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Use of non-invasive mechanical ventilation in the Emergency Department, clinical outcomes and correlates of failure

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Abstract

Background: Despite several studies having been carried in this organizational context, there is an absence of information about the effectiveness of non-invasive mechanical ventilation (NIV) in Emergency Departments (ED), based on a number of suitable patients with acute respiratory failure (ARF) of different aetiology. In particular, it has not yet been defined as to whether the context of the ED suits the necessary requirement of quality for the correct application of the method and if the obtained results are different from those taken in other studies in general or respiratory intensive care unit.
Finally there are few data related to the predictive factors to NIV failure (endotracheal intubation, in-hospital mortality) when applied in the emergency setting.
Methods: To answer these questions we have retrospectively studied a population of 210 patients (95 with COPD exsacerbation ; 92 with acute cardiogenic pulmonary oedema; 23 with severe community acquired pneumonia) treated for ARF in the "critical area" of four Italian level II Emergency Departments. For all patients demographic data; some comorbidities (diabetes, dementia, sopraventricular arrhythmias, obesity); the physiological scores (Kelly, SAPS II, Apache II); the need for pharmacological sedation; vital and blood gas parameters (evaluated at entry, after one hour of treatment and before its suspension); the ventilatory modality applied (CPAP or PSV + PEEP) and some parameters of in-hospital stay (duration of the hospitalization in the critical area, duration of ventilation, compliance to the treatment, patient's refusal to continue it, development of skin necrosis, need for endotracheal intubation, in-hospital mortality) were considered. Finally demographic, event of death with Cox regression or to the need for ETI through linear regression analysis.
Results: Globally, in-hospital mortality reached 13,3%, the percentage of failure with consequent endotracheal intubation amounted to 10,4% . Considering the single aetiologic groups in the patients with COPD, exsacerbation mortality and ETI percentage were 12,6% and 13,7% respectively; in ACPO patients these data respectively amounted to 3,3% and 4,3%; while for patients with severe CAP they respectively reached 34,7% and 21,7%. The following factors were independently correlated with in-hospital mortality: SAPS II > 35, presence of dementia for COPD patients; SAPS II > 35; presence of dementia, presence of sopraventricular arrhythmias for ACPO patients; SAPS II > 35, presence of sopraventricular arrhythmias, presence of dementia for CAP patients. Considering the whole population of 210 patients, the predictive factors of in-hospital mortality were the following: SAPS II > 35; presence of dementia; presence of sopraventricular arrhythmias; maintenance of a respiratory rate above 24 bpm during tratment. The following were factors independently correlated with the need for endotracheal intubation: male gender, pH < 7,32, respiratory rate > 24 bpm, mean arterial pressure > 96 mmHg, all measured at one hour of treatment, for COPD patients; male gender sex, pH < 7,32 , respiratory rate > 24 bpm, $PaCO_2$ > 54,5 mm Hg all measured after one hour treatment for ACPO patients. Given the low number of patients, it was not possible to perform the logistic regression and to calculate the matrix of covariance of the parameter for the CAP group. Considering the whole series of patients, the factors independently correlated to ETI resulting in the following: male gender; diagnosis of COPD; pH < 7,32, respiratory rate > 24 bpm, mean arterial pressure > 96 mm Hg, $PaCO_2$ > 54,5 mm Hg, all measured after one hour treatment.
Conclusions: In conclusion, our study shows that NIV is practicable in the ED with safety and clinical results

comparable to those obtained in the general or respiratory intensive care units. In addition, it points out some factors, quickly obtainable, correlated to a greater probability of in-hospital death or need for ETI. Such factors can contribute more properly to a better selection of the patient candidate to NIV in the ED with obvious effects on organization and saving of resources. The validation of these results on the general plan would suggest the need for future prospective studies.

Key words: non-invasive ventilation, prognostic factors, CPAP, pressure support ventilation

Introduction

Non-invasive mechanical ventilation (NIV) has been proven to be able to reduce: necessity of endotracheal intubation (ETI), in-hospital mortality and the duration of the stay in hospital both in intensive care unit (ICU), and in conventional hospitalization, in the patients struck by acute respiratory failure (ARF), on the basis of a certain number of randomized prospective and controlled studies. Such results appear particularly evident in the studies devoted to the exacerbation of chronic obstructive pulmonary disease (COPD) [1-5], while in the field of acute hypoxaemic respiratory failure, except for acute cardiogenic pulmonary oedema (ACPO) [6-10], NIV performance remains controversial [11-15] with regard to the aforesaid endpoints.

When compared to conventional ventilation, NIV offers the indisputable advantage of an intermittent application, allowing the patient a tolerably good quality of life, and it is not usually asked the employment of deep sedation.Above all, the incidence of nosocomial pneumonia during treatment with NIV is sensitively shown as inferior in comparison to that of the intubated patient submitted to conventional ventilation [16]. NIV use out of the ICU in well selected patients seems to be conceivable without any risks and with a good saving of resources [5]. In fact some clinical studies about NIV employment have been conducted in full, or partly, in the Emergency Department (ED) [17-24] with positive results, although with monocentric studies and with a not elevated number of patients. According to the American Thoracic Society guidelines on NIV utilization in the acute respiratory failure published in 2001 [25], the use of this method in the Emergency Department would have at least some theoretical advantages: Á) the possibility of a timely intervention to prevent a further evolution of the respiratory failure to a more severe condition which could reduce the effectiveness of the non invasive approach ; B) the possibility to provide respiratory support to patients who are not candidates to the intensive care setting ; C) the possibility to treat conscious patients out of a psychologically "stressful" environment such is an intensive care unit. However, it must be observed that the operational context of the ED, especially in Italy, differs a lot from the intensive care unit standards for monitoring technologies and numerical ratio of nurses to patients. In many institutions there is not an "intermediate unit" where critical patients struck by ARF could be treated adequately for a short period. Furthermore the ED, due to often inadequate personnel equipment shows a lack of nurses who can look after a patient under NIV. According for example, to the criteria of the British Thoracic Society guidelines published in 2002.As a matter of fact, BTS suggests that the ED is not considered the ideal place to apply this method [26].

Another field of detective interest concerns the prognostic aspects. Despite the good NIV results referring to specific endpoints already mentioned, the method is not effective in all treated patients. Furthermore it has been looked out upon the hypothesis that NIV would cause in some cases a delay of a necessary intubation with a consequent decay of patient's prognosis [14, 27].

Identification of patients for which this technique has a greater probability of failure is therefore important for a number of reasons. Firstly, it could avoid the discomfort of repeated attempts on non-invasive treatment and prevent the risks of a delay of a necessary intubation in patients in which a NIV failure is to be expected.

Secondly, it is important to consider the possibility of optimizing resources: a patient with a high risk of failure and a candidate to endotracheal intubation (ETI) should be managed in an ICU , whereas a patient with good

probability of success of the method could effectively be treated in a different operational context.

Now a certain number of studies concerning prognostic factors about NIV success/failure are available, mainly in the field of COPD exacerbations and acute hypoxaemic respiratory failure [28-34]. They deal with investigations conducted in the context of general or respiratory intensive care units and their results are not always transferable to the ED.

Available studies devoted to clinical results of NIV in the ED setting are primarly monocentric. In one recent study focusing on prognostic factors of NIV success/failure [35] a special NIV protocol, not uniformly applicable outside the single institution in which the study was conducted, has been employed. This study and others [18] have focused their attention on the predictive value of blood gas analysis and of vital parameters taken before the treatment or shortly thereafter (30 minutes, one hour). Although this approach shows sure clinical utility, especially in emergency, it doesn't allow to detect other factors (physiological and neurological score of the patient, presence of remarkable comorbidities, necessity of sedation, compliance to the treatment, ventilatory mode applied present at arrival to the ED, which could subsequently correlate with an eventual NIV failure or with an inauspicious prognosis.

In a few words, there are two important reasons why the emergency physicians should acquire the highest amount of information about a potential candidate to NIV. First the ED should be the ideal place to apply NIV in order to prevent ARF evolution. Secondly the ED is generally the place from where patients are transferred to the intensive care units.

Patients and methods

Aim of this work was to document clinical results of NIV application in the setting of acute respiratory failure, and to define the predictive factors of its success/failure in the daily operational practice of the ED. For this purpose, we conducted a retrospective study on the clinical cases treated with this technique in the Intermediate Care Unit, defined as "Critical Area", afferent to the Emergency Department of four II level, University-associated Italian metropolitan hospitals (Policlinico S.Orsola Malpighi, Bologna, Policlinico Gemelli, Rome, S. Maria Annunziata Hospital, Florence, S. Giovanni Bosco Hospital, Turin) in the period 01.01.2003-01.06.2003. In this sector of the ED, equipped for NIV, conventional ventilation and for non-invasive monitoring, endowed with a nurses/patients ratio not lower than 1:4, patients who need respiratory or haemodynamic stabilization for different acute pathologies are hospitalized from the Accident and Emergency. The selection of patients to be treated with NIV conformed to previously published criteria [36].

Shortly, fundamental inclusion and exclusion criteria for NIV treatment are the following:

Inclusion criteria

- Moderate-severe dyspnoea at rest, accessory respiratory muscles recruitment , toraco-abdominal dissyncronism
- Respiratory rate (RR) > 25 bpm..
- PaCO2 > 45 mmHg (or an acute increase of 15-20 mmHg)
- pH < 7.35 (but > 7.10)
- PaO2/FiO2 < 250 in hypoxaemic patients brathing air or in ventimask at a FiO2 of 50%
- Acceptable level of consciousness (Kelly score maximum: 3)

Exclusion criteria

- Immediate necessity to protect the airways
- Haemodynamic instability (systolic pressure < 90 mmHg despite vasopressors and fluid bolus)
- Major arrhythmias
- PNX
- Impossibility of adaptation to the mask
- Compromised state of consciousness.
- RR < 12 bpm.
- Respiratory arrest
- Inability to cohoperate

Criteria for tracheal intubation

- Heart or respiratory arrest
- Haemodynamic instability
- Greater arrhythmias (with haemodynamic instability)
- Excess of secretions
- Impossibility to adapt the interface after repeated attempts
- Depression of consciousness during NIV
- Worsening of the dyspnoea or the RR during NIV
- Worsening or missed improvement of blood gas exchange during NIV

The patients are submitted to endotracheal intubation (ETI) from the medical personnel of the ED and they continue the treatment in the same Critical Area in which they have initially been hospitalized. In Italy there is not a postgraduate course in Emergency Medicine and

all the physicians who operate in the ED came from postgraduate studies in internal medicine.

The ventilatory modes employed during NIV consist in continuous positive airways pressure (CPAP) given through flow-generators or in pressure support (PSV) with application of a positive end expiration pressure (PEEP), on the basis of the clinical condition of the patient and the decision of the physician in charge.

CPAP is applied through a facial mask beginning from a level of PEEP of 5 cms H2O, with following increases of 2 cms H2O up to reach a RR < 25/bpm and a SpO2 > 90%. In the patients with ACPE or with acute hypoxaemic respiratory failure, PEEP values around 10 cms H2O are employed, with attention to haemodynamic parameters, while in the patients with COPD exacerbation a level of 5 cms H2O is not overcome.

The pressure support, administered via a facial mask, is initially set to 8 cms H2O and it is subsequently increased with steps of 2 cms H2O to attain an expired current volume of 7-8 ml/Kgs and a RR < 25/min. The level of PEEP is initially applied at 3 cms H2O and then increased in following steps, parallel to the pressure support, up to 5-6,5 cms H2O in the COPD patient or 10 cms H2O in the hypoxaemic or ACPO patient to obtain a SpO2 > 90%. During ventilation, the patient chest is lifted to 45° in order to assist with diaphragmatic action and to avoid gastric relaxation or inhalation. The FiO 2 is set to obtain a SpO2 > 90% in hypoxaemic patient and a value of 88-90% in COPD patients. Facial mask dimension is selected on the basis of the physiognomic characteristic of the patient; the pillow is inflated to support as far as possible the adaptation, to limit air losses and to avoid the development of incongruous pressures on some parts of the face. At the beginning of the treatment, for some minutes , the mask is supported by the operator's hand to avoid claustrophobic reactions. Thereafter the head straps are passed behind patient's nape and fixed with enough tension to avoid greater air losses, but not such to create cutaneous lesions by pressure.

During the treatment with NIV all the patients receive a medical standard therapy (diuretics, nitrocompound, vasopressors, beta-2 agonists, steroids, antibiotic or fluid) without restrictions, according to the indications and the judgment of the responsible physician.

All centers involved in the present study apply the criteria and the operational protocol in an uniform way.

Clinical data for the analysis and statistic elaboration have been obtained from the clinical briefcase of the patients recorded on paper or computer support and presented on a trial sheet. At all times during the analysis, the security of all personal "sensitive" data was guaranteed by the supervision of the director of every ED involved. When available data were insufficient, the patient was excluded from the study. Equally excluded were those patients who underwent intubation at less than one hour from the beginning of NIV.

What follows is a list of the considered variables in the present study for every single patient. Acute respiratory failure aetiology: COPD, acute cardiogenic pulmonary oedema (ACPO), severe community acquired pneumonia (CAP); demographic parameters: age, sex, presence of comorbidities (diabetes, dementia, acute or chronic sopraventricular arrhythmias, obesity); physiological Parameters: Apache II (Acute Physiology And Chronic Health Evaluation), SAPS II (Simplified Acute Physiology Score), Kelly's neurological score; ventilatory mode: CPAP, PSV + PEEP; sedation necessity: aloperidol, midazolam, propofol, morphine; clinical parameters: respiratory rate, mean arterial pressure, heart rate, transcutaneous oxygen saturation (SpO2); blood gas parameters: pH, PaO2, PaCO2, PaO2/FIO2; hospital-stay parameters: duration of stay in the critical area (days), duration of NIV (hours), compliance to the treatment (present/absent), in-hospital mortality (%), necessity of ETI (%). ARF aetiology was derived by the clinical history, previous documented diagnosis or functional investigations, by the recording of the physical findings, and radiographic signs. For the low number, patients with restrictive pulmonary illness or pulmonary embolism were excluded from the study; likewise, patients with end-stage neoplastic diseases were excluded. Clinical and blood gas parameters were recorded at arrival in the ED (T0), at one hour from the beginning of NIV (T1) and at the suspension of the treatment (T-end) for stabilization or necessity of ETI. All considered parameters were first evaluated inside every single aetiological group (COPD, ACPO, CAP), then compared among the groups. The clinical and blood gas parameters at T0, T1 and T-end were compared inside every single group in order to document significant variations.

Demografic, physiological, sedation, clinical and blood gas parameters were correlated to the variables of "in-hospital death" and "need for intubation." Such correlation was made in the single aetiological groups and in the whole population of patients also inserting the variable

"aetiology" in the logistic and multivariate regression analysis.

Statistic analysis

Statistic analysis has foreseen the calculation of the averages (standard deviations) for the quantitative variable and of the percentages of the formalities "yes" for the qualitative variable, for the three patients' groups (COPD, ACPO and CAP). The differences among groups was tested using the Kruskal Wallis test for the quantitative variables (since the variables taken into examination were not normally distributed), and the chi-square test for the qualitative variables. In addition, within every group of patients, the medians of the quantitative variables and the percentages of the positive answers were compared in the two groups "CPAP yes" and "CPAP no" using the Mann-Whitney non parametric test. Statistically significant level has been fixed to $p < 0.05$.

In order to chronologically sort quantitative variables, boxplots were used to highlight the course of any single variable for every group of patients, and an analysis of the variance had been conducted for repeated measures.

A logistic regression analysis was conducted considering as the dependent variable the "need for ETI". The results are shown as Odd Ratio (OR) and relative intervals of confidence to 95% (IC 95%).

Finally Cox regression multivariate analysis was conducted considering the time of follow-up up to patient's death as the dependent variable. All the variables that showed a $p < 0.25$ at univariate analysis were inserted into the model. The stepwise method was employed, with backward elimination, and the Hazard Ratios (HR) were calculated, with relative intervals of confidence to 95%. In such multivariate analysis the clinical parameters have not been included. This kind of regression and Cox analysis had been conducted both considering each group of patients separately, and the entire series of patients.

With the aim of analyzing cut-off values of the predictive factors for the two dependent variables (ETI and in-hospital mortality) the ROC curves have been drawn (receiver operateing characteristic), considering the best predicted value as the one in which the balancing between sensibility and specificity (area under the curve) was the best.

Statistic analysis has foreseen the employment of the statistic program SPSS for Windows (release 12.0).

Results

For the considered period (01.01.2003-01.06.2003) the clinical documentation of 265 patients treated with NIV for ARF was available in the four Emergency Departments involved in the study. 11 out of these patients were not considered in the subsequent elaboration because they were carriers of restrictive pulmonary pathology, 7 for the diagnosis of terminal neoplasia and 2 for the presence of pulmonary embolism. In the case of 35 patients there were insufficient data.

210 patients had been therefore considered for the following elaboration. Among these, 95 (45,2%) have been treated for COPD exacerbation, 92 (43,8%) for acute cardiogenic pulmonary oedema (ACPO), 23 (10,9%) for severe community acquired pneumonia (CAP) . In the group of patients with COPD exacerbation, 83 (87,3%) had been treated with PSV + PEEP, 12 (12,6%) with CPAP; among the patients with ACPO, 52 (56,5%) had been treated with CPAP and 40 (43,4%) with PSV + PEEP. As to CAP patients, 12 (52,1%) underwent CPAP and 11 (47,8%) PSV + PEEP.

Table 1 shows the demographic characteristics and comorbidities of the whole population of patients as well as of each single aetiological group considering the modality of ventilatory assistance. As evidenced, the three groups showed significantly different according to average age (older in the CAP group), the presence of diabetes (prevailing among CAP and ACPO patients), dementia (prevailing in the CAP group), obesity (greater in the COPD group) and almost significantly different with regard to ($p = 0.083$) sopraventricular arrhythmias (prevailing in the ACPO and CAP groups). Even though a higher prevalence of diabetics among the COPD patients treated with CPAP, no significant differences were noted with respect to the above-mentioned parameters inside the single aetiological groups when considering the ventilatory treatment applied.

Table 2 shows the physiological scores in the whole patient population and the single aetiological groups with reference to ventilatory modality. No meaningful differences were noted in the average values of Apache II, SAPS II and Kelly neurological score among the three aetiological groups. It must be observed, however, that in the ACPO group all three scores were significantly greater in the patients treated with PSV + PEEP when compared to the patients treated with CPAP. Likewise, in the COPD group the average value of SAPS II was significantly greater in the patients treated with PSV + PEEP in

Table 1. Demographic parameters and comorbidities.

Variable	COPD			ACPO			CAP			P (°)
	Total *(95)*	***CPAP*** *(12)*	PSV + PEEP *(83)*	Total *(92)*	CPAP *(52)*	PSV + PEEP *(40)*	Total *(23)*	CPAP *(12)*	PSV + PEEP *(11)*	
Average age (SD)	75,02 (11,09)	72,08 (16,8)	75,45 (10,08)	79,68 (7,56)	80,83 (7,81)	78,78 (7,2)	81,30 (9,43)	82,42 (7,57)	80,09 (11,37)	0,004
Male Gender (n°)	50,5 % (49)	33,3 % (4)	53 % (45)	51,1 % (47)	44,2 % (24)	60 % (23)	56,5 % (13)	50 % (6)	63,6 % (7)	0,872
Diabetes (n)	18,9 % (18)	41,7% (5) *	15,7 % (13)	38 % (35)	36,5 % (19)	40 % (16)	43,5 % (10)	50% (6)	36,4 % (4)	0,006
Dementia (n)	4,2 % (4)	16,7 % (2)	2,4 % (2)	5,4 % (5)	5,8 % (3)	5,0 % (2)	21,7 % (5)	25% (3)	18,2 % (2)	0,008
Obesity (n)	10,5 % (10)	8,3 % (1)	10,8 % (9)	5,4 % (5)	1,9 % (1)	10 % (4)	0,0 % (0)	0,0 % (0)	0,0 % (0)	0,0149
Arrhythmia (n)	17,9 % (17)	8,3 % (1)	19,3 % (16)	31,5 % (29)	38,5 % (20)	22,5 % (9)	30,4 % (7)	41,7 % (5)	18,2 % (2)	0,083

* level of significance within group $p < 0.05$ (Mann-Whitney test)
(°) The level of significance refers to the differences in the means (medians) and in the proportions of the variables between the three groups (COPD, ACPO and CAP) (Kruskal-Wallis test)

Table 2. Physiological parameters.

Variable (n)	COPD			ACPO			CAP			P (°)
	Total *(95)*	**CPAP** *(12)*	**PSV + PEEP** *(83)*	Total *(93)*	**CPAP** *(52)*	**PSV + PEEP** *(40)*	Total *(23)*	**CPAP** *(12)*	**PSV + PEEP** *(11)*	
APACHE II (DS)	18,56 (5,38)	16,75 (5,58)	18,83 (3,34)	18,63 (5,20)	17,35* (4,68)	20,30* (5,43)	18,83 (5,53)	20,08 (5,92)	17,45 (4,97)	0,929
SAPS (DS)	34,62 (9,85)	28,58* (4,62)	35,49* (10,11)	35,65 (9,52)	33,23* (9,02)	38,87* (9,31)	36,70 (9,3)	35,58 (8,07)	37,91 (10,75)	0,460
Kelly (DS)	1,89 (1,02)	1,67 (0,89)	1,93 (1,05)	1,53 (0,69)	1,31* (0,506)	1,84* (0.789)	1,78 (0,90)	1,50 (0,67)	2,09 (1,04)	0,065

* level of significance within group $p < 0.05$ (Mann-Whitney test)
(°) The level of significance refers to the differences in the means (medians) and in the proportions of the variables between the three groups (COPD, ACPO and CAP) (Kruskal-Wallis test)

Table 3. Sedation parameters.

Variable (n)	COPD			ACPO			CAP			P (°)
	Total (95)	**CPAP** (12)	**PSV + PEEP** (83)	Total (92)	**CPAP** (52)	**PSV + PEEP** (40)	Total (23)	**CPAP** (12)	**PSV + PEEP** (11)	
Haloperidol (n)	16,8 % (16)	0,0 % (0)	19,3 % (16)	0,0 % (0)	0,0 % (0)	0,0 % (0)	4,3 % (1)	0,0 % (0)	9,1 % (1)	*< 0,001*
Midazolam (n)	8,4 % (8)	8,3 % (1)	8,4 % (7)	2,2 % (2)	1,9 % (1)	2,5 % (1)	4,3 % (1)	0,0 % (0)	9,1 % (1)	*0,0156*
Propofol (n)	7,4 % (7)	8,3 % (1)	7,2 % (6)	0,0 % (0)	0,0 % (0)	0,0 % (0)	0,0 % (0)	0,0 % (0)	0,0 % (0)	*0,012*
Morphine (n)	5,3 % (5)	25 % (3)*	2,4 % (2)	12 % (11)	11,5 % (6)	12,5 % (5)	4,3 % (1)	8,3 % (1)	0,0 % (0)	*0,192*

* level of significance within group $p < 0.05$ (Mann-Whitney test)
(°) The level of significance refers to the differences in the means (medians) and in the proportions of the variables between the three groups (COPD, ACPO and CAP) (Kruskal-Wallis test)

Table 4. Clinical and blood gas parameters at To.

Parameter	COPD				ACPO				CAP			
Values expressed as mean (Standard Deviation)	T0	T1	T-end	p*	T0	T1	T-end	p*	T0	T1	T-end	p*
pH	7,28 (0,10)	7,32 (0,09)	7,38 (0,09)	< 0.001	7,22 (0,09)	7,34 (0,09)	7,41 (0,08)	< 0.001	7,31 (0,10)	7,38 (0,08)	7,40 (0,13)	0.005
PaO_2 mmHg	64,6 (35,5)	81,16 (31,3)	76,20 (21,8)	0.001	64,8 (30)	119,14 (67,3)	99,86 (43,2)	< 0.001	51,8 (13,1)	76,06 (24)	70,83 (15)	0.009
$PaCO_2$ mmHg	69,3 (18,6)	67,64 (16,6)	60,54 (15,8)	< 0.001	54,5 (19,1)	47,94 (14,4)	43,41 (12,3)	< 0.001	51,6 (17,6)	46,67 (13,5)	47,19 (17,9)	0.106
PaO_2/FiO_2	188,2 (74,9)	223,48 (82,7)	234,75 (79,5)	< 0.001	161,1 (87,4)	230,05 (115,2)	238 (85,2)	< 0.001	155,7 (67,6)	168,5 (60,5)	182,6 (59,9)	0.956
Respiratory rate bpm.	31,8 (5,87)	27,03 (7,3)	22,15 (6,9)	< 0.001	33,3 (7,5)	26,23 (7,6)	20,74 (7,5)	< 0.001	33,4 (10,2)	30,89 (10)	27,32 (11,1)	0.304
Heart rate bpm.	105,6 (24,9)	98,45 (20,3)	90,91 (16,5)	< 0.001	106,1 (23,6)	91,8 (17,9)	83,59 (14,9)	< 0.001	101, 9 (24)	99,52 (21,5)	90,55 (15,2)	0.237
Mean arterial pressure mmHg	97 (12,2)	92,83 (13,3)	94,56 (15,9)	0.027	118,2 (32)	92,8 (14,9)	96,17 (22,2)	< 0.001	101,3 (29,1)	91,78 (10,2)	90,24 (22,8)	0.103
SpO_2%	82,14 (13,9)	92,88 (4,7)	93,51 (4,3)	< 0.001	85 (9,5)	95,79 (4,4)	96,39 (3,12)	< 0.001	78,9 (12,4)	92,79 (6,3)	92,09 (5,8)	0.002

* p-value derived from the ANOVA for repeated measures

Table 5. In-hospital stay parameters.

Variable	COPD			ACPO			CAP			P (°)
(n)	Total *(95)*	*CPAP (12)*	PSV + PEEP *(83)*	Total *(92)*	CPAP *(52)*	PSV + PEEP *(40)*	Total *(23)*	CPAP *(12)*	PSV + PEEP *(11)*	
Length of hospital stay (SD)	3,79 (3,6)	1,42 (0,79)*	4,13 (3,71)	2,19 (2,10)	1,29 (1,05)	3,36 (2,55)	2,52 (3,14)	3,17 (4,13)	1,82 (1,33)	< 0.01
NIV duration (SD)	44,05 (74,48)	6,67 (3,47)*	49,66 (78,39)	9,80 (12,62)	1,29 (1,05)	14,38 (17,67)	26,83 (31,86)	29 (35,73)	24,45 (28,58)	< 0.01
Compliance (n)	65,3 % (62)	83,3 % (10)	62,7 % (52)	89,1 % (82)	90,4 % (47)	87,5 % (35)	95,7 % (22)	100 % (12)	90,9 % (10)	< 0,001
In-hospital death (n)	12,6 % (11)	8,3 % (1)	12 % (10)	3,3 % (9)	9,6 % (5)	10 % (4)	34,7 % (8)	41,7 % (5)	27,3 % (3)	0,061
ETI (n)	13,7 % (13)	8,3% (1)	14,5% (12)	4,3 % (4)	0%* (0)	10% (4)	21,7 % (5)	8,3 % (1)	36,4 % (4)	0,038
Skin necrosis (n)	4,2 % (4)	0,0 % (0)	4,8 % (4)	2,2 % (2)	0,0 % (0)	5 % (2)	0,0 % (0)	0% (0)	0% (0)	0,526
Refusal (n)	9,5 % (9)	8,3 % (1)	9,6 % (8)	1,1 % (1)	0,0 % (0)	2,5 % (1)	0,0 % (0)	0% (0)	0% (0)	0,032

* level of significance within group $p < 0.05$ (Mann-Whitney test)
(°) The level of significance refers to the differences in the means (medians) and in the proportions of the variables between the three groups (COPD, ACPO and CAP) (Kruskal-Wallis test)

Table 6. Cox regression with dependent variable: time up to patient's death.

	ALL		COPD		ACPO	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Gender Male (reference) Female	1 0.23 (0.006-0.9)	**0.035**	1 0.18 (0.03-1.28)	**0.087**	1 0.12 (0.01-1.46)	**0.096**
Aetiology COPD (reference) ACPO	1 0.17 (0.04-0.73)	**0.017**				
pH < 7.32 T1 No (reference) Yes	1 10.60 (2.62-42.84)	**0.004**	1 8.63 (1.38-54.05)	**0.021**	1 1.35 (0.05-33.66)	**0.854**
RR < 24bpm T1 Yes (reference) No	1 18.42 (1.96-173.48)	**0.011**	1 16.44 (1.45-186.54)	**0.032**	1 3.05 (0.25-37.60)	**0.383**
MAP < 96 T1 Yes (reference) No	1 5.99 (1.30-27.70)	**0.022**	1 5.22 (0.85-32.20)	**0.075**	n.a.	
$PaCO_2$ <54.5 T1 Yes (reference) No	1 3.91 (0.63-24.43)	**0.144**			1 16.77 (1.39-201.87)	**0.026**
Goodness of fit of the model (Hosmer-Lemeshow test)	**0.350**		**0.447**		**0.938**	

n.a. = not applicable

Table 7. Logistic regression with dependent variable: endotracheal intubation

	ALL		COPD		ACPO		CAP	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% There)	p
SAPSII >35.8 No (reference) Yes	1 9.48 (2.99-29.99)	<0.001	1 18.91 (2.19-163.29)	0.008	1 16.43 (1.45-185.82)	0.024		
Dementia No (reference) Yes	1 11.28 (3.97-32.02)	<0.001	1 10.35 (1.40-76.719	0.022	1 12.06 (1.26-115.18)	0.031	1 33.67 (1.62-701.9)	0.023
Arrhythmia No (reference) Yes	1 3.72 (1.46-9.53)	0.006			1 11.23 (1.48-85.45)	0.019	1 9.66 (1.09-85.63)	0.042
RR T-end > 24 No (reference) Yes	1 4.67 (1.66-13.14)	0.003			1 24.87 (2.07-298.44)	0.011	1 23.72 (1.14-495.7)	0.041

comparison to those treated only with CPAP.

In the whole studied population 46 patients (21,9%) needed pharmacological sedation (table 3). The need for it was more frequent among COPD patients, when compared to the others, without any sensible difference in the use of haloperidol, midazolam or propofol. No differences were observed in the use of morphine when considering ARF aetiology. Nevertheless, among COPD patients morphine employment resulted more frequent in those treated with CPAP.

For what concerns ventilatory treatment effectiveness, considering the entire series of patients, all the variations observed for blood gas and clinical variables (pH, paO2, paCO2, FiO2, PaO2/FiO2, respiratory rate, heart rate, mean arterial pressure, SpO2), from T0 to T-end resulted statistically significant ($p < 0.001$ for all the variations).

In table 4 the clinical and blood gas parameters are identified in the three aetiological groups at different times and the significant variation of every single variable in the three groups is illustrated (ANOVA for repeated measures). It is possible to observe that while for ACPO and COPD patients, the found variations resulted significant for all the considered variables, the same did not happen for the patients with community acquired pneumonia, for which only the variations of pH, PaO2 and SpO2 came out to be significant along the treatment period.

From the whole studied population, 22 patients (10,4%) underwent ETI, while 28 (13,3%) died during their hospitalization. Table 5 illustrates the course of the in-hospital stay variables (average duration of stay in the critical area and in hospital, duration of the ventilatory treatment, compliance to the treatment, in-hospital mortality, ETI, development of facial skin necrosis, patient's refusal to continue the therapy) considering ARF aetiology and the type of ventilatory treatment applied. Except for the development of skin necrosis, indifferent among the three groups, they significantly differed for all the other parameters. Particularly, the duration of the hospitalization in Critical Area resulted longer in the patients with COPD as was the duration of the ventilatory treatment. Patients' compliance to the treatment was inferior in the COPD group, in which, also, the interruption of ventilation resulted more frequent. ETI and in-hospital mortality were more frequent, on the other hand, in the CAP group. As to the ventilatory mode applied, the duration of the treatment resulted sensitively inferior in COPD patients treated with CPAP, compared to those treated with PSV + PEEP, while the percentage of ETI in ACPO patients was superior in the subgroup treated with PSV + PEEP when compared to the one treated with CPAP.

Tables 6 and 7 respectively illustrate Cox regression results (dependent variable: time up to the patient's death) and logistic regression results (dependent variable: ETI). Considering the COPD group the following factors resulted independently correlated with inhospital mortality: SAPS II > 35; presence of dementia. For the ACPO patients, the factors correlated to in-hospital mortality were SAPS II > 35, presence of dementia, presence of sopraventricular arrhythmias, while for the CAP group they were SAPS II > 35, presence of sopraventricular arrhythmias, presence of dementia. Considering the whole population of 210 patient, the factors independently correlated to in-hospital mortality resulted the following: SAPS II > 35; presence of dementia; presence of sopraventricular arrhythmias; RR > 24bpm at T-end. For what concerns the factors independently correlated with ETI, for the COPD group they resulted to be: male sex, pH < 7,32 after one hour of treatment, respiratory rate > 24 bpm after one hour of treatment, mean arterial pressure > 96 mmHg after one hour of treatment. In the ACPO group the significant factors resulted to be male sex, pH < 7,32 after one hour of treatment , respiratory rate > 24 bpm after one hour of treatment; PaCO2 > 54,5 mm Hg after one hour of treatment.

Due to the low number of patients, it was not possible to perform the logistic regression and calculate the matrix of covariance of the parameter for the CAP group. Considering the whole series of patients the factors independently correlated to ETI resulted the following: male sex; pH < 7,32 after one hour of treatment; diagnosis of COPD; respiratory rate > 24 bpm. after one hour of treatment; mean arterial pressure > 96 mm Hg after one hour of treatment; PaCO2 > 54,5 mm Hg after one hour of treatment.

Discussion

Although some studies [17-22], show that NIV can be applied in safety and with good results in the ED, the real potential of the method in this setting is not yet clear. The more often quoted results in the literature frequently refer to data obtained in general or respiratory intensive care units. However, the operational and organizational context in which the treatment is performed is very important referring to the outcome of the patient. On one hand the Emergency Department represents the ideal place for the earliest and effective NIV application in the progress of ARF, on the other one the presence of a proper skilled personnel/patients ratio, not always obtainable in the ED, appears pivotal for the results and the good quality of the method [37]. Some devoted studies have shown that the first 12 hours of NIV treatment, as those necessary to the "adaptation" of the patient to the technique, require a continuous presence of the sanitary personnel next to the patient [38]. The British Thoracic Society guidelines on NIV use [26] point out how such method can be applied in a wide variability of clinical contexts (conventional department, pneumological department , respiratory intensive care unit, general intensive care unit) according to the severity of the patients treated. Although there are no comparative studies about NIV effectiveness especially in reference to the organizational context of application, BTS guidelines recommend that NIV is used in devoted structures endowed with trained personnel and with appropriate technologies, inserted in the organizational logic of the whole hospital, for the purpose to guarantee the patient an effective and individualized intervention for his/her clinical severity.The BTS doesn't recognize in the ED the ideal place for this kind of intervention.

Our study, entirely conducted in ED, is, to our knowledge, the most consistent among those performed in this setting for the number of considered patients (210). Globally, in-hospital mortality has been of 13,3%, the percentage of failure with consequent ETI amounted to 10,4%. Considering the single aetiological groups, among the patients with COPD exacerbation mortality has been of 12,6% and the need for ETI of 13,7% ; among ACPO patients such data respectively amounted to 3,3% and 4,3%; while for the patients with severe CAP they respectively reached 34,7% and 21,7%. Such data must be compared to those derived from the historical studies conducted in ICU that showed a percentage of ETI between 9% and 26% and an in-hospital mortality of 6-10% [39] for patients with COPD exacerbation; that ranged between 4 and 15% and 4,5% and 30% respectively for ACPE, also considering the most recent studies [23, 24, 40, 41]. For severe CAP, a mortality of 25-53% and a need for ETI of 21-66% have been reported in different papers [12, 13, 25]. Considering that basal patient characteristics in our study were not, for every aetiological group, sensitively dissimilar from those of the patients treated in the aforementioned studies, NIV use in the Emergency Department appears safe and offers clinical results comparable to those obtained in the context of the intensive care units. Moreover, with limitation to patients with community acquired pneumonia, we observed in our series better results. While considering the impossibility to effect a comparison among deeply different studies, this could suggest a greater NIV effectiveness in this pathological condition when precociously applied in its clinical course that is, ideally, soon after arrival to the Emergency Department. In a recently published retrospective study conducted in the ED on a series of 104 patients, primarily affected with COPD exacerbation and acute cardiogenic pulmonary oedema, Merlani and coworkers [35], reported a resort to ETI of 31%. Such a percentage, sensitively superior to ours, doesn't easily appear explainable. It must be observed however that according to the protocol of intervention brought in the study, the patients were treated in the ED with NIV for one hour only, with following suspension in case of clinical improvement or transfer to the ICU for intubation or the prosecution of noninvasive treatment in case of failure or persistence of clinical or BGA signs of ARF. As already mentioned, the first 12 hours of intervention appear the most strategic for NIV result and those during which greater is the personnel commitment to get the adaptation of the patient to NIV. In all the four Emergency Departments involved in our study, after triage and an initial treatment in the Emergency Room, patients were transferred and

continued ventilation in an area of the Emergency Department, defined as "critical area", in which the patient received care by medical personnel and nurses well trained on NIV and strongly motivated to the result of this technique. It is therefore possible that 'too short' a period of treatment doesn't reflect the real potentialities of NIV in the ED context. Moreover, it must be observed that following interventional protocol in the Merlani study no pharmacological sedation was used. One of the recognized advantages of NIV over conventional ventilation is the lesser necessity of patient sedation. In our study 46/210 patients (21,9%) have required pharmacological sedation to improve the adaptation phase, with clear prevalence of use in patients with COPD exacerbation, but without appreciable differences in the type of drugs used. Although the resort to pharmacological sedation did not result "independently" correlated to the success or the failure of the ventilatory method, it is possible that its early employment can improve the compliance of the patient in the initial phase of the treatment allowing to others, more important, factors to condition the NIV global success.

Unlike other studies, ours has considered the effectiveness of the different ventilatory modalities used (CPAP vs PSV + PEEP) in the three aetiological groups studied. Among ACPO patients, those treated with CPAP resulted to have lower physiological and neurological scores (Apache II, SAPS II, Kelly score) in comparison with the patients treated with PSV + PEEP. It is possible that this difference reflects the retrospective design of the study in that the physician in charge may have been induced to treat "more serious" patients using a double level of pressures. This difference between subgroups might also account for the difference in the percentage of resort to ETI (greater in the patients treated with PSV + PEEP). Nevertheless, coherent with recent data [23, 24 ,41] it was not observed in this category of patients any appreciable differences between subgroups in terms of mortality, duration of stay in critical area, duration of the treatment and compliance to the treatment. In our study a small number of patients with COPD exacerbation (12/95, 12,6%) had been treated only with CPAP. These patients were less seriously ill (SAPS II), than those treated with PSV + PEEP, received a shorter ventilatory treatment and had a shorter permanence in critical area. While the use of double level of pressure techniques is widely considered as the golden standard of NIV treatment in patients with COPD exacerbation, some studies recognize to CPAP a possible employment in this condition [42-46]. Although future prospective studies opportunely designed are necessary, it is possible to believe that in well selected patients, precociously treated in the progress of COPD exacerbation, the only use of CPAP is enough to prevent the worsening of this clinical condition, with obvious effects on organization, considering the simplicity of this technique.

NIV results in the treatment of ARF secondary to a severe CAP, in the various available studies, are not comparable to those obtained in the patients with COPD exsacerbation or ACPO. Coherently, in our study, we noted a greater incidence of deaths and a greater need for ETI in this group of patients in comparison to the other two aetiological groups. Furthermore, in the time course analysis, it is possible to observe that COPD and ACPO patients have improved all the clinical and blood gas parameters during NIV treatment (table 4, ANOVA for repeated measures), while in the patients with CAP such improvement only concerned PaO2, SpO2 and pH. Interestingly in this group of patients it was not observed any significant differences in any variables, when considering the ventilatory modality applied (CPAP vs PSV + PEEP): the indication to employ one of these modalities or the other remains in this condition opened to future prospective, opportunely designed studies.

Our study has underlined some important differences among the various aetiological groups concerning variables as the duration of the stay in critical area and of the ventilatory treatment (longer in the COPD group), patients' compliance to the treatment (inferior in the group with COPD), the percentage of patients that has opposed a refusal to continue the treatment once NIV was initiated (greater in COPD patients). Patients with COPD exacerbation are those that mostly required a pharmacological sedation. These data furtherly stress the importance of a motivated approach to the patient with ARF candidate to NIV and the necessity of an organized operational context. In addition, they contribute to explain the results obtained by Merlani and co-workers whose patients were in prevailing percentage affected of COPD exacerbation and managed by one team only for a short time.

Other factors in our series were unevenly distributed among different ARF aetiologies. Average age, for example, and the percentage of patients with dementia were clearly superior in the CAP group in comparison to the others; diabetic patients were more frequent in the CAP

and ACPO groups as were patients with sopraventricular arrhythmias; obesity prevailed in the group with COPD exacerbation. The difference in these prevalences cannot surprise: the advanced age and the presence of dementia are factors conditioning the severity (and the mortality) of CAP needing mechanical ventilation in the major severity scores of this condition; diabetes is a recognized risk factor for cardiovascular illnesses and their complications (as acute pulmonary oedema); this clinical condition can be associated to a greater severity of infectious diseases (among which the pneumonias); sopraventricular arrhythmias, conditioning a reduced ventricular filling, can worsen or cause an acute pulmonary oedema and, in case of a lowered cardiac output, worsen the negative effects of the intrathoracic pressure increases during mechanical ventilation. Obesity adds an important restrictive component to the obstructive characteristic of COPD, able to accelerate the development of ARF and affect its response to the ventilatory treatment.

Our aim was also to point out specific factors correlated to failure of NIV when precociously used in the ED, considering both the single indications and the total of the patients treated with this method.

In patients with COPD exacerbation SAPS II > 35 and presence of dementia were found to be independently correlated with in-hospital mortality; in the same category of patients, male sex, along with the following factors (vague, revision needed) (measured after one hour of treatment) were independently correlated with the necessity of ETI: respiratory rate > 24 bpm, pH < 7,32, mean arterial pressure > 96 mmHg; PaCO2 > 54.5 mms Hg. While the importance of male sex as a negative prognostic factor, although frequently observed in patients with a respiratory pathology, is difficult to analyze, the importance of the physiological score, of pH value and the respiratory rate after one hour of treatment appear coherent with the available studies on this condition [28-33]. Our results confirm these results and extend them to the evaluation of other factors. The presence of dementia as a negative prognostic factor for mortality, can be explained making reference to the potential difficulty of the patient with this condition to adapt to NIV, as this requires an elevated degree of co-operation, hardly obtainable in a patient with this clinical condition, and to the potential effect of the further worsening of their hypercapnia due to their respiratory failure. The importance of a value of mean arterial pressure above 96 mmHg, after one hour of treatment in conditioning the probability to resort to ETI is less clear, but it is possible that it reflects an increased level of adrenergic activation in the patient with acute respiratory failure with consequences on the oxygen consumption, on the respiratory muscles performance and, also, on the adaptation of a conscious patient to NIV. Although intuitively consistent with the patophysiology of this condition, the subsistence of an elevated PaCO2 value at T1 as a negative prognostic factor independent from the pH values arises a certain curiosity. While both PaCO2 and pH are known to correlate to the severity and acuteness of the respiratory failure, the level of pH correlates, more than that of PaCO2 also with the "metabolic" state of the patient, reflecting in general the perfusion state and oxygenation of the peripheral tissues, adding therefore additional information, not inferable from the value of PaCO2.

In the ACPO group of patients the following factors were independently correlated with in-hospital mortality: SAPS II > 35; presence of dementia; presence of sopraventricular arrhythmias; respiratory rate > 24 bpm for the whole duration of the treatment (T-end). In the same group the following factors were independently correlated with the necessity of endotracheal intubation: male sex; PaCO2 > 54,5 mmHgs after one hour of treatment, and, at a lesser extent pH < 7,32 and respiratory rate > 24 bpm after one hour treatment. For what concerns the influence of a serious dementia in determining a higher short-term mortality, the above mentioned considerations are to be repeated. While the importance of an elevated physiological score and the missed improvement at an hour of some clinical and blood gas parameters (respiratory rate, pH) appear consistent with previous studies [15, 34, 35], some observations should be made with limitation to the importance of PaCO2 values at T1. Some studies suggest that "hypercapnic" ACPO patients are intrinsically more responsive to the ventilatory treatment in comparison to "normo" or "hypocapnic" ones [21, 47, 48]. The importance of an elevated PaCO2 level at one hour of treatment, independently from its absolute value before starting ventilation, is then a strong predictive factor for ETI in these patients, in that it is possible that its persistence in a condition usually characterized by a rapid improvement of gas exchange during NIV, directly preludes to its failure. The influence of acute or chronic sopraventricular arrhythmias in determining a higher incidence of short-term mortality in ACPO

patients treated with NIV in the ED represents an unpublished datum. As already observed, it is possible to infer that the haemodynamic effect of the arrhythmia can cause a greater severity of the clinical condition and, especially a greater influence of the effects of mechanical ventilation on the cardiac output.

In patients with severe CAP the presence of dementia, sopraventricular arrhythmias and the maintenance of a respiratory rate > 24 bpm during the whole period of treatment (T-end) were all independently correlated with in-hospital mortality, while the low number of patients did not allow the elaboration of a linear regression model to individualize factors independently correlated to the event "ETI". Dementia is a recognized factor of gravity in severe pneumonias, while the influence of sopraventricular arrhythmias could be framed in analogy to what was speculated for ACPO patients considering their haemodynamic impact on a condition often characterized by severe hypotension, systemic hypoperfusion and necessity of fluid replacement.

Extending Cox regression for the in-hospital mortality and the linear regression with dependent variable “ETI” to the whole studied population, considering the aetiological category as one of the variables to insert in the model, the following factors were independently correlated with the mortality: SAPS II > 35, dementia, presence of sopraventricular arrhythmias, respiratory rate persistently > 24 bpm during the treatment. The following factors, instead, resulted to predict resort to ETI: male sex; presence of COPD; pH < 7,32, respiratory rate > 24 bpm, mean arterial pressure > 96 mm Hg, PaCO2 > 54,5 mmHg (all measured after one hour treatment). It should be observed that neither the necessity of pharmacological sedation, nor the ventilatory modality used (CPAP vs PSV + PEEP) were correlated to NIV failure in the whole studied population, as in the single aetiological groups.

In ED daily practice, the patient with ARF is often treated with NIV before a clinical diagnosis is set with certainty. It is therefore important to be able to identify prognostic factors correlated with in-hospital mortality or the necessity of ETI, independently from the patient's ARF aetiology. Above all it is necessary that such factors are quickly obtainable in the operational context of the emergency without the need of invasive procedures or prolonged observation. Except SAPS II, usually obtainable within the first day of permanence of the patient in ED, the suitable variables considered in the present study conform to these necessities, being determinable within the first phases of patient treatment, through anamnesis (presence/absence of dementia; history of COPD), clinical examination, arterial blood gas analysis or radiographic investigation (presence/absence of pneumonia). In this sense our data confirm the results of Merlani and coworkers [35] with regard to the importance of the evaluation of pH and respiratory rate after one hour of treatment. However, having studied a greater and more variegated series of patients they force us to extend consideration to other factors not mentioned in their study, as physiological score, presence of dementia, haemodynamic instability and ventilatory performance. The presence of COPD as a factor correlated to NIV “failure”, may deal at some extent with the lesser compliance to the ventilatory treatment shown in our study by the COPD patients who more frequently refused to continue on treatment once initiated, and required sedation in comparison to the other aetiological groups. Although COPD exacerbation represents one of the main indications to NIV, it should be also considered that this result came from a linear regression model in which the only other aetiological variable was represented by ACPO, an usually rapidly resolving condition during ventilatory treatment. Nevertheless our data point out the necessity to treat this condition with the maximum caution, in an equipped environment, endowed with skilled personnel, available to devote the whole necessary time to the initial difficult adaptation of the patient to the ventilation.

In conclusion, our study shows that NIV is practicable in the ED with safety and clinical results comparable to those obtained in general or respiratory intensive care units, provided that an adequate level of motivated and trained personnel is guaranteed, in order to fully answer to the necessities of the first phases of the ventilatory treatment. Furthermore, it indicates some factors, quickly obtainable, that are correlated to a greater probability of in-hospital death or need for ETI. Such factors can contribute to a more appropriate selection of patients for NIV in the ED and to a rapid identification of those more appropriately amenable to be hospitalized in he ICU, with obvious effects on organization and saving of resources. The validation of these results, on the general plan, would benefit from future prospective studies.

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