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Noninvasive ventilation in hypercapnic acute respiratory failure due to chronic obstructive pulmonary disease vs. other conditions: effectiveness and predictors of failure

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Abstract *Objective:* This study compared the effectiveness of noninvasive ventilation (NIV) and the risk factors for NIV failure in hypercapnic acute respiratory failure (ARF) due to chronic obstructive pulmonary disease (COPD) vs. non-COPD conditions. *Design and setting:* Prospective cohort study in the medical intensive care unit of a university hospital. *Patients and participants:* 111 patients with hypercapnic ARF, 43 of whom had COPD exacerbations and 68 other conditions. Baseline characteristics of the two groups were similar. *Measurements and results:* The risk of NIV failure, defined as the need for endotracheal intubation, was significantly lower in COPD than in other conditions (19% vs. 47%). High APACHE II score was an independent predictor of NIV failure in COPD (OR 5.38 per 5 points). The presence of pneumonia (OR 5.63), high APACHE II score (OR 2.59 per 5 points), rapid heart rate (OR 1.22 per 5 beats/min), and high $PaCO_2$ 1 h after NIV (OR 1.22 per 5 mmHg) were independent predictors of NIV failure in the non-COPD group. Failure of NIV independently predicted mortality (OR 10.53). *Conclusions:* Noninvasive ventilation was more effective in preventing endotracheal intubation in hypercapnic ARF due to COPD than non-COPD conditions. High APACHE II score predicted NIV failure in both groups. Noninvasive ventilation was least effective in patients with hypercapnic ARF due to pneumonia.

Keywords Noninvasive ventilation · Hypercapnic acute respiratory failure · Chronic obstructive pulmonary disease · Pneumonia

Introduction

Noninvasive ventilation (NIV) has been used increasingly to support patients with various forms of acute respiratory failure (ARF) [1, 2, 3]. Nevertheless, the evidence for the use of NIV remains strongest in patients with hypercapnic ARF due to exacerbations of chronic obstructive pulmonary disease (COPD) [4, 5, 6]. While there is emerging evidence to support the use of NIV in ARF unrelated to COPD, most studies in this area have focused on patients with hypoxemic ARF [7, 8]. The role of NIV in hypercapnic ARF due to conditions other than COPD remains unclear [1, 2]. Moreover, the predictors of failure of NIV in hypercapnic ARF due to non-COPD conditions are not well described in the literature, in contrast those regarding COPD [1, 2].

The aim of this study was therefore to compare the effectiveness of NIV in hypercapnic ARF due to COPD vs. non-COPD conditions and to elucidate the risk factors for NIV failure in these two groups.

Table 1 Characteristics of patients immediately before to noninvasive ventilation (after nebulizations in the COPD group) and 1 h after treatment (*COPD* chronic obstructive pulmonary disease, $PaCO_2$ partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, APACHE Acute Physiology and Chronic Health Evaluation)

	COPD (n=43)		Non-COPD (n=68)		p
	Baseline	After 1 h	Baseline	After 1 h	
Age (years)	72±10	–	67±15	–	0.05
Sex: M/F	35/8	–	39/29	–	0.009
APACHE II	23±4	–	25±6	–	0.06
Respiratory rate (breaths/min)	32±7	24±6*	32±8	25±9*	0.66
Heart rate (beats/min)	116±21	110±22*	113±24	106±25*	0.57
Systolic blood pressure (mmHg)	148±34	128±29*	140±35	130±29*	0.29
pH	7.24±0.07	7.29±0.07*	7.24±0.07	7.30±0.08*	0.89
$PaCO_2$ (mmHg)	74.3±17.1	64.8±14.9*	71.9±19.5	65.5±21.8*	0.50
PaO_2 (mmHg)	93.1±38.8	101.1±40.5	97.6±50.2	116.3±80.9	0.62

*p<0.001 vs. baseline

Materials and methods

We conducted a prospective cohort study on NIV for hypercapnic ARF in the medical intensive care unit (ICU) of our university hospital from May 2000 to August 2004.

Patients

We treated 111 patients with hypercapnic ARF with NIV during the study period. We differentiated those with COPD exacerbations (n=43) from those with other conditions: pneumonia (n=37), neuromusculoskeletal disorders (n=11), pulmonary edema (n=9), bronchiectasis (n=5), sepsis (n=3), and asthma (n=3). Other than a greater proportion of men among the COPD patients the baseline characteristics of the two groups immediately before NIV were similar (Table 1). Also, the median time from presentation at the emergency department to initiation of NIV differed in the two groups: 6 h (0.5–99) in those with COPD and 16 h (1–646 h) in those without COPD; many non-COPD patients developed ARF only in the days after admission. Noninvasive ventilation was initiated in the ICU for 107 patients and in the emergency department for 4 (with COPD).

Before initiating NIV three investigators (P.J., K.H.L., T.K.L.) made the diagnoses together when the patients presented during office hours. After office hours the diagnoses were made by managing physicians on duty prior to NIV and were subsequently verified by the investigators together; in these situations the investigators were not blinded to the outcome of NIV. Forty-six patients were started on NIV by managing physicians on duty after office hours, and investigators revised these physicians' diagnoses on the next morning in four cases.

Definitions

We defined hypercapnic ARF as the presence of all the following: respiratory rate higher than 25 breaths/minute, arterial pH below 7.35, and partial pressure of arterial carbon dioxide ($PaCO_2$) in excess of 45 mmHg. We included only the first episode of NIV for each patient during the study period. We excluded patients with severe hemodynamic instability, impending respiratory arrest, inability to protect airway, excessive airway secretions, pneumothorax, acute upper gastrointestinal bleeding, epistaxis, facial deformity/trauma, hypersensitivity to mask material, and patients for which active treatment and intubation were deemed inappropriate.

We diagnosed COPD based on either existing medical records and pulmonary function tests, or a compatible history, physical examination, and chest radiography. We diagnosed an acute exacerbation if patients were admitted for one or more of the following symptoms due to COPD: increased dyspnea, sputum volume, or sputum purulence [9] without any new infiltrate on chest radiography. We treated all patients with COPD exacerbations with systemic steroids and three consecutive nebulizations of salbutamol with ipratropium, driven by compressed air at a flow rate of 9 l/min. We repeated arterial blood gas measurements after these nebulizations and applied NIV only if hypercapnic ARF persisted despite this initial therapy. We started antibiotic therapy for Anthonisen type I exacerbations [9].

We subclassifed the patients in the non-COPD group into the following diagnoses: pneumonia (n=37), neuromusculoskeletal disorders (n=11), pulmonary edema (n=9), bronchiectasis (n=5), sepsis (n=3), and asthma (n=3). We diagnosed pneumonia in the presence of a new infiltrate on chest radiography accompanied by one or more acute symptoms and signs: dyspnea, cough, sputum production, fever higher than 38.0°C, abnormal breath sounds, and rales [10]. We provided supplemental oxygen for all patients (using nasal prongs for COPD patients during nebulizations) if necessary to keep the pulse oximeter reading between 92% and 95% before NIV.

Noninvasive ventilation protocol

We administered NIV with the BiPAP Vision (Respironics, Murrysville, Pa., USA) in the spontaneous/timed mode with the assistance of respiratory therapists and trained nurses. We started with an inspiratory positive airway pressure (IPAP) of 18 cmH_2O and an expiratory positive airway pressure (EPAP) of 4 cmH_2O. We adjusted ventilator settings based on continuous oximetry (keeping the oxygen saturation at 92–95%) and arterial

blood gas measurements (at 1 h and periodically thereafter as clinically indicated) and to maximize patient comfort. We made available three oronasal masks to optimize patient comfort: Spectrum Disposable Full Face Mask, Spectrum Reusable Full Face Mask, or Respironics Total Face Mask (all from Respironics), tightly securing them with head straps to minimize leaks. After 24 h we allowed a nasal mask (Contour Deluxe Disposable Nasal Mask, Respironics) if the patient did not tolerate the oronasal mask. We applied NIV initially for at least 6 h, lengthening this period according to the patient's tolerance.

We recommended the following indications for endotracheal intubation: respiratory arrest, respiratory pauses with loss of alertness or gasping, psychomotor agitation requiring sedation, systolic blood pressure higher than 70 mmHg, and pH below 7.26 after 1 h of NIV. Ultimately, clinical judgment was applied in the decision to intubate. The duration of NIV and the time to stop NIV were also determined based on clinical judgment and arterial blood gas values.

Endpoints

The primary outcome was NIV failure, defined as the need for endotracheal intubation during the ICU stay. Secondary endpoints were the lengths of ICU and hospital stay, and ICU and in-hospital mortality rates.

Data collection

We prospectively collected the following data: basic demographics, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, time from presentation at the emergency department to initiation of NIV, respiratory rate, heart rate, systolic blood pressure, and arterial blood gas measurements immediately before NIV and at 1 h after NIV, duration spent on NIV, and reasons for NIV failure. We recorded available spirometric data for each COPD patient performed within the year preceding NIV.

Statistical methods

We compared the characteristics and outcomes in COPD and non-COPD patients using univariate analysis. We present the data as frequencies for nominal variables and as means ±standard deviation or medians with range for continuous variables. We performed univariate analyses using the χ^2 test or Fisher's exact test for nominal variables, the *t* test for means, and the Mann-Whitney *U* test for medians.

To identify factors predictive of NIV failure we first performed a univariate analysis to compare those with NIV success vs. failure. We entered variables with *p* values less than 0.10 into a forward stepwise logistic regression analysis using an entry level of 0.05 and a removal level of 0.10. We calculated the adjusted odds ratio (OR) with 95% confidence intervals (95% CI) for all independent predictors of NIV failure. We checked for multicollinearity by computing the tolerance between variables. We first performed these steps on all patients together. We then repeated these steps separately in the COPD and the non-COPD groups. We performed a similar analysis to determine the predictors of in-hospital mortality. We considered differences with a *p* value less than 0.05 as statistically significant; all tests were two-tailed. We used the SPSS statistical software package (version 12.0).

The variables included in the above analyses were: age, sex, time from presentation at the emergency department to initiation of NIV, respiratory rate, heart rate, systolic blood pressure, pH, $PaCO_2$, and PaO_2 immediately before NIV and at 1 h after NIV, and APACHE II score. In the analysis of the entire group we included the presence of COPD as a variable. In the analysis of the non-COPD group we included the presence of pneumonia as a variable.

Results

After initial adjustments the mean IPAP and EPAP values were similar in the two groups (IPAP: 18±4 vs. 18±3 cmH_2O, p=0.55; EPAP: 6±2 vs. 7±2 cmH_2O, p=0.26). Both groups showed improved respiratory rate, heart rate, systolic blood pressure, pH, and $PaCO_2$ 1 h after NIV. NIV failure rate was lower in COPD patients than in non-COPD patients (19% vs. 47%, p=0.002) (Table 2). The in-hospital mortality rate was lower in COPD patients (12% vs. 35%, p=0.006), and the average length of stay was also shorter. Reasons for NIV failure were worsening of blood gas measurements (95% of failures), deterioration in clinical status including respiratory rate, heart rate and systolic blood pressure (90%), drowsiness (78%), and mask nontolerance (5%).

Multivariate analysis in the overall series of patients revealed four independent predictors of NIV failure: diagnosis other than COPD, high APACHE II score, rapid heart rate, and high $PaCO_2$ 1 h after NIV (Table 3). There was no association between NIV failure rate, and the time from presentation at the emergency department to NIV initiation (p=0.70).

Only one variable was associated with NIV failure on univariate analysis in the COPD group: high APACHE II score (OR 5.38 per 5 points, 95% CI 1.61-18.38, p=0.007). No patient with APACHE II score below 23 required intubation. Spirometric data obtained during the year preceding NIV was available in 27 COPD patients. The mean postbronchodilator forced expiratory volume

Table 2 Primary and secondary outcomes for noninvasive ventilation (NIV) (*COPD* chronic obstructive pulmonary disease)

	Overall (*n*=111)	COPD (*n*=43)	Non-COPD (*n*=68)	*p*
Number intubated in ICU after NIV failure	40 (36%)	8 (19%)	32 (47%)	0.002
Number intubated within 24 h of starting NIV	27 (24%)	7 (16%)	20 (29%)	0.12
Number died in ICU	17 (15%)	3 (7%)	14 (21%)	0.05
Number died in hospital	29 (26%)	5 (12%)	24 (35%)	0.006
Duration of NIV (h; range)	15 (1–157)	20 (2–124)	13 (1–157)	0.09
ICU length of stay (days; range)	3 (1–36)	3 (1–30)	4 (1–36)	0.04
Hospital length of stay (days; range)	10 (1–90)	8 (2–33)	11 (1–90)	0.03

Table 3 Variables associated with failure of noninvasive ventilation for all patients (*CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *APACHE* Acute Physiology and Chronic Health Evaluation)

	p, univariate analysis[a]	Multivariate analysis[b]		
		Odds ratio	95% CI	*p*
Baseline				
Diagnosis other than COPD	0.003	4.18	1.39–12.56	0.01
APACHE II	<0.001	2.82 per 5 points	1.69–4.83	<0.001
Heart rate	0.04	–	–	–
After 1 h				
Respiratory rate	0.04	–	–	–
Heart rate	0.005	1.22 per 5 beats/min	1.05–1.34	0.005
pH	0.01			
$PaCO_2$	0.05	1.22 per 5 mmHg	1.05–1.40	0.007

[a] Only variables with *p* values less than 0.10 on univariate analysis are shown
[b] The same variables with *p* values less than 0.10 on univariate analysis are included and entered into a forward stepwise logistic regression analysis

Table 5 Variables associated with failure of noninvasive ventilation in patients not diagnosed with chronic obstructive pulmonary disease (*CI* confidence interval)

	p, univariate[a]	Multivariate analysis[b]		
		Odds ratio	95% CI	*p*
Baseline				
Pneumonia	0.001	5.63	1.43-22.22	0.01
APACHE II	<0.001	2.59 per 5 points	1.34–5.19	0.005
Heart rate	0.02	–	–	–
After 1 h				
Respiratory rate	0.01		–	–
Heart rate	0.004	1.22 per 5 beats/min	1.00-1.40	0.03
pH	0.02	–	–	–
$PaCO_2$	0.04	1.22 per 5 mmHg	1.05-1.47	<0.001

[a] Only variables with *p* values less than 0.10 on univariate analysis are shown
[b] The same variables with *p* values less than 0.10 on univariate analysis are included and entered into a forward stepwise logistic regression analysis

in 1 s (FEV_1) was 0.69±0.24 l (33±13% of predicted), postbronchodilator forced vital capacity (FVC) 1.60±0.54 l (53±17% of predicted), and postbronchodilator FEV_1/FVC ratio 45±11%. There were no significant differences in the spirometric data of COPD patients with and without NIV failure.

In the non-COPD group the diagnosis with the most NIV failures (65%) was pneumonia (Table 4). On multivariate analysis of the non-COPD group there were four independent predictors of NIV failure: presence of pneumonia, high APACHE II score, rapid heart rate, and high $PaCO_2$ 1 h after NIV (Table 5). Among the 37 patients with pneumonia 22 had a previous history of COPD. These 22 patients were classified under the non-COPD group because it was the primary diagnosis of pneumonia and not a usual exacerbation that triggered their hypercapnic ARF. Failure rates in these 22 patients (59%) did not differ significantly from those in patients

Table 4 Outcomes of noninvasive ventilation in patients not diagnosed with chronic obstructive pulmonary disease by specific diagnosis

	n	Intubated in ICU		ICU deaths		Hospital deaths	
		n	%	*n*	%	*n*	%
Pneumonia	37	24	65	12	32	19	51
Neuromusculoskeletal disorders	11	3	27	0	–	1	9
Pulmonary edema	9	2	22	1	11	2	22
Bronchiectasis	5	2	40	0	–	1	20
Sepsis	3	1	33	1	33	1	33
Asthma	3	0	–	0	–	0	–

with pneumonia without COPD (73%; p=0.37). The in-hospital mortality rate also did not differ significantly (46% vs. 60%, p=0.39).

Univariate analysis of the overall series showed NIV failure to be associated with higher ICU mortality (43% vs. 0%), and in-hospital mortality (55% vs. 10%), and longer ICU length of stay (median 7 vs. 3 days; p<0.001). Factors associated with in-hospital mortality included a diagnosis other than COPD (p=0.006) and high APACHE II score (p<0.001). However, on multivariate analysis the only independent predictors of in-hospital mortality that remained were NIV failure (OR 10.53, 95% CI 3.62-30.30, p<0.001) and rapid respiratory rate 1 h after NIV (OR 1.47 per 5 breaths/min, 95% CI 1.05-2.01, p=0.02). There was no multicollinearity between the independent variables (tolerance >0.7).

Discussion

To our knowledge, this is the first prospective study to compare the effectiveness of NIV in hypercapnic ARF due to COPD vs. conditions other than COPD and to elucidate the risk factors associated with NIV failure in these patients. Noninvasive ventilation was most effective in patients with hypercapnic ARF due to COPD. A diagnosis other than COPD was a risk factor for NIV failure. Specifically, NIV was least effective in patients with hypercapnic ARF due to pneumonia.

There is little evidence for the efficacy of NIV in hypercapnic ARF due to conditions other than COPD. Controlled trials for acute applications of NIV in conditions such as obstructive sleep apnea, bronchiectasis, and restrictive lung diseases are lacking [1, 2]. Although a meta-analysis suggests that NIV is more effective in COPD exacerbations than other conditions [6], most studies in non-COPD conditions involve hypoxemic ARF and do not focus on hypercapnic ARF [7, 8]. One study compared NIV in COPD vs. chronic restrictive pulmonary diseases, but this was a retrospective study, and not all patients had hypercapnic ARF [11]. We found that NIV failure (47%) and in-hospital mortality rates (35%) were significantly higher in hypercapnic ARF not due to COPD than in COPD. Even after controlling for the severity of illness a primary disorder other than COPD was an independent predictor of NIV failure. Such poor outcomes suggest a need for caution when applying NIV in these patients.

The role of NIV specifically in pneumonia with hypercapnic ARF has never been evaluated definitively. The only study which demonstrated that NIV lowered both intubation rates and ICU mortality in pneumonia excluded hypercapnic patients [12]. Other studies on NIV in pneumonia evaluated heterogeneous groups of patients with hypoxemia and/or hypercapnia. One such study carried out by Confalonieri et al. [13] found that NIV decreased intubation rates from 50% to 21% in patients with pneumonia (25 with hypercapnia, 31 without), but not mortality rates. Other studies showed poorer outcomes for NIV in pneumonia, with intubation rates ranging from 38% to 100% [14, 15, 16, 17], and with all five hypercapnic patients in one study requiring intubation [14]. In our study the presence of pneumonia was an independent predictor of NIV failure in the non-COPD group. Patients with pneumonia had the worst outcomes (65% intubated, 51% died). Caution is required when applying NIV on patients with severe pneumonia and hypercapnic ARF.

Confalonieri et al. [13] observed that NIV reduced intubation rates (from 55% to 0%) in 23 patients who had pneumonia plus a previous history of COPD. However, the NIV failure (59%) and in-hospital mortality rates (46%) in our patients with pneumonia and a previous history of COPD were much higher (n=22). Although there was a trend towards lower NIV failure (p=0.37) and in-hospital mortality rates (p=0.39) among these 22 patients than in the other 17 patients with pneumonia but no COPD, this did not reach statistical significance. This discrepancy between our data and those of Confalonieri et al. [13] may be because our patients had higher mean APACHE II scores (24 vs. 20) and were older (74 vs. 68 years).

The risk factors for NIV failure in hypercapnic ARF due to non-COPD conditions are not well defined in the literature. Aside from pneumonia, the independent predictors of NIV failure in the non-COPD group in our study were a high APACHE II score, rapid heart rate, and high $PaCO_2$ 1 h after NIV. Other than tachycardia these factors are similar to the predictors of NIV failure in COPD studies [18, 19, 20, 21].

In contrast to the non-COPD group, the NIV failure rate in our COPD patients was only 19%, similar to the pooled failure rate of 21% [22] from four trials on NIV in COPD [23, 24, 25, 26]. This is despite a lower mean baseline pH of 7.24 in our COPD patients, compared to that of 7.28 [22] from these same trials [23, 24, 25, 26]. Similarly, a recent study found only eight COPD patients to have NIV failure, compared to 110 successes with a mean pH of 7.24 [27]. Therefore, although previous NIV studies have excluded patients with a baseline pH of less than 7.25 [28, 29], it is likely that NIV may be initiated when the pH is between 7.20 and 7.25. Indeed, it has been shown that NIV benefits patients with severe and not mild exacerbations [5]. A previous meta-analysis also suggested that baseline pH does not affect the risk of NIV failure [6]. We urge caution, however, when the pH is below 7.20. Although one ICU's extensive experience in NIV resulted in low failure rates of 16% when the mean pH was 7.20 [21], there were high failure rates (52% and 63%) in two other studies (mean pH 7.20 and 7.18, respectively) [30, 31].

The only predictor of NIV failure in our COPD patients was high APACHE II score, which also featured in

previous studies [18, 19, 21]. Hence it would be prudent to evaluate a patient's overall condition rather than focus on isolated variables when considering NIV in COPD patients.

Interestingly, although a diagnosis other than COPD and a high APACHE II score were associated with higher in-hospital mortality on univariate analysis, the only independent predictors of in-hospital mortality in all patients were NIV failure and a rapid respiratory rate 1 h after NIV on multivariate analysis. This suggests that much of the higher mortality in non-COPD patients than in COPD patients may be due to a poorer response to NIV in non-COPD patients.

Limitations of our study include the lack of a control arm; unlike other studies which compared NIV vs. usual management, we administered NIV to all patients and compared outcomes in the two groups. The other subgroups in the non-COPD group were comparatively small except for that of pneumonia patients. Nevertheless, there was a trend towards poorer outcomes in all diagnoses than in COPD, except asthma. It is possible that only the APACHE II score was identified as a predictor of NIV failure in the COPD group while four predictors were found in the non-COPD group because the COPD group was smaller. Finally, the investigators were not blinded to NIV outcomes when verifying the on-call physicians' diagnoses in 46 patients; this, however, is unlikely to be a significant limitation since the diagnoses were revised in only four patients.

In conclusion, we found that NIV was significantly more effective in patients with hypercapnic ARF due to COPD than in other conditions, even after controlling for baseline severity. A high APACHE II score was a predictor of NIV failure in both COPD and non-COPD patients. The presence of pneumonia, rapid heart rate, and high $PaCO_2$ 1 h after NIV were predictors of failure in non-COPD patients. Failure of NIV was an independent predictor of in-hospital mortality.

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