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Predictors of outcome for patients with severe respiratory failure requiring non invasive mechanical ventilation

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Abstract. – OBJECTIVE: Failure to identify patients in whom non-invasive ventilation (NIV) would be unsuccessful may cause inappropriate delay in intubation. Aim of this study was to determine predictors of NIV failure.

PATIENTS AND METHODS: We retrospectively evaluated COPD patients, undergoing NIV for at least 12h because of hypercapnic acute respiratory failure.

Univariable and multivariable analyses were performed on: age, gender, APACHE II and GCS, gas exchange at admission, during NIV and at discharge/death, length of stay. ROC analysis for pH START and APACHE II were performed.

RESULTS: Among 201 individuals enrolled, NIV failed in 50. In the logistic regression model only APACHE II was found to have an independent effect on the outcome (p < 0.0001, OR 1.179, 95% CI 1.101-1.263 as quantitative variable; p < 0.0001, OR 3.753, 95% CI 1.798-7.835, as qualitative variable, > 20.5).

CONCLUSIONS: APACHE II may be a crucial parameter in predicting NIV failure; further multicentric studies are needed to better define NIV indications.

Key Words:
Acute respiratory failure, COPD, Non invasive mechanical ventilation, Predictive factors.

Introduction

Non-invasive ventilation (NIV) has been successfully applied in patients acute respiratory failure (ARF) due to COPD, with a significant reduction of mortality rate, need for endotracheal intubation (ETI), and length of stay, compared to standard therapy[1-4].

Both NIV and invasive mechanical ventilation (IMV) are effective in determining a significant improvement in gas exchange, with similar length of stay in Intensive Care Unit (ICU) and in-hospital mortality[5]. Moreover, NIV has been associated with a lower risk of nosocomial infections, shorter lengths of stay in ICUs[6], less hospitalizations in the following 12 months[5]. In In addition, in the last years, it has been investigated the effect of NIV on systemic and pulmonary inflammation in COPD[7].

Because of failure rates ranging from 5% to 50%, NIV guidelines recommend not to use it as a substitute for IMV, in patients in whom the latter is more appropriate[1,2]. Failure to identify individuals who are likely to fail NIV may cause inappropriate intubation delay, increasing morbidity and mortality[8].

Recent literature has evaluated the presence of prognostic factors predicting NIV failure: ARF severity[9-11], response to NIV in the first hours of treatment[10,12], Acute Physiology and Chronic Health Evaluation (APACHE) II score[9,11,12], Glasgow Coma Scale (GCS)[9,12], C-Reactive Protein (CRP) levels, comorbidities[12], age[13], Body Mass Index (BMI)[14], and initial glycaemia values[11].

This study aims to determine factors affecting the likelihood of NIV failure in patients admitted for acute exacerbation of COPD and hypercapnic ARF.

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Patients and Methods

We evaluated a population of COPD patients, who were referred to our centers between January 2009 to June 2011, showing hypercapnic ARF due to COPD exacerbation and undergoing mechanical ventilation for at least 12h.

The COPD diagnosis and the identification criteria for respiratory failure were determined according current guidelines[15,16].

At admission, the following parameters were recorded: demographics, comorbidities, respiratory rate (RR), arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) partial pressure and arterial pH, heart rate (HR), GCS[17] and APACHE II[18].

We excluded from evaluation patients affected by severe renal or heart failure or myocardial infarction, neoplastic disease, and acute cerebrovascular event.

The decision of starting mechanical ventilation (MV) was based on the lack of improvement in gas exchange despite a 1 hour aggressive medical management in spontaneous breathing and controlled oxygen-therapy.

In presence of acute alteration of consciousness, patients underwent ETI and IMV.

The following criteria allowed the beginning of NIV: mental status (i.e. ability to follow simple commands and to clear secretions) and a cardiovascular stable condition[19]; after the beginning of NIV, the following conditions were criteria for switch to IMV: cardiac or respiratory arrest; non-respiratory organ failure; upper-airway obstruction; inability to protect the airway (and/or high risk of aspiration) and to clear secretions[8].

Blood gas balance was measured on admission, 1h after modifying the ventilator's setting, within 2-4 hours following initiation and after cessation of NIV (at discharge/death/ETI).

Standard medical therapy (bronchodilators, corticosteroids, antibiotics, and controlled oxygen) was maintained all along during in-hospital stay.

Length of stay, need for ETI (and tracheostomies), success (and failure) rate, number of deaths, discharges, transfers to other wards or ICUs were also recorded.

A retrospective analysis was conducted on all patients to identify characteristics that could predict a poor outcome.

The outcome variable was defined as failure of NIV due to invasive ventilation or death.

Results are presented as number (percentage) or mean; median (standard deviation) unless otherwise stated.

Continuous variables were analyzed using a Student's *t* test (normal distributed data) or Mann-Whitney *U*-test (non-normal distributed data); categorical values were analyzed using the χ^2 test or the Fisher's exact test.

Statistical significance was assumed at a *p* value less than 0.05.

For the variables pH START and APACHE II score we calculated sensitivity, specificity, likelihood ratios and their confidence intervals, and we performed the receiving operating characteristics (ROC) curve. Finally we choose two cut-off values (7.20 for pH START and 20.5 for APACHE II) and then "dichotomized" the two continuous variables on the basis of these two cut-offs.

Multivariable logistic regression was used to analyze the independent effect of each variable on the outcome: age, gender and variables with $p \leq 0.25$ in univariate analysis were included in logistic regression model. APACHE II and pH START were considered both as continuous variables and as dichotomized variables. Variables with a p value < 0.05 were considered statistically significant and are reported as odds ratios (OR) with 95% confidence intervals.

We finally selected two subgroups of patients: (1) with pH START > 7.20 and ≤ 7.25, and (2) with APACHE II > 20.5, and for each of the two subgroups we repeated univariable and multivariable analysis.

Statistical Analysis

Statistical analysis was performed using the statistical package SPSS (version 19; SPSS Inc.; Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

Analysis of the Entire Cohort

Among 379 patients evaluated, one hundred and seventy-eight patients were excluded for exitus or ETI in the first 24 hours, for inability to tolerate NIV, or because of the presence of other exclusion criteria (e.g. contraindications to NIV or severe medical disorders).

Demographic characteristics, baseline parameters at admission and evaluated outcomes are shown in Table I.

Patients in whom NIV succeeded had: lower APACHE II score (20.02 ± 4.81 vs 24.84 ± 6.35, $p < 0.001$) and $PaCO_2$ at admission (93.10 ± 15.08 vs 98.45 ± 16.09, $p = 0.029$) and after 2-4

Table I. Demographic characteristics, baseline parameters at admission and evaluated outcomes.

Number of individuals	201
Gender (m/f)	107/94
AGE (years)	71.63; 73.00 (8.69)
GCS	12.52; 13.00 (2.78)
APACHE II	21.22; 20.00 (5.62)
PaO_2 start (mmHg)	57.01; 55.00 (17.27)
$PaCO_2$ START (mmHg)	94.43; 93.00 (15.47)
pH START	7.26; 7.27 (0.06)
RR START breaths/min)	24.93; 25.00 (8.00)
PaO_2 NIV (mmHg)	67.87; 66.00 (13.00)
$PaCO_2$ NIV (mmHg)	78.74; 77.00 (14.14)
pH NIV	7.34; 7.34 (0.06)
PaO_2 END (mmHg)	67.07; 65.00 (11.44)
$PaCO_2$ END (mmHg)	70.43; 65.00 (21.13)
pH END	7.37; 7.38 (0.08)
Lenght of stay (days)	13.00; 10.00 (11.34)
Success/Failure	151/50
ETIs (n)	23 (11.4%)
Tracheostomies (n)	9 (4.5%)
Deaths (n)	33 (16.4%)
Discharges/transfers to other units other units (n)	157 (78.1%)
Transfers to ICU	10 (4.97%)

hours of NIV (77.62 ± 13.62 vs 82.12 ± 15.24, *p* = 0.044), and higher pH at admission (7.26 ± 0.06 vs 7.23 ± 0.08, *p* = 0.033), and GCS score (12.94 ± 2.44 vs 11.24 ± 3.32, *p* = 0.001).

In the ROC analysis the AUC for pH START was 0.601 (95% CI 0.506 to 0.696), while for APACHE II was 0.718 (95% CI 0.632-0.804). Cut off values were, respectively 7.255 (sensitivity 0.616; specificity 0.500; LR 1.23) and 20.50 (sensitivity 0.583; specificity 0.720; LR 2.08).

To evaluate the independent effect of each variable on the outcome we considered also the pH START cut off value of 7.205 (sensitivity 0.841; specificity 0.340; LR 1.27).

In the univariate analysis and in the logistic regression model the variables pH START and APACHE II score were considered both as absolute values (continuous variables) and as dichotomized values (APACHE II ≤ or > 20.5; pH START ≤ or > 7.205 or 7.255; categorical variables). Patients in whom NIV was successful had a pH START > 7.20 (*p* = 0.006, OR 0.37, 95% CI 0.18-0.76), and an APACHE II score ≤ 20.5 (*p* < 0.001, OR 3.59, 95% CI 1.79-7.21). In the logistic regression model only APACHE II was found to be an independent predictor of the outcome (Table II).

None of the examined variables were found to have an independent effect on the outcome in the univariate and in the multivariate analysis in the subgroup of patients with pH START > 7.20 and ≤ 7.25 (data not shown).

In the subpopulation of individuals with APACHE II score > 20.5 patients in whom NIV succeeded had lower APACHE II score (24.54 ± 3.16 vs 27.72 ± 4.91, *p* = 0.001); in the logistic regression model APACHE II and was found to be independent predictors of the outcome (Table III).

Discussion

In our study we found that, among a panel of different parameters, APACHE II score has a crucial role in predicting NIV failure, being the only variable to have an independent effect on the outcome.

Univariate analysis, consistently with other papers, showed that successfully treated patients had higher initial GCS score and arterial pH, and lower $PaCO_2$ values (at admission and after 2-4 hours of NIV) and APACHE II score[9-12].

Being the most commonly applied index to assess illness severity[20], APACHE II score has been evaluated by several authors as predicting factor in patients treated with NIV. Since 90s, Ambrosino et al[10] found increased values of APACHE II among patients who failed to improve with NIV. Successively Confalonieri et al[9] using logistic regression analysis found that APACHE II, arterial pH, RR and GCS are all able to independently influence the outcome.

In our paper the results of multivariable analysis showed that pH value, RR and GCS were not significantly associated with NIV failure; in accordance with the hypothesis that the risk of failure of a therapeutic approach (NIV), may be especially affected by several associated factors (i.e. age, comorbidities) that may in turn increase each other effect on the outcome and not only by the severity of the respiratory disease.

In line with this Jeffrey and coworkers[21] and Chakrabarti et al[11] respectively found that higher blood urea concentrations and hyperglycaemia were associated with a poorer outcome, suggesting a more systemic involvement in subject going to fail NIV.

With regard to pH, ROC analysis lead us to individuate two pH threshold values (7.20 and 7.25), that drew a undefined area in which this variable lacks its ability to be a clear-cut predictor of success or failure of NIV.

Table II. Analysis of the association of the evaluated variables with the outcome: multivariable analysis (entire cohort, n = 201).

Continuous variables		Failure *p*	OR	95% CI
Age (years)		0.379	1.022	0.974-1.072
GCS		0.464	1.073	0.889-1.295
APACHE II		0.000	1.179	1.101-1.263
pH START		0.915	0.585	0.000-10962.531
RR START (breaths/min)		0.725	1.008	0.964-1.053
$PaCO_2$ START (mmHg)		0.514	0.989	0.958-1.022
pH NIV		0.543	6.915	0.014-3498.494
PaO_2 NIV (mmHg)		0.577	1.008	0.980-1.038
$PaCO_2$ NIV (mmHg)		0.083	1.022	0.997-1.048
ΔPaO_2 (NIV-START) (mmHg)		0.354	1.009	0.990-1.028
Categorical variables		**Failure *p***	**OR**	**95% CI**
Gender	M	0.252	1	0.310-1.359
	F		0.649	
Dichotomized pH START	≤ 7.20	0.457	1	0.192-2.101
	> 7.20		0.635	
Dichotomized APACHE II	≤ 20.5	0.000	1	1.798-7.835
	> 20.5		3.753	
Dichotomized pH START	≤ 7.25	0.384	0.707	0.324-1.543
	> 7.25		1	

Variables with $p < 0.25$ at univariate analysis were included in multivariate linear regression model, with age and gender considered as possible confounders. GCS: Glasgow Coma Scale; APACHE II: Acute Physiology and Chronic Health Evaluation II; RR: respiratory rate; $PaCO_2$: partial pressure of arterial carbon dioxide; NIV: Non invasive ventilation; PaO_2: partial pressure of arterial oxigen; ΔPaO_2: variations of PaO_2 after 2-4 hours of treatment. OR: Odds ratio; 95% CI: 95% confidence interval.

Table III. Analysis of the association of the evaluated variables with the outcome: multivariable (subgroup analysis of patients with APACHE II score > 20.5, n = 99).

Continuous variables		Failure *p*	OR	95% CI
Age (years)		0.491	1.022	0.960-1.088
GCS		0.651	1.045	0.863-1.266
APACHE II		0.001	1.222	1.087-1.375
PaO_2 NIV (mmHg)		0.041	1.034	1.001-1.067
Lenght of stay (days)		0.955	0.999	0.961-1.039
ΔPaO_2 (NIV-START) (mmHg)		0.629	0.994	0.968-1.020
$\Delta PaCO_2$ (START-NIV) (mmHg)		0.783	0.995	0.964-1.028
Categorical variables		**Failure *p***	**OR**	**95% CI**
Gender	M	0.449	1	0.278-1.762
	F		0.700	

Variables with $p < 0.25$ at univariate analysis were included in multivariate linear regression model, with age and gender considered as possible confounders.GCS: Glasgow Coma Scale; APACHE II: Acute Physiology and Chronic Health Evaluation II; PaO_2: partial pressure of arterial oxigen; NIV: Non invasive ventilation; ΔPaO_2, $\Delta PaCO_2$: variations of PaO_2 and $PaCO_2$ after 2-4 hours of treatment. OR: Odds ratio; 95% CI: 95% confidence interval.

Conclusions

A scoring procedure of systemic disease severity, as APACHE II, may be considered a complete and effective prognostic factor, able to predict the outcome in patients with hypercapnic acute respiratory failure due to COPD exacerbation treated with NIV. In addition, arterial pH confirms to be an useful indicator of the severity of respiratory failure, but, alone, a weak prognostic factor, lacking the ability to predict the likelihood of NIV failure.

Our data, together with the recent technological advancements and the improved physician practice in the treatment of hypercapnic respiratory failure due to COPD exacerbation, point out the need for further multicentric studies aimed to better define NIV indication in this subset of patients, with special reference to pH thresholds.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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