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ORIGINAL ARTICLE

Severe exacerbations of chronic obstructive pulmonary disease: management with noninvasive ventilation on a general medicine ward

Ventilazione non invasiva per il trattamento delle riacutizzazioni di entità severa della broncopneumopatia cronica ostruttiva in un reparto di medicina generale

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Abstract
Introduction: Recent evidence suggests that, with a well-trained staff, severe exacerbations of chronic obstructive pulmonary disease (COPD) with moderate respiratory acidosis (pH > 7.3) can be successfully treated with noninvasive mechanical ventilation (NIMV) on a general respiratory care ward. We conducted an open prospective study to evaluate the efficacy of this approach on a general medicine ward.
Material and methods: This study population consisted in 27 patients admitted to a general medicine ward (median nurse:patient ratio 1:12) December 1, 2004 May 31, 2006 for acute COPD exacerbation with hypercapnic respiratory failure and acidosis (arterial pH $\leq$ 7.34, $PaCO_2$ > 45 mmHg). All received assist-mode NIMV (average 12 h / day) via oronasal masks (inspiratory pressure 10-25 cm H_2O, expiratory pressure 4-6 cm H_2O) to maintain O_2 saturation at 90-95%. Treatment was supervised by an experienced pulmonologist, who had also provided specific training in NIMV for medical and nursing staffs (90-day course followed by periodic refresher

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sessions). Arterial blood pressure, O_2 saturation, and respiratory rate were continuously monitored during NIMV. Based on baseline arterial pH, the COPD was classified as moderate (7.25-7.34) or severe (< 7.25).

Results: In patients with moderate and severe COPD, significant improvements were seen in arterial pH after 2 ($p < 0.05$) and 24 h ($p < 0.05$) of NIMV and in the $PaC0_2$ after 24 hours ($p < 0.05$). Four (15%) of the 27 patients died during the study hospitalization (in-hospital mortality 15%), in 2 cases due to NIMV failure. For the other 23, mean long-term survival was 14.5 months (95% CI 10.2 to 18.8), and no significant differences were found between the moderate and severe groups. Over half (61%) the patients were alive 1 year after admission.

Conclusions: NIMV can be a cost-effective option for management of moderate or severe COPD on a general medicine ward. Its proper use requires: close monitoring of ventilated subjects, optimum staff:patient ratio, well-trained staff dedicated to NIMV, and supervision by a pulmonologist with experience in NIMV. The treatment was effective at improving arterial blood gases in both groups of COPD patients. The severity of the COPD did not significantly affect length of hospital stay, in-hospital mortality, or long-term survival.

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (COPD) with decompensated respiratory acidosis cause repeated hospital admissions and are associated with high mortality [1—3]. In the last years several randomised clinical trials have suggested that non-invasive mechanical ventilation (NIMV) is an effective treatment for severe exacerbated COPD patients with respiratory acidosis [1—6]. NIMV advantages, in comparison to invasive mechanical ventilation, include a reduced intubation need and in-hospital mortality as well as a decreased hospitalisation length and infectious complications, particularly pneumonia. In addition, NIMV may be used with an intermittent modality, doesn't require sedation, is generally well-tolerated and remarkably some evidences suggest that this therapeutic approach may be performed successfully not only in the Intensive Care Unit (ICU) but also in the intermediate respiratory care unit (IRCU) [7]. This ventilation modality may help to decrease the number of ICU admissions in a general situation of reduced high-dependency bed availability and health costs control [8].

Unfortunately we have only 25 accreditated IRCU in Italy [9], while the need of NIMV exceeds intensive bed provision. In fact, at least 20% of exacerbated COPD patients admitted to hospital with acute respiratory failure (ARF) need NIMV specialist units [10].

In addition, there is recent evidence that NIMV may also be performed successfully in general respiratory ward in patients with pH > 7.30, if a well-trained hospital personnel is provided [4].

We had the opportunity to treat COPD patients with acute respiratory acidosis in the general medical ward of Budrio District Hospital, devoid of respiratory ward and ICU.

The primary aim of this prospective study was to assess whether NIMV was effective in a general medicine ward with a well-trained personnel at improving arterial blood gases of exacerbated COPD patients, with moderate (pH $\geq$ 7,25) and severe (pH < 7.25) respiratory acidosis.

The secondary end point was to evaluate the in-hospital mortality and one year survival of COPD patients discharged alive after NIMV.

Materials and methods

This prospective study was performed in the general medicine unit of Budrio District Hospital in Italy, with a median nurse: patient ratio 1:12. The study period extended from December 1th 2004 to May 31th 2006. The ward medical and nursing staff received a specific training to ventilation delivery use, before starting this therapeutic approach, for a term of 90 days, with periodic retraining. This specific and continuous practice was provided by the chest physician, working in the medicine ward.

Eligible patients were those who were admitted for acute exacerbation of COPD and hypercapnic respiratory failure (pH value $\leq$ 7.34 with PaC02 $>$ 45 mmHg) who received NIMV at admission. We excluded patients admitted to the emergency unit with ARF without history of COPD or multiorgan failure defined as the presence of at least one organ failure, excluding the lung; these patients are transferred by protocol to ICU or IRCU.

Patients' treatment included standard medical therapy plus pressure support ventilation through a oronasal mask (Resmed Ultra Mirage, Savigny - Le Temple, France). NIMV was provided with bilevel assist-mode ventilator (Helia-Saime, North Ryde, Australia).

The usual inspiratory pressure was 10 cm H_2O to 25 cm H_2O and the expiratory pressure was 4 cm H_2O to 6 cm H_2O. An arterial oxygen saturation ranging between 90% and 95% was obtained with oxygen supply. NIMV was performed as much as possible and usually for periods of 12 hours each day, according to patients' tolerance. Informed consent was obtained from the patients. Arterial blood gas parameters were measured at admission and after 2, 24 and 48 hours of continuous NIMV and at discharge.

Patients treated with NIMV were defined responders, if they showed an objective improvement after few hours of ventilation. Objective criteria considered for response included an increase in pH value $\geq$ 7.35, a drop in PaCO2 of $>$ 15-20%, with oxygen saturation (SO_2) $\geq$ 90% and a decrease in respiratory rate $\geq$ 20% compared with spontaneous breathing, according to previous reports [11].

NIMV was progressively discontinued if clinically indicated. Patients were proposed for intubation if they met objective

criteria for NIMV failure: pH $\leq$ 7.20 with an increase in PaCO2 of $>$ 15-20% in comparison with a former arterial blood gas analysis, or sensory worsening.

Arterial blood pressure, oxygen saturation and respiratory rate, were continuously monitored during NIMV.

In addition to NIMV, COPD patients received standard medical therapy, including aerosolised bronchodilator drugs, i.v. steroid, and, when necessary, antibiotics and furosemide.

Follow-up was achieved at monthly intervals after discharge and survival was assessed to death or 31 January 2007.

The following data were collected: age, sex, co-morbidities quantified according to the Charlson index, Glasgow Coma Scale at admission, baseline arterial blood gases and within 2, 24 and 48 hours after NIMV and at discharge. In addition, length of hospital stay, in-hospital mortality and one year survival after discharge were recorded.

Lung function test was performed in all patients at discharge according to standard protocol [12].

The present study agrees to the Helsinky principles and a consent has been obtained by all the participants.

Statistical analysis

Continuous variables were analysed by Mann-Whitney test (data comparison between patients with pH $<$ 7.25 and pH $\geq$ 7.25 at admission) and by Friedman test and SNK statistic for multiple comparisons; categorical variables were analysed with Fisher exact test. P values $<$ 0.05 were considered significant.

Results

A total of 132 patients with acute exacerbations of COPD were admitted to general medicine unit of Budrio Hospital between December 1th 2004 and May 31th 2006. Ninety-eight patients with pH $>$ 7.34 did not receive NIMV and were excluded. Seven COPD patients with ARF and pH $<$ 7.34 were sent to an ICU because of the presence of severe acute comorbidities: 3 patients had an associated pneumothorax, 4 patients had respiratory distress syndrome. Twenty-seven patients (20.5% out of 132), meeting inclusion criteria, were enrolled for data analysis. Characteristics of COPD patients at enrolment are reported in *table 1*.

An arterial pH $<$ 7.25 is considered a severe condition in COPD subjects with acute exacerbations [13]. Based on this issue, our patients were stratified according to their pH arterial blood at admission and two subgroups were considered: group 1 with pH $<$ 7.25 and group 2 with pH between 7.25 and 7.34.

Four patients died during in hospital stay. Two patients met objective criteria for NIMV failure (1 man and 1 woman, respectively aged 84 and 88 years) and died due to cardiorespiratory arrest, since intubation was denied. Two patients (one man and one woman, respectively aged 89 and 69 years) died due to stroke and to myocardial infarction. Twenty-three patients were effectively treated with NIMV and subsequently discharged. The overall length of hospitalisation for alive patients was 14.5 $\pm$ 8.6 days.

Mean values of arterial blood gases at admission, 2, 24 and 48 hours and at discharge for 23 COPD patients discharged alive are reported in *table 2*. There was a progressive improvement of arterial pH and PaCO2 *(figg. 1 and 2)*. A quick improvement of acidosis was recorded after 2 hours of NIMV, with stable and significant improvement of pH, confirmed by further measures at 24, 48 hours and at discharge ($p < 0.05$). Arterial carbon-dioxide blood tension decreased significantly after 24 hours of treatment in comparison to baseline values [($p < 0.05$) *table 2*].

Clinical characteristics of enrolled patients divided in the two subgroups, length of hospitalisation are shown in *table 1*.

At admission no differences in age, arterial oxygen and carbon-dioxide blood tension were observed, whereas GCS was significantly lower in the group 1 in comparison to group 2.

There was a significant difference between groups in mean Charlson index [14]: (group 1: mean $\pm$ SD 1.7 $\pm$ 0.7; group 2: 1.4 $\pm$ 0.5, $p < 0.0001$). COPD patients with pH $<$ 7.25 had the following comorbidities: four patients diabetes type 2 with associated systemic hypertension, four subjects systemic hypertension, three patients chronic atrial fibrillation (one patient had an associated previous stroke) two subjects a previous myocardial infarction (one patients had an associated diabetes type 2).

Table 1 Mean (SD) demographic, clinical and functional characteristics of 27 patients with acute exacerbations of COPD, divided according to pH arterial blood (pH$<$ 7.25 or pH $\geq$ 7.25) at admission.

Characteristics at enrollement	Patients with pH$<$ 7.25 (group 1)	Patients with pH$\geq$ 7.25 (group 2)	P value
Number	15	12	n.s.
Age (yr)*	77.9 $\pm$ 11.5	78.7 $\pm$ 11.0	n.s
Sex (M/F)	9/6	4/8	n.s
Glasgow Coma Scale (score)*	10.2 $\pm$ 3.4	13.0 $\pm$ 2.5	0.041
Respiratory rate (breaths/min)*	34.4 $\pm$ 3.85	30.5 $\pm$ 3.2	0.009
FEV 1 at discharge (% pred)	$\geq$30% to $<$80%: 7 pts $<$30%: 5 pts	$\geq$30% to $<$80%: 7 pts $<$30%: 4 pts	n.s
PaO_2/FiO_2	236.0 $\pm$ 67.1	227.5 $\pm$ 39.6	n.s
PaCO2 (mmHg)	85.0 $\pm$ 16.6	75.4 $\pm$ 15.9	0.075
Length of hospital stay (days)	14.3 $\pm$ 8.86	14.8 $\pm$ 8.8	n.s
Charlson index	1.7 $\pm$ 0.7	1.4 $\pm$ 0.5	$<$0.0001
Deaths	3	1	n.s

* data are expressed as mean $\pm$ SD.

Table 2 Mean (SD and range) of arterial blood gas values of 23 patients with acute exacerbations of COPD discharged alive. Comparison are between admission, 2, 24, 48 hours after admission and at discharge.

Caracteristichs of patients	at enrollement	After 2 hours	After 24 hours	After 48 hours	At discharge
PaO2/FiO2	232.9 ± 58.1 (155-385)	246.8 ± 76.3 (121-445)	277.7 ± 87.7 (154-521)	281.7 ± 73.9 (160-428)	305.2 ± 60.6 * (193-440)
PaCO2 (mmHg)	79.2 ± 14.9 (51-106)	69.22 ± 14.4 (42-96)	60.4 ± 11.3 * (42-80)	55.3 ± 12.6 * § (35-84)	45.9 ± 1.3 * § (26-62)
PH	7.22 ± 0.08 (7.01-7.32)	7.29 ± 0.08 * (7.05-7.39)	7.36 ± 0.05 * § (7.17-7.44)	7.39 ± 0.05 * § (7.27-7.47)	7.42 ± 0.05 * § (7.34-7.55)

- * <0.05 in comparison to admission.
- § <0.05 in comparison to 2 hours of treatment.
- # <0.05 in comparison to 24 hours of treatment.

Three patients with a pH ≥ 7.25 died during in hospital stay. Deaths were due to:

- myocardial infarction in one patient, occurred 37 days after admission;
- stroke occurred in one subject, 2 days after admission;
- NIMV late failure with cardiorespiratory arrest occurred in one patient 7 days after admission.

Only a death for NIMV late failure with cardiorespiratory arrest was reported in the group with pH ≥ 7.25, 10 days after admission.

The length of the hospital stay did not differ between two groups. All 23 patients were followed up to either death or January 31th 2007. The mean long-term survival for 23 patients was 14.5 months (95% CI 10.2 to 18.8) with 61% surviving at 1 year.

No significant differences in in-hospital mortality, as many as in global survival after a year of follow-up were observed between two groups.

Discussion

The study shows that NIMV performed on a general medical ward was clinically effective at improving arterial blood gases of exacerbated COPD patients with respiratory acidosis. The treatment was effective in COPD patients both with pH < 7.25 and pH ≥ 7.25 at admission and the in-hospital mortality and the long-term mortality did not differ in the two subgroups.

In the past years randomised controlled trials strongly recommended NIMV in all COPD patients with respiratory acidosis and pH < 7.35 (2,4,10,15). In such patients NIMV has been proved to reduce both the need for intubation and in-hospital mortality. The early use of NIMV for mildly and moderately acidotic patients with COPD was proved effective both in general wards [4] and also in the emergency room [16].

Based on these evidences 27 patients, admitted to our general medical unit for acute hypercapnic respiratory failure due to exacerbated COPD were treated with NIMV and considered for data analysis, according to a baseline pH ≥ 7.25 or pH < 7.25. Among twenty-seven patients on NIMV, twenty-three (85,6%) were effectively treated and subsequently discharged, whereas four (14.4%) died during in-hospital stay. The in-hospital mortality was slightly higher in comparison to Plant's study [10] but within the range reported in literature [17]. It is noteworthy that the mean age of patients included in our study was higher than mean age of subjects enrolled in Plant's study [10]; further, we treated patients with severe acidosis (pH < 7.25) at admission. Predictive strong risk factors for NIMV failure included a lower baseline pH, 7.22 versus 7.28 [17], one or more comorbidities at admission, an impairment of daily living activities [11]. In addition, the in-hospital stay of 23

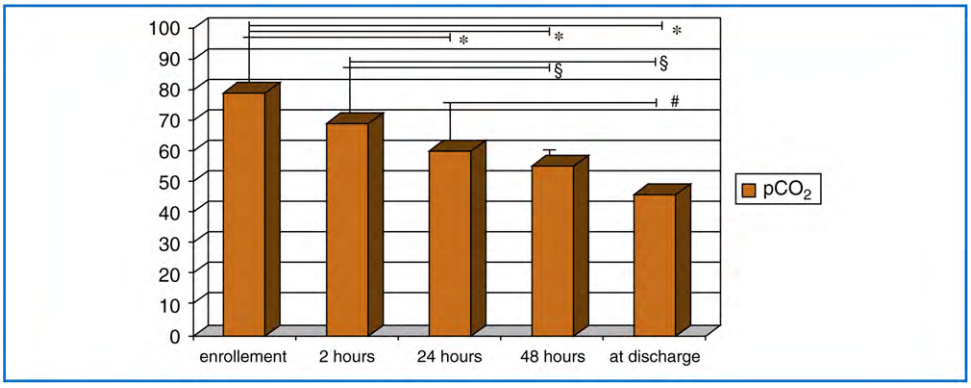

Figure 1 Arterial blood pCO2 values of 23 patients with acute exacerbations of COPD discharged alive. Comparison are between admission, 2, 24, 48 hours after admission and at discharge.

- <0.05 in comparison to admission.
- § <0.05 in comparison to 2 hours of treatment.
- # <0.05 in comparison to 2 hours of treatment.

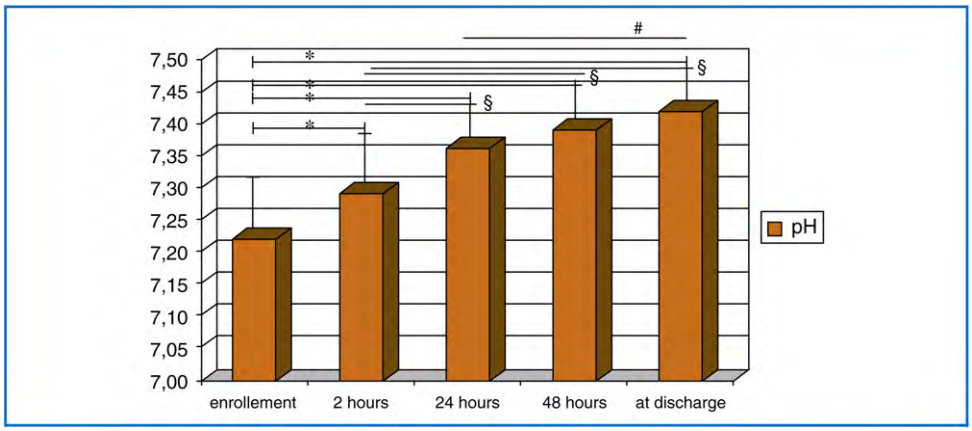

Figure 2 Arterial blood pH values of 23 patients with acute exacerbations of COPD discharged alive. Comparison are between admission, 2, 24, 48 hours after admission and at discharge.
- * <0.05 in comparison to admission.
- § <0.05 in comparison to 2 hours of treatment.
- # <0.05 in comparison to 2 hours of treatment.

alive patients was in accordance with data reported in previous reports [10]. According to previous studies [2,4], our experience indicated that following 2 hours of treatment NIMV induced a rapid improvement in pH with a non-significant decrease in PaCO2. Subsequently a significant fall in PaCO2, in an expected amplitude for the pH change, was observed within 24 hours. These findings show that NIMV is able to unload fatigued ventilatory muscles, reducing substantially the work of breathing.

The hallmark emerging from this study is that NIMV results useful and effective in a general medical ward, even in patients with severe respiratory acidosis and clinical comorbidities.

In a previous study Plant et al. [4] doesn't recommend NIV treatment in general medical ward for patients with a pH lower than 7.30, because the risk of failure in these subjects is more than threefold higher. The discordance between our results and Plant's study may be only apparent. In our experience, specific and continous nursing staff training was provided for NIMV, as described previously [8,18]. In addition, COPD patients were subjected to a strict supervision in the ward, although a low nurse: patient ratio.

Further, one-year survival of study patients was 61%, irrespective of Ph $\geq$ 7.25 or $<$ 7.25 at admission, this value being in accordance to previous reports, [10,15,19,20,21]. Nevertheless an accurate comparison between these results may be questionable, because of several factors, such as differences in study design, age and number of patients enrolled or interventions received during hospitalisation [15,19,20,22]. In addition, recent trials shows that NIMV is cost effective both in ICU and in general pneumological wards. In two recent reports both Brochard and Elliott [18,20] asked if NIMV may be applied in general medicine unit too. Although our study has some limiting factors, such as the low number of patients enrolled, the suboptimal nurse: patient ratio, our trial may provide a positive answer to the question.

In addition, NIMV use provision has very important economic implications; it has been clearly shown that this therapeutic option decreases hospitalisation length and global costs for patients care, in terms of medical and nursing staff or equipment for invasive ventilation delivery [23].

Based on these observations our study supports the use of NIMV in a general medicine ward provided that important conditions are considered and observed:
- an accurate supervision of COPD ventilated patients by a chest physician with a proved experience in NIMV, with problem-solving ability;
- a nursig staff devoted to this therapeutic option, convinced of NIMV efficacy and subjected to a specific, and repeated educational training;
- a continuous monitoring during NIMV of pulsoximetry, ECG, and strict arterial blood gases measurements and ventilator/patient synchrony control;
- a rapid access to invasive ventilation when considered appropriate.

Our results, both in terms of outcome and cost efficacy suggest that NIMV could be a very effective approach also in non-ICU environment, according to local organisations, resources and availability of intensive beds. It is necessary to consider that NIMV is often the last chance of surviving for severely-ill COPD patients. Nevertheless potential important problems, connected to this therapeutic option, should be carefully considered before starting this therapeutic approach in a general medicine ward [18,24].

Conflict of interest statement

The authors have no conflict of interest.

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