>8.5 ± 4.2</td>
<td>4.7 ± 4.1</td>
<td>105</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.
†Blood gas samples were obtained at 1.2 ± 1.1 L oxygen at baseline and 0.9 ± 1.1 L oxygen at follow-up.
‡The follow-up visit occurred 6.7 ± 2.8 mo after the initiation of NPPV.
§Patients with data available at both baseline and follow-up visit.
predictors of mortality. Consistent with this finding, a reduction of these risk factors after initiation of NPPV was associated with improved survival in patients at higher risk. Compared to PaCO₂, BE turned out to be a more reliable and consistent predictor. These data indicate the importance of a multidimensional approach in both assessment and treatment of patients with severe COPD and CHRF, including the long-term use of NPPV.

Since the early 1990s, NPPV has been widely used in chronic hypercapnic COPD. However, data on long-term survival are limited. Moreover, prognostic parameters have not been evaluated under these conditions, although patients might be at high risk for readmission or life-threatening events. The present study comprised a 10-year observation period, a mean follow-up of 32 months and, to our knowledge, the largest population of COPD patients

Figure 1. Kaplan-Meier survival curves from respiratory causes referring to BMI (top left, A; p < 0.0001), RV/TLC (top right, B; p < 0.0001) and BE (bottom, C; p = 0.0004) in the total group of patients. The cutoff values used are indicated within the plots.
during NPPV. Prognostic factors were evaluated regarding respiratory causes of death, as detailed information was obtained predominantly from professionals.

In accordance with major studies involving different severities of COPD, BMI was a strong predictor of mortality, and a cutoff value < 25 kg/m² was associated with poor outcome. As in normal subjects, underweight is usually defined by a BMI < 20 kg/m²; this finding indicates that changes in body

![Kaplan-Meier survival curves for an increase vs reduction of BMI (top left, A) at the follow-up visit after initiation of NPPV in patients with BMI < 25 kg/m² (n = 68; p = 0.0289). Top right, B: analogous data for patients with a decrease of RV/TLC ≥ 4.0% vs < 4.0% (median decrease 3.9%) at the follow-up visit in patients with RV/TLC ≥ 73% (n = 73; p = 0.0341). Bottom, C: analogous curves for a reduction of BE < 50% vs ≥ 50% at the follow-up visit in patients with BE ≥ 9 mmol/L (n = 75; p = 0.0150). The median reduction of BE with all patients was 50.5%.](#)
composition in patients with severe COPD are not adequately represented by BMI. Indeed, fat-free mass has been described as a superior predictor of mortality. Although pulmonary cachexia is highly prevalent in severe COPD, its optimal treatment remains unresolved. However, since an increase in body weight resulted in improved prognosis in patients with BMI < 25 kg/m2, the assessment of nutritional status in regular intervals seems to be worthwhile in CHRF. In addition to NPPV, nutritional support and exercise could be promising approaches in malnourished patients.

Hyperinflation in terms of IC/TLC and RV/TLC was another independent predictor of mortality. It has been reported to be superior to FEV1 in a mixed population of patients with COPD and a wide range of airway obstruction as well as in patients with emphysema. We also found that in patients with RV/TLC > 73%, a marked reduction of hyperinflation was associated with better survival as a result of both medical treatment and NPPV. Conversely, as all patients received similar therapy, smaller improvements, or even an increase in lung hyperinflation, could be indicative of a progression of the disease. However, our results probably indicate that hyperinflation is both, a marker of prognosis and target of therapeutic interventions.

The prognostic value of hypercapnia in COPD is much more intricate. A low PaCO2 level might be a negative prognostic factor, yet another study found similar survival in normocapnia (< 45 mm Hg) vs hypercapnia (≥ 45 mm Hg). Patients, however, received predominantly or exclusively LTOT, and their hypercapnia was less pronounced than in the present population. In contrast, mortality in the first year was high if PaCO2 was > 55 mm Hg, and severe hypercapnia was associated with higher mortality in patients with exacerbation. In our analysis, most patients showed severe persistent hypercapnia, which is particularly indicative of poor prognosis compared to reversible hypercapnia.

While these investigations did not provide data on BE, in the present study CHRF was indicated by both elevated PaCO2 and BE, demonstrating renal compensation of persistently elevated PaCO2. In stable COPD with less severe hypercapnia (PaCO2, 48.8 mm Hg; BE, 3.6 mmol/L), there was no association between hypercapnia or BE and long-term survival. Perhaps BE only provides valuable information when certain threshold values are exceeded. While PaCO2 is more prone to short-term fluctuations, BE reflects the long-term metabolic response to chronic persistent hypercapnia that requires hours to be initiated. Thus, due to this inertia of compensatory mechanisms, BE assessed at daytime might reflect respiratory acidosis following nocturnal hypoventilation. Indeed, hypoventilation and acidosis are known to be exaggerated in the type of patients we studied but might be masked during the daytime by augmented ventilation. It could be argued that diuretic therapy might promote alkalosis, thus confounding BE. However, when evaluating only patients receiving diuretics (n = 139), the prognostic value of BE was still significant (p = 0.01, data not shown).

Six months after initiation of NPPV there was a reduction in PaCO2 and BE. When comparing patients showing a decrease in BE by ≥ 42% or 50% with those showing no or smaller changes, reductions in BE were associated with improved survival in patients showing BE ≥ 9 mmol/L at baseline. This observed reduction was probably the combined result of NPPV and concomitant treatment and specifically suggests that BE, an easily obtainable measure, is worth being explored further in patients with CHRF.

As a limitation of our study, PaO2 was measured in only approximately 50% of patients in the absence of oxygen administration, as patients were already receiving LTOT on study inclusion or had severe dyspnea. Thus, the present data do not allow the evaluation of the role of hypoxemia. There is clear evidence for this and the benefits of LTOT in COPD.

Judged by clinical criteria, some patients experienced an exacerbation at baseline, but these were not associated with increased mortality. Thus, we considered it justified to include all patients in the analysis. This was corroborated by the lack of association between CRP or leukocyte levels and survival. Perhaps the reduction of in-hospital mortality in acute exacerbation by NPPV counterbalanced the effect of exacerbations.

In summary, our data revealed that, in patients with severe COPD and CHRF, the degree of metabolic compensation of chronic hypercapnia, expressed as BE, is an independent predictor of mortality that is not accounted for by PaCO2. Moreover, nutritional status and lung hyperinflation were important prognostic factors beyond CHRF itself. The finding that a reduction in BE or lung hyperinflation and an increase in BMI resulted in improved long-term prognosis indicated the consistency of the data. Our results highlight these variables as suitable for the assessment of prognosis under the condition of NPPV and suggest a multidimensional therapeutic approach and monitoring of patients with COPD and CHRF.
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