

## Acute exacerbations in patients with COPD: predictors of need for mechanical ventilation

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**ABSTRACT:** Predictive factors in mechanically-ventilated patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) have been extensively studied but not in spontaneously breathing patients. The aim of this retrospective study was to evaluate the contribution of parameters of respiratory mechanics, clinical and nutritional status in predicting the need for mechanical ventilation (MV) in COPD patients treated with medical therapy for an acute exacerbation.

Anthropometric data, Acute Physiology and Chronic Health Evaluation (APACHE) II score, bedside spirometry, breathing pattern, respiratory mechanics and blood gases were measured in 39 COPD patients upon hospital admission for exacerbation of their disease. Fourteen patients in whom MV was necessary were compared with 25 patients in whom medical therapy was enough for a good outcome.

The discriminant analysis showed, with decreasing order of power, that nutritional prognostic index (NPI), APACHE II score, forced expiratory volume in one second/forced vital capacity (FEV<sub>1</sub>/FVC) ratio, vital capacity (VC) (% predicted) and FVC (% pred) provided a significant distinction between the two groups. The discriminant equation considering NPI, and FVC (% pred) could correctly predict the success in 76% of the patients. A multiparametric stepwise regression analysis showed that APACHE II score was significantly correlated with NPI, VC (% pred), pressure time index (PTI) and duty cycle, *i.e.* fraction of inspiration to duration of total breathing cycle ( $t_i/t_{tot}$ ).

In conclusion, underlying general conditions as assessed by malnutrition and APACHE II score were shown to be unfavourable indices of outcome for chronic obstructive pulmonary disease patients who experienced an exacerbation of their disease and were treated with medical therapy. Flow limitation data as assessed by the forced expiratory manoeuvre may provide additional information.

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Assessment of therapeutic response and prediction of prognosis are two of the major goals of bedside respiratory monitoring [1]. Some studies have investigated the outcome of chronic obstructive pulmonary disease (COPD) patients requiring mechanical ventilation (MV). In these patients, several indices have been proposed as predictive of the outcome and weaning possibility [2, 3]. Acute Physiology and Chronic Health Evaluation (APACHE) II severity score upon admission has been shown to have a significant correlation with outcome and mortality in patients with different pathologies, including COPD [2, 4]. Nutritional status was found: 1) to be an independent factor influencing the prognosis of stable COPD [5]; 2) to influence the need for Intensive Care Unit (ICU) admission for COPD patients with respiratory insufficiency [6] and 3) to be a predictive parameter for the outcome of noninvasive MV in exacerbations of COPD [2].

Whilst predictive factors in mechanically-ventilated patients have been extensively studied [7], to our knowledge, only one study has been performed on predictive parameters for outcome in COPD patients suffering from an acute exacerbation treated with medical therapy alone

[8]. In that study patients who died tended to be older and were significantly more acidotic, hypotensive and uraemic compared with those who survived [8]. The recent availability of a new device for bedside monitoring of respiratory mechanics and ventilatory pattern may allow additional risk factors for respiratory diseases to be assessed [9]. The purpose of this paper was to evaluate whether respiratory physiological measurements detectable at the bedside may improve the power of clinical and nutritional indices in predicting the need for MV in spontaneously breathing COPD patients with an acute exacerbation of their disease.

### Methods

#### Patients

Thirty nine patients consecutively admitted to our respiratory department (RD) due to an acute exacerbation of their disease were studied. The diagnosis of COPD

was made according to the American Thoracic Society (ATS) criteria [10]. The patients had been admitted because of increased coughing, production of purulent sputum, fever, severe bronchospasm with lack of response to inhalation therapy, or increased dyspnoea without radiological signs of parenchymal infiltrates. Criteria for exclusion from the study were pneumonia (demonstrated by chest radiography and positive sputum culture), presence of concomitant severe chronic diseases, cancer, cerebrovascular accident, dilated cardiomyopathy, comatose status, and inability to perform bedside measurements due to need for immediate MV.

Thirty out of the 39 patients were habitually followed by our institution, 21 out of 39 had been on long-term oxygen therapy for  $28 \pm 13$  months (no previous clinical history was available for three patients). All patients underwent standard medical and oxygen therapy by means of a 24–28% Venturi mask. Standard medical treatment consisted of theophylline, antibiotics, steroids and beta-agonists or both, *i.v.*, either orally or *via* aerosol [11]. No patients received respiratory stimulants.

Patients gave informed consent to the study which was approved by the Ethics Committee of Salvatore Maugeri Foundation.

### Measurements

All data were recorded in the same session at the bedside, with the patients in a semirecumbent position, shortly after admission. Blood gas analysis (BGA) was performed first, while the other measurements were assessed in a random order.

**Nutritional data.** Percentage of ideal body weight (% IBW) was computed referring to the Metropolitan Life Insurance Company table [12]; Nutritional prognostic index (NPI) was calculated as proposed by MULLEN *et al.* [13]. NPI is an index describing the nutritional status as good (<30%), bad (30–59%) or very bad (>60%), taking into account anthropometric, serological and immunological data (see Appendix). In patients with peripheral oedema, nutritional status was assessed after disappearance of oedema following diuretic therapy.

**Blood gases.** BGA was performed by means of an analyser (EGA system; Ciba Corning Rome, Italy) on blood samples drawn from the radial artery while patients were breathing: room air (31 out of 54); or with a 24% O<sub>2</sub> Venturi mask (12 out of 54); or with a 28% O<sub>2</sub> Venturi mask (11 out of 54).

**Lung function tests.** Dynamic lung volumes were measured by means of a portable spirometer (Pony class 1 Type B, Cosmed, Rome, Italy); both digital read-out and paper tracings were obtained. The highest value of three different tests was considered and expressed as percentage of the predicted value (% pred) [14].

**Breathing pattern and respiratory mechanics.** A specific device (Bicore, CP-100; Bicore, Irvine, CA, USA) has been used for bedside monitoring of mechanics and breathing pattern. Volumes and flows were assessed by

means of a flow transducer (Var Flex Flow transducer, CP-100; Bicore Irvine, CA, USA). Values of inspiratory tidal volume (VT,I), expiratory tidal volume (VT,E), respiratory frequency (*f*<sub>R</sub>), expiratory minute ventilation (V'E), the *f*<sub>R</sub>/VT ratio, and the duty cycle, *i.e.* inspiratory time/total time ratio (*t*<sub>I</sub>/*t*<sub>tot</sub>) were measured. A noseclip avoided leaks. Oesophageal pressure (*P*<sub>oes</sub>) was measured by means of an oesophageal catheter with a 10 cm balloon at the distal end (part No. 700-3-100 Bicore, Irvine, CA, USA) passed transnasally and positioned in the lower third of the oesophagus. The position of the catheter was checked by means of the occlusion technique [15]. Airway pressure, airway flow and *P*<sub>oes</sub> were transmitted to a monitor (CP-100 Bicore) and recorded on a paper recorder (ThinK Jet Hewlett Packard, Waltham, MA, USA). Work of breathing (WOB), *P*<sub>oes</sub> swings, intrinsic positive end-expiratory pressure (PEEP<sub>i</sub>), dynamic compliance (*C*<sub>dyn</sub>), maximal static inspiratory pressure (MIP), pressure-time product and index (PTP and PTI, respectively) were calculated from *P*<sub>oes</sub>, flow and volume data. All data were recorded for at least 2 min after the patients had developed a "steady-state" in their breathing pattern and had reached good confidence with the oesophageal catheter for at least 15 min. The final data were collected as average data of at least 30 breathing acts, eliminating those affected by artifactual *P*<sub>oes</sub> variations. The Appendix shows further details of measurements and calculated parameters (for parameter abbreviations see the Appendix).

MIP was assessed on the paper recording during a maximal inspiratory effort generated after manual occlusion of the flow transducer starting from functional residual capacity (FRC). The subjects were verbally encouraged to achieve maximal strength. The highest value of three tests was considered in data analysis. Reliability and accuracy of the Bicore CP-100 pulmonary device has been described previously [9, 16].

**APACHE II score.** This prognostic score was assessed at admission. It includes 12 physiological variables: body temperature, mean systemic arterial blood pressure, heart rate, respiratory rate, oxygenation status, pH, blood serum sodium and potassium, creatininaemia, haematocrit, white cell count, the neurological status expressed by the Glasgow coma score, age and underlying conditions [4].

**Outcome.** Patients who needed MV in spite of adequate medical therapy, *i.e.* with a rapid deterioration in neurological status, or an acute onset of respiratory distress, (severe hypercapnia with an arterial carbon dioxide tension (*P*<sub>a,CO<sub>2</sub></sub>)>8.7 kPa (65 mmHg), acute decrease in pH <7.35) or a worsening in tachypnoea and the presence of paradoxical abdominal breathing pattern, were defined as the "Failure Group". Patients with a good outcome after medical therapy alone were defined as the "Success Group". Choice of modality of MV (invasive *versus* non-invasive) was made according to the severity of acute respiratory failure (ARF), acceptance *vs* noninvasive MV and physician's familiarity with the procedure [2].

Causes of death were obtained from hospital registers and from our own knowledge. Pulmonary embolism was confirmed by lung perfusion scan. Gastric bleeding was diagnosed by clinical evidence. Multiple organ failure (MOF) was defined on clinical and functional basis.

### Statistical analysis

All variables used were analysed by means of Skewness, Kurtosis and Shapiro, and Wilk's W Statistic for testing normality. Either a Mann-Whitney or a parametric t-test was used to show: 1) baseline differences between Failure and Success Groups; and 2) baseline differences between dead and surviving patients of Failure Group. The predictive models were developed using stepwise discriminant analysis. Multiple stepwise correlations were performed between the single APACHE II score index and nutritional, lung function, respiratory mechanics and breathing pattern data. To use the parametric discriminant analysis and correlation tests, the variables found to be nonparametric were logarithmically transformed [17]. Arterial oxygen tension ( $P_{a,O_2}$ ) and pH were not taken into account for outcome prediction because they were included in the APACHE II score.  $P_{a,CO_2}$  was not included in the statistical analysis because it was influenced by  $P_{a,O_2}$  values obtained with different levels of inspiratory oxygen fraction ( $F_{I,O_2}$ ). A p-value of less than 0.05 was considered to be significant. All the results of multiple comparison were corrected using the Bonferroni test.

### Results

From 30 out of 39 patients regularly followed by our institution, 21 subjects had been on long-term oxygen therapy for  $28 \pm 13$  months. Seventy percent of patients were admitted with cough, sputum retention and fever, 66% with severe bronchospasm and lack of response to inhalation bronchodilators, 44% with peripheral oedema, and 98% with severe dyspnoea.

Demographic, anthropometric characteristics and success rate of patients in the study are shown in table 1. In comparison with patients in the Success Group, the Failure Group had significantly reduced body weight as a % IBW, a higher NPI, and a lower transferrin and triceps skinfold thickness, indicating a poorer nutritional status. APACHE II score was more severe in the Failure Group patients (table 1).

Table 2 shows lung function tests upon admission:  $P_{a,O_2}/F_{I,O_2}$ , arterial oxygen saturation ( $S_{a,O_2}\%$ ), forced expiratory volume (FEV<sub>1</sub>) (% pred) and FVC (% pred) were significantly lower, and  $P_{a,CO_2}$  significantly higher, in patients from the Failure Group, in comparison to patients from the Success Group.

All patients tolerated respiratory mechanics evaluation. Table 3 shows respiratory mechanics upon admission: WOB,  $P_{oes}$ , PTP, PTI and PEEP<sub>i</sub> were significantly greater in patients from the Failure group in comparison to Success Group.

Discriminant analysis showed that, in decreasing order of power, NPI (F=20.15), APACHE II (F=18.92), FEV<sub>1</sub>/FVC ratio (F=14.09), VC% pred (F=9.17) and FVC % pred (F=9.07) were the significant parameters which provided distinction between the two groups.

As shown in table 4, the final discriminant equation including NPI and FVC % pred could correctly predict the outcome in 76% of patients. In particular, it could correctly predict the need for MV in 64% of the patients and success of medical therapy in 83% of the patients.

Table 1. – Demographic, nutritional data and APACHE score at admission

	Failure Group (n=14)	Success Group (n=25)	p-value
Sex M/F	12/2	20/5	
Age yrs	61±9 (38–73)	64±6 (38–82)	NS
Weight kg	53±12 (33–83)	67±16 (39–123)	<0.01
NPI*	46±22 (20–74)	24±8 (13–38)	<0.001
Albumin g·dL <sup>-1</sup>	3.8±0.35 (2.6–4.1)	4.1±0.4 (3.5–4.6)	
TSF mm	9±5 (4–20)	22±11 (13–31)	
Transferrin mg·dL <sup>-1</sup>	168±31 (126–206)	194±29 (153–280)	
Anergy %	95	69	
IBW* %	86±21 (47–110)	109±31 (77–170)	<0.01
APACHE II*	20±7 (15–29)	12±3 (10–22)	<0.001

\*: data tested by means of Mann-Whitney analysis. Values are presented as mean±SD, and range in parenthesis. Failure: unsuccessful medical therapy; Success: successful medical therapy; M: male; F: female; TSF: triceps skinfold; Anergy: no cutaneous response to tine test; IBW: ideal body weight; NPI: nutritional prognostic index; APACHE: Acute Physiology and Chronic Health Evaluation; NS: nonsignificant.

Multi-parametric stepwise regression analysis showed that APACHE II score was significantly correlated with NPI (r=0.73; p<0.0001), with VC (r=0.42; p<0.0001) and with PTI and  $t/t_{tot}$  (r=0.45; p<0.01).

Table 2. – Lung function at admission

	Failure Group (n=14)	Success Group (n=25)	p-value
$P_{a,O_2}/F_{I,O_2}$	2.26±0.10 (2.1–2.4)	2.60±0.13 (2.21–2.70)	<0.01
$P_{a,CO_2}$ kPa	7.8±1.3 (4.5–9.1)	6.2±1.0 (4.2–8.2)	<0.001
pH	7.34±0.03 (7.30–7.40)	7.36±0.03 (7.33–7.42)	<0.05
HCO <sub>3</sub> <sup>-</sup> mmol·L <sup>-1</sup>	35±5 (22–43)	30±6 (21–39)	<0.05
$S_{a,O_2}$ * %	82±9 (62–93)	89±7 (69–94)	<0.01
FEV <sub>1</sub> * % pred	26±11 (15–44)	41±18 (17–60)	<0.001
FVC* % pred	37±9 (18–49)	53±19 (30–68)	<0.001
VC* % pred	44±10 (29–60)	60±18 (24–70)	<0.005
FEV <sub>1</sub> /FVC* %	37±11 (22–59)	51±11 (30–64)	<0.05

Values are presented as mean±SD, and range in parenthesis. BGA values are on different  $F_{I,O_2}$ . \*: data tested by means of Mann-Whitney analysis.  $P_{a,O_2}$ : arterial oxygen tension;  $F_{I,O_2}$ : inspiratory oxygen fraction;  $P_{a,CO_2}$ : arterial carbon dioxide tension; HCO<sub>3</sub><sup>-</sup>: serum bicarbonate level;  $S_{a,O_2}$ : arterial oxygen saturation; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; VC: vital capacity; BGA: blood gas analysis.

Table 3. – Respiratory mechanics at admission

	Failure Group (n=14)	Success Group (n=25)	p-value
$V_T$ mL	401±225 (100–780)	345±146 (130–700)	NS
$f_R$ breath·min <sup>-1</sup>	25±11 (11–47)	26±7 (12–44)	NS
$V'E$ L·min <sup>-1</sup>	9±5 (2–24)	8±4 (3.1–17)	NS
$f_R/V_T$	116±146 (10–400)	105±74 (30–285)	NS
WOB J·L <sup>-1</sup>	1.74±0.49 (0.9–2.86)	1.22±0.6 (0.34–2.48)	<0.001
$P_{oes}$ cmH <sub>2</sub> O	19±7 (10–44)	14±6 (5.1–27)	<0.005
PEEP <sub>i</sub> cmH <sub>2</sub> O	3.3±2.4 (1.1–11)	1.5±1.9 (0–7)	<0.01
$C_{dyn}$ mL·cmH <sub>2</sub> O	63±36 (33–235)	67±53 (15–208)	NS
$t_I/t_{tot}$	0.36±0.06 (0.22–0.49)	0.41±0.06 (0.27–0.5)	<0.05
MIP cmH <sub>2</sub> O·s <sup>-1</sup> ·min <sup>-1</sup>	40±22 (18–65)	50±19 (13–72)	<0.05
PTP cmH <sub>2</sub> O·s <sup>-1</sup> ·min <sup>-1</sup>	326±101 (157–480)	265±135 (28–510)	<0.005
PTI	0.17±0.09 (0.07–0.45)	0.11±0.06 (0.02–0.30)	<0.01

Values are presented as mean±SD, and range in parenthesis. Data tested by means of Mann-Whitney analysis except  $t_I/t_{tot}$ .  $V_T$ : tidal volume;  $f_R$ : respiratory frequency;  $V'E$ : minute ventilation; WOB: work of breathing;  $P_{oes}$ : oesophageal pressure; PEEP<sub>i</sub>: intrinsic positive end-expiratory pressure;  $C_{dyn}$ : dynamic compliance;  $t_I/t_{tot}$ : duty cycle; *i.e.* fraction of inspiration to duration of total breathing cycle; MIP: maximal inspiratory pressure; PTP: pressure-time product; PTI: pressure-time index; NS: nonsignificant.

In the Failure Group (14 subjects), medical therapy failed after a mean duration of treatment of 26±31 h (range 1–120 h) necessitating MV: invasive in five patients (35%), noninvasive in nine patients (65%). At the time of starting MV, the patients in the Failure Group had pH=7.25±0.07;  $P_{a,CO_2}$ =13±1.6 kPa (98±12 mmHg);  $P_{a,O_2}/F_{I,O_2}$ =1.80±0.25; APACHE II score=26±4. Six patients (43%) died in spite of MV. The final causes of death were: one pulmonary embolisms as confirmed by lung scan; one severe gastric bleeding; two severe pneumonia; and two MOF. Four out of these six patients died in an Intermediate Intensive Care Unit affiliated to our department; all of them were being ventilated invasively. Two patients died in our RD during noninvasive MV.

The total success rate of noninvasive MV was 77% (total duration of the two ventilation modalities was

Table 4. – Accuracy of the equation to predict outcome

	Accuracy	Sensitivity	Specificity	PPV	NPV
Failure	0.76	0.69	0.79	0.64	0.83
Success	0.76	0.79	0.69	0.83	0.64

Failure=(NPI × 0.21)+(FVC% × 0.14) -8.28. Success=(NPI × 0.11)+(FVC% × 0.20) -7.53. PPV: positive predictive value; NPV: negative predictive value; NPI: nutritional prognostic index; FVC: forced vital capacity.

4.2±2.2 vs 12±5 days for noninvasive and invasive MV, respectively), whilst one out of five (20%) patients invasively ventilated survived.

Patients of the Failure Group who died differed significantly from patients surviving only with respect to the following parameters, assessed at admission: NPI (61±13 vs 30±20; p<0.01); % IBW (76±14 vs 97±20%; p<0.05); serum albumin (3.2±0.37 vs 4.2±0.34 g·dL<sup>-1</sup>); serum transferrin (140±12 vs 196±25 mg·dL<sup>-1</sup>); APACHE II score (26±3 vs 14±6; p<0.005), MIP (30±13 vs 48±21 cmH<sub>2</sub>O; p<0.05) and PTI (0.23±0.13 vs 0.13±0.04; p<0.05). In comparison to eight survivors, when submitted to MV, patients who died showed significantly (p<0.05) worse values for pH (7.23±0.05 vs 7.29±0.03), and  $P_{a,O_2}/F_{I,O_2}$  (1.69±0.45 vs 2.1±0.41).

## Discussion

This study has shown that in a group of COPD patients admitted to a Respiratory Department due to an acute exacerbation of their diseases: 1) NPI and FVC (% pred) could correctly predict the outcome in 76% of the patients; 2) NPI, APACHE II, FEV<sub>1</sub>/FVC ratio, VC % pred and FVC % pred were significant in predicting the need for MV; 3) NPI has to be considered a main prognostic index; 4) NPI, VC (% pred), PTI and  $t_I/t_{tot}$  were the variables best correlated with APACHE II score; and 5) APACHE II score, NPI, % IBW, MIP and PTI were significantly more compromised in patients who died in comparison to survivors of the Failure Group.

**Nutritional parameters.** Our data confirm that severe undernutrition, as assessed by an increase in NPI and a reduction in % IBW, appears to be a risk factor for prognosis confirming the findings of previous reports [2, 5, 18–20]. The association between malnutrition and COPD has been recognized for many years. Factors related to the nutritional status are considered as an independent influence on the course of stable COPD [5]. Poor nutritional status can adversely affect pulmonary function, not only by impairment of respiratory muscle strength and exercise tolerance [21, 22], but also by decreased ventilatory drive and altered lung defence mechanisms [23]. Percentage of IBW was previously found to be an important predictive factor for admission into the ICU [6]. LAABAN *et al.* [20] found that malnutrition was more frequent and more severe in COPD patients requiring MV, suggesting that assessment of nutritional status should be systematically performed in COPD patients with ARF. In our study, patients with worse outcome showed normal levels of serum albumin in spite of their low body weight. This may be surprising. In a study by MENZIES *et al.* [24] on patients in weaning from MV, the mean serum albumin was 2.8 g·dL<sup>-1</sup>, but in a study by RIEVES *et al.* [25] serum albumin levels were similar to ours. Visceral proteins are considered to reflect the severity of injury and prognosis in critically ill hospitalized patients, but they often do not accurately reflect nutritional status or adequacy of nutritional support [26, 27].

**Breathing pattern and respiratory mechanics.** The  $f_R/V_T$  ratio was not different in the patients in the two groups. A high  $f_R/V_T$  ratio has been considered as a predictive

index of difficult weaning [7]. To our knowledge, this is the first report of  $fR/V_T$  ratio in the prediction of the outcome of acute exacerbation in spontaneously breathing COPD patients. A breathing pattern with high  $fR$  and low  $V_T$  in stable COPD patients has been considered as a useful strategy in avoiding inspiratory muscle overload and failure [28].

WOB was increased in both groups but statistically more so in patients in the Failure Group. During an exacerbation, the presence of high airway resistance and reduction in pulmonary compliance makes COPD patients prone to develop dynamic hyperinflation, with an increase in WOB and a decrease in inspiratory muscles function [11].  $P_{oes}$  was found to be high in both groups, the Failure Group showing a value double that of the Success Group, indicating a greater load on inspiratory muscles. In this study of spontaneously breathing patients, PEEP<sub>i</sub> was detectable with a mean value that was greater in patients from the Failure Group (table 3). Our results confirm those by other authors, showing that PEEP<sub>i</sub> is commonly detectable in patients with moderate to severe airway obstruction without acute respiratory failure [29]. In more severe COPD patients needing MV, APPENDINI *et al.* [30] found a PEEP<sub>i</sub> value of 5.6 cmH<sub>2</sub>O. PTP was significantly higher in the Failure Group. PTP has been shown to be an index of energy consumption of the respiratory muscles indicating the patient's effort to breathe [31].

PTI, also referred to as the tension time index [32], can be found to be increased by any combination of increased resistance, decreased compliance, inspiratory muscle weakness and undernutrition [33]; our data confirmed these observations. BELLEMARE and GRASSINO [32] showed that a tension time index (TTI) of 0.15 may be considered a critical level for development of fatigue. Respiratory muscle fatigue could be identified in less than 10% of COPD patients who were hospitalized for worsening dyspnoea [34]. In agreement with this observation, we found that patients in the Failure Group in comparison to the Success Group showed a mean PTI level of  $0.17 \pm 0.09$  and  $0.11 \pm 0.06$ , respectively, and a mean MIP value of  $40 \pm 22$  and  $50 \pm 19$  cmH<sub>2</sub>O respectively, indicating a fatiguing pattern. On admission, in the six patients from the Failure Group who died, PTI and MIP were significantly different from those in the eight patients who survived.

**Spirometry.** Most studies have shown that the degree of airflow limitation is a very reliable index of the severity and of the outcome of pulmonary disease [35]. Moreover, POSTMA and SWITER [36] concluded that a rapid decrease in FEV<sub>1</sub> indicates a rapid progression of the natural history of disease, leading to inevitable death. Our study confirms our previous report that the time course of obstruction indices is useful in predicting ICU necessity in COPD patients with respiratory insufficiency [6].

**Outcome.** In the study by JEFFREY *et al.* [8], 12% of COPD patients with an exacerbation died, being more acidotic, uraemic upon admission and having a lower systolic blood pressure than those patients who survived. These findings probably reflect the severity of the systemic disturbance underlying the exacerbation. Indeed,

in the present study, we show that APACHE II score, a well-known comprehensive index of severity [4], had a high predictive value for MV necessity. APACHE II score was also found to be significantly different upon admission for patients in the Failure Group who died in comparison to patients who survived. The overall mortality rate (15%) of our patients was higher than that reported by JEFFREY *et al.* (12%) [8]. In the literature, mortality rate ranged 6–34% [8]. Direct comparison of the mortality between studies is difficult, as the criteria for inclusion, medical therapy and, moreover, indication and use of MV between countries are different.

The accuracy of the predictive equation found may be insufficient to allow the clinician to perform MV early (26% of those predicted to fail did not) or to treat less aggressively with medication (17% of those predicted to be successful actually required MV). Nevertheless, the usefulness of these values is enhanced by the recent availability of noninvasive modalities of MV, which may spare unfavourable side-effects and complications in comparison to an unnecessary endotracheal intubation [37].

**Limitations of the study.** The use of a multiparametric index (NPI) to assess nutritional status must be interpreted with caution, in particular because the single parameters may express the level of inflammation rather than the actual nutritional depletion. The use of the APACHE II score has some limitations. It could offer an advantage or a disadvantage to individual ICUs, depending on the kind of patients treated [38]. The major limitation appears to be the lack of information about specific characteristics of respiratory patients. At admission, in comparison to the Success Group, the Failure Group had a higher APACHE II score which further worsened when MV was needed. Thus, the APACHE II score can prognostically stratify patients and is correlated with nutritional status, VC and respiratory muscle function. Reliability of invasive measurements in patients with acute exacerbations of COPD may be questioned, due to factors such as fever, bronchospasm, increased secretions, lack of collaboration, *etc.*, preventing the correct performance of manoeuvres. However, patients unable to perform the manoeuvres correctly due to immediate need of MV were excluded from the study.

A retrospective study may be criticized. The predictive factors found in this study are not yet validated and will therefore, require further prospective studies. Validating these predictive indices might improve decision making in early institution of MV in these patients.

In conclusion, underlying general conditions, as assessed by malnutrition and APACHE II score, were shown to be unfavourable indices of outcome for chronic obstructive pulmonary disease patients who experienced an exacerbation of their disease and were treated with medical therapy. Flow limitation data as assessed by the forced expiratory manoeuvre may provide additional information.

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## Appendix

Nutritional prognostic index (NPI) =  $(150 - 16.6 \times (\text{ALB}) - 0.78 \times (\text{TSF}) - 0.20 \times (\text{TF}) - 5.8 \times (\text{DH}))$ ; where, ALB = serum albumin (g·dL<sup>-1</sup>); TSF = triceps skinfold (mm); TF = serum transferrin (mg·dL<sup>-1</sup>); DH (dermal hypersensitivity) = response to tine test (0 = no reaction, 1 = <5 mm; 2 = >5 mm).

PEEP<sub>i</sub> is calculated as the difference in  $P_{\text{oes}}$ , between the  $P_{\text{oes}}$  plateau (as measured at the end of expiration) and the  $P_{\text{oes}}$  reading at the start of inspiratory flow [29].

WOB expressed as J·L<sup>-1</sup> was calculated from the area subtended by the  $P_{\text{oes}}$  developed during inspiration and the relaxation curve of the chest wall (estimated chest wall compliance equal to 200 mL·cmH<sub>2</sub>O<sup>-1</sup>).

Delta  $P_{\text{oes}}$  was calculated as the negative swing in  $P_{\text{oes}}$  from the measured end- $P_{\text{oes}}$  plateau to the minimal value.

$C_{\text{dyn}}$  was calculated as follows:  $C_{\text{dyn}} = V_{\text{T}} / (P_{\text{tp},1} - P_{\text{tp},2})$ ; where  $V_{\text{T}}$  = tidal volume;  $P_{\text{tp},1}$  = transpulmonary pressure at maximum volume zero flow;  $P_{\text{tp},2}$  = transpulmonary pressure at minimum volume zero flow.

PTP was calculated with the following formula: Integral  $((\text{PEE} - P_{\text{oes}}) + (\text{Vol}/C_{\text{cw}})) dt / t_{\text{min}}$  ( $\text{PEE} = \text{end-}P_{\text{oes}}$ ;  $P_{\text{oes}}$  = current oesophageal pressure; Vol = current tidal volume;  $C_{\text{cw}}$  = chest wall compliance;  $t_d$  = sample time;  $t_{\text{min}}$  = duration of breath in minutes).

PTI was calculated as mean  $P_{\text{oes}} / \text{MIP} \times t_i / t_{\text{tot}}$ .

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