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Noninvasive vs invasive ventilation in COPD patients with severe acute respiratory failure deemed to require ventilatory assistance

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Abstract *Objective:* To determine whether non-invasive ventilation (NIV) may be an effective and safe alternative to invasive mechanical ventilation in chronic obstructive pulmonary disease (COPD) patients with acute respiratory failure (ARF) meeting criteria for mechanical ventilation. *Design and setting:* Matched case-control study conducted in ICU. *Patients and intervention:* NIV was prospectively applied to 64 COPD patients with advanced ARF. Their outcomes were compared with those of a control group of 64 COPD patients matched on age, FEV_1, Simplified Acute Physiology Score II, and pH at ICU admission, previously treated in the same ICU with conventional invasive mechanical ventilation. *Methods and results:* NIV failed in 40 patients who required intubation. Mortality rate, duration of mechanical ventilation, and lengths of ICU and post-ICU stay were not different between the two groups. The NIV group had fewer complications ($P = 0.01$) and showed a trend toward a lower proportion of patients remaining on mechanical ventilation after 30 days ($P = 0.056$). Compared to the control group, the outcomes of the patients who failed NIV were no different. Compared to the patients who received intubation, those who succeeded NIV had reduced mortality rate and lengths of ICU and post-ICU stay. *Conclusions:* In COPD patients with advanced hypercapnic acute respiratory failure, NIV had a high rate of failure, but, nevertheless, provided some advantages, compared to conventional invasive ventilation. Subgroup analysis suggested that the delay in intubation was not deleterious in the patients who failed NIV, whereas a better outcome was confirmed for the patients who avoided intubation.

Keywords Noninvasive positive pressure ventilation · Respiratory failure · Chronic obstructive lung disease · Intensive care · Endotracheal intubation

Introduction

Non-invasive ventilation (NIV) has been proposed both as a means to prevent endotracheal intubation in early stage acute respiratory failure (ARF) [1, 2, 3, 4, 5, 6, 7, 8, 9] and as an alternative to conventional mechanical ventilation through an endotracheal tube (ETMV) in more severe patients deemed to require ventilatory assistance [10, 11, 12, 13, 14].

In patients with COPD and mild to moderate hypercapnic ARF, the addition of NIV to the medical treatment has been proven to be effective in relieving dyspnea [1],

improving vital signs and gas exchange [1, 2, 3, 4, 6], preventing endotracheal intubation [1, 2, 3, 6], and improving hospital survival [2, 3, 6, 14]. Consequently, there is a general consensus on the early use of NIV in such patients [15, 16]. Does this occur in the real world? In a recent survey conducted in French medical ICUs, NIV was the first choice for ventilatory treatment in 50% of all COPD patients receiving mechanical ventilation [17]. A large cohort study based on data collected from 361 ICUs in North America, South America, and Europe indicated that NIV was used in 17% of all COPD patients receiving mechanical ventilation [18]. Another recent cohort study evaluating the outcomes of 166 COPD patients mechanically ventilated in ICU, reports that a trial of NIV was performed before intubation only in two patients, despite an average pre-intubation hospital stay of 3 days [19]. Indeed, when the clinical presentation is characterized by an abrupt onset and rapid progression or when logistic aspects make NIV unfeasible in the medical ward or in the emergency department, ARF may worsen to a point at which mechanical ventilation becomes mandatory.

The use of NIV as an alternative to ETMV has been reported by Meduri et al. in small subsets of patients with advanced hypercapnic ARF who had refused intubation [20, 21]. Only recently, a randomized controlled trial has compared NIV with ETMV in patients with severe ARF due to COPD exacerbation who had previously failed standard medical treatment in the emergency ward [13]. In this study, 12 of 23 patients (52%) in the NIV group required endotracheal intubation and conventional mechanical ventilation. Although the patients who received NIV showed a trend toward a lower incidence of nosocomial pneumonia during the ICU stay and a better outcome at a 1 year follow-up, this study failed to detect significant differences in ICU and hospital mortality, overall complications, duration of mechanical ventilation, and ICU stay between the two groups. However, this study enrolled a relatively small number of patients, encompassing the risk of a type II error and not allowing subgroup analysis to evaluate whether or not the patients who failed NIV could be harmed by the delayed institution of intubation, a concern that is particularly referred to the more severely ill patients [22, 23].

The objective of the present study was to re-evaluate in a larger number of patients the relative effectiveness of NIV compared to conventional mechanical ventilation in COPD patients with advanced hypercapnic acute respiratory failure meeting criteria for mechanical ventilation and the potential for harm in using NIV in this setting.

Methods

The study was performed in the Intensive Care Unit (ICU) of the S. Luigi Gonzaga Hospital between September 1998 and August 2000. Patients or their next of kin gave their informed consent to participate in the study which was conducted in accordance with the Declaration of Helsinki.

Patients and protocol

Cases

All the patients included were COPD with hypercapnic ARF who worsened despite maximal medical treatment in the ward and were deemed to require mechanical ventilation. They were prospectively selected to be included in the study. The diagnosis of COPD was based on clinical history, physical examination, and prior pulmonary function tests.

To be included in the study the patients had to meet all the following criteria: 1) ARF due to COPD exacerbations or to the onset of community-acquired pneumonia (CAP); 2) severe respiratory acidosis ($pH \leq 7.25$ and $PaCO_2 \geq 70$ torr) while breathing room air or low flow oxygen; 3) respiratory rate ≥ 35 breaths/min; 4) severe dyspnea; and 5) activation of accessory respiratory muscles. CAP was defined by the presence, on hospital admission, of new chest radiographic infiltrates and concomitantly at least two of the following: a) temperature higher than 38 °C; b) white blood cells >12,000 mm^3; c) purulent secretions. Predefined exclusion criteria were: 1) any kind of ventilatory assistance before being admitted into the ICU; 2) respiratory arrest or bradypnea; 3) unconsciousness; 4) inability to clear secretions; 5) hypotensive shock, cardiac ischemia, or uncontrolled life-threatening arrhythmias; 6) nosocomial pneumonia (i.e., persistent lung infiltrates on chest radiographs acquired at least 48 h after hospital admission, associated with hyperthermia or hypothermia, leukocytosis, and increased purulent tracheal secretions); 7) gastrointestinal bleeding; 8) facial deformities; 9) cancer, hematologic malignancy, or other disease with poor short-term prognosis; 10) denial or refusal of endotracheal intubation; and 11) enrolment in other research protocols.

NIV was delivered in the ICU via a facial mask with an inflatable soft cushion seal and a disposable foam spacer to reduce dead space (Gibeck, Upplands Vasby, Sweden) using standard ICU ventilators (Bear 5 and 1000, Bear Medical Systems, Riverside, Calif., USA) set in Pressure Support (PSV) mode. To avoid unwarranted prolongations of the mechanical insufflation into the patient-initiated expiration due to air-leaks interfering with the flow-based cycling-off criteria, these ventilators could be set for cycling from inspiration to expiration according to a preset inspiratory time [24]. Following a protocol already in use in the ICU for COPD patients receiving invasive ventilation, the preset inspiratory pressure was adjusted to obtain an exhaled tidal volume of 6–8 ml/kg (ideal body weight). Positive end-expiratory pressure (PEEP) was initially set at 5 cmH_2O. FiO_2 was adjusted to maintain oxygen saturation between 92% and 94% as measured by pulse-oximetry. Further adjustments of the ventilator settings were made on the basis of continuous monitoring, clinical data, and arterial blood gas assessments. Nurses paid special attention to minimize mask leakage. NIV was delivered intermittently for at least 18 h/day. However, during the first 24–48 h most of the patients required almost continuous ventilatory assistance. Initially, disconnection from NIV was allowed for less than 1 h to permit eating, drinking, and expectoration. During these intervals of spontaneous unassisted breathing, oxygen supplementation was delivered via a nasal canula to keep oxygen saturation at 90%, as measured by pulse-oximetry.

As previously described [10], PSV was reduced progressively, in accordance with the clinical improvement, by 2 cmH_2O steps (twice a day). NIV was discontinued when the patient could sustain spontaneous breathing without evidence of respiratory distress, with an oxygen saturation >90% at $FiO_2 \leq 0.4$, with PSV + PEEP <10 cmH_2O. NIV discontinuation was considered successful when the unassisted spontaneous breathing was sustained for 48 con-

secutive hours without respiratory distress, with a pH $\geq$ 7.35 and a $PaO_2 \geq 60$ torr while breathing via a Venturi mask at $FiO_2 \leq 0.4$.

NIV was considered successful when intubation was avoided. Predefined criteria for intubation were: 1) lack of improvement in arterial blood gases within 2 h since NIV institution; 2) worsening of respiratory distress; 3) deterioration of the neurological status, including psychomotor agitation requiring sedation; 4) mask intolerance; 5) inability to clear secretions; and 6) life-threatening cardiovascular alterations.

Controls

Controls were all COPD patients taken from a large database of patients who had been admitted in the previous 2 years to the same ICU from the same wards for severe hypercapnic ARF due to COPD exacerbation or to the occurrence of CAP and were treated with ETMV within the first 6 h of ICU admission. We excluded all patients with any of the same aforementioned contraindications and those who had received a NIV trial prior to intubation. As a result, 298 patients were eligible as controls. Controls were selected according to the following matching criteria: 1) age ± 5 years; 2) Simplified Acute Physiology Score (SAPS) II [25], assessed within the first 24 h after ICU admission, ± 6 points; 3) FEV_1 ± 5% from the most recent pulmonary function test prior to the episode of ARF; and 4) pH values before institution of mechanical ventilation, ± 0.02.

Following the protocol in use in the ICU all control patients were sedated and in some cases paralyzed in order to be intubated. The ventilators utilized were the same described for the NIV group. Mechanical ventilation in controlled mode was used for less than 24 h. When spontaneous breathing reappeared, PSV was initiated. The preset inspiratory pressure was set to achieve a tidal volume of 6–8 ml/kg, while PEEP was initially set at 5 cmH_2O for all patients. The criteria regulating the decrease of support and the discontinuation of mechanical ventilation were the same previously described for NIV. Extubation was considered successful when spontaneous unassisted breathing was sustained for 48 h, meeting the same criteria already described for successful NIV discontinuation.

Data collection and statistical analysis

In addition to the matching variables, we collected for each patient (cases and controls) gender, diagnosis on admission, arterial blood gases immediately before mechanical ventilation, dates of hospital and ICU admissions, dates of ICU and hospital discharges, days spent on mechanical ventilation (NIV included), and the occurrence of serious complications (as listed in Table 2) in the ICU. Nosocomial pneumonia acquired while receiving either ETMV or NIV was diagnosed on the base of new persistent pulmonary infiltrates on chest radiographs, occurring at least 48 h after the beginning of either invasive or noninvasive mechanical ventilation and at least two of the following: 1) core temperature >38 °C or <36 °C; 2) white blood cells >12,000 mm^3 or <4,000 mm^3; and 3) increased purulent tracheal secretions. Sepsis and multiple organ failure (MOF) were diagnosed according to previously described criteria [26, 27]. In the NIV group, arterial blood gases were also collected approximately 2 h after NIV institution and, for those who failed NIV, just before intubation.

Results are given as mean ± SD unless otherwise specified. All statistical tests were two-tailed. Comparisons of normally distributed variables between cases and controls were performed with a paired *t*-test, while qualitative variables were analyzed using the McNemar test, as required for matched case-control studies [28]. Additional subgroup analysis involving comparisons between unmatched groups were made with the unpaired *t*-test and chi-square or Fisher's exact tests, as indicated. We used the analysis of variance for repeated measures to evaluate trends over time and the Student-Newman-Keuls test for comparisons between specific time points. Longitudinal analysis was applied to determine the probability of successful weaning over time and the differences between curves were assessed using the log-rank. *P* values lower than 0.05 were considered statistically significant.

Results

We evaluated 110 consecutive patients. Thirty-six patients met the exclusion criteria and were not enrolled. Of the remaining 74 patients, a complete matching was possible only for 58 patients. Six patients who did not completely match one of the four predefined criteria (age 6 years for one patient, FEV_1 ± 6% for two patients, pH ± 0.03 for three patients) were also included. As a result the study included 64 cases and 64 controls.

The mean values for the matching variables and other relevant characteristics at enrolment and the outcomes of the two groups are shown in Table 1. Although not reported in the table, the inspiratory pressure assistance initially applied was on average 14.8 ± 2.6 cmH_2O and

Table 1 Comparison between noninvasive ventilation and conventional invasive ventilation groups. Data are presented as mean±SD unless otherwise stated. [*NIV* indicates patients receiving noninvasive ventilation as first ventilatory treatment, *ETMV* indicates patients receiving invasive mechanical ventilation as first ventilatory treatment (controls), *FEV_1* indicates forced expiratory volume in one second, *SAPS II* Simplified Acute Physiology Scale, *VC* vital capacity, *ICU* Intensive Care Unit, *ARF* acute respiratory failure, *CAP* community-acquired pneumonia]

	NIV (*n*=64)	ETMV (*n*=64)	*P* value
MATCHING CRITERIA			
Age, years	69 (6)	70 (5)	.51
FEV_1 ,% of predicted	35 (7)	34 (6)	.62
SAPS II, score	35 (7)	35 (6)	.95
pH before ventilation	7.18 (0.05)	7.18 (0.06)	.91
CHARACTERISTICS			
Male/ Female, *n*	50/14	44/20	.34
VC, % of predicted	58 (10)	58 (10)	.67
Pre-ICU hospital stay, days	6 (4)	5 (4)	.40
Cause of ARF			
Exacerbation, *n* (%)	43 (67)	45 (70)	
CAP, *n* (%)	21 (33)	19 (30)	.70
PaO_2 before ventilation, torr	43 (9)	44 (8)	.37
$PaCO_2$ before ventilation, torr	104 (14)	100 (13)	.06
HCO_3 before ventilation; mmol/L	39 (4)	38 (4)	.07
Body mass index (kg/m^2)	23.2 (3.4)	23.1 (3.4)	.86
OUTCOMES			
ICU mortality, *n* (%)	5 (8)	11 (17)	.14
Post-ICU hospital mortality, *n* (%)	6 (9)	5 (8)	.74
Duration of ventilation, days	10 (8)	12 (3)	.39
ICU stay, days	13 (8)	15 (3)	.43
Post-ICU hospital stay, days	10 (3)	11 (4)	.34
Patients with serious complications, *n*(%)	26 (41)	42 (66)	.012

Table 2 Serious complications. Cardiovascular complications include hypotension requiring treatment (five patients in NIV, nine patients in ETMV), myocardial infarction (one patient in NIV, one patient in ETMV) and tachi-arrythmias requiring treatment (three patients in NIV, two patients in ETMV). (*NIV* indicates patients receiving noninvasive ventilation as first ventilatory treatment, *ETMV* patients treated with endotracheal intubation and invasive mechanical ventilation as first ventilatory treatment, *MOF* indicates Multiple Organ Failure)

	NIV (*n*=64)	ETMV (*n*=64)	*P* Value
Nosocomial pneumonia, *n*(%)	8 (12)	12 (19)	.54
Pneumothorax, *n* (%)	0 (0)	2 (3)	.79
Hemoptysis	1 (2)	0 (0)	.93
Sepsis and MOF, *n* (%)	3 (5)	11 (17)	.18
Cardiovascular, *n* (%)	9 (14)	12 (19)	.66
GE Bleeding, *n* (%)	3 (5)	3 (5)	.93
Cerebrovascular, *n* (%)	2 (3)	0 (0)	.79
Renal failure, *n* (%)	1 (2)	2 (3)	.93

16.7 ± 3.6 cmH_2O for the NIV and the ETMV group, respectively. There were no differences between the two groups in gender, incidence of CAP as cause of ARF, vital capacity, time spent in the hospital before ICU admission, and arterial blood gases before institution of mechanical ventilation, despite a trend toward higher $PaCO_2$ and HCO_3^- in the NIV group.

NIV failed in 40 patients (62.5%) who then required endotracheal intubation. In these patients the average duration of NIV before intubation was 7.5 h (range 0.5–43 h). Fifteen patients were intubated because they did not improve or worsened respiratory function (arterial blood gases, respiratory distress, excessive secretions), while in the remaining 25 patients endotracheal intubation was due to mask intolerance (15 patients), cardiovascular instability (six patients), neurological deterioration (three patients), and hemoptysis (one patient). As depicted in Table 1, overall ICU and post-ICU hospital mortality rates, duration of mechanical ventilation, ICU stay, and post-ICU hospital stays were not significantly different between NIV and ETMV groups. Two patients (3%) in each group were discharged from the ICU on long-term mechanical ventilation, after tracheotomy. A reduced rate of serious complications (Table 2) in the NIV group was the only significant difference between the two groups (43% and 66% for NIV and ETMV, respectively, $P< 0.05$).

The percentages of patients in the two groups who could not be successfully weaned off the ventilator over time, including those who died while on mechanical ventilation, are shown in Fig. 1a. Although a significant difference was not found, there was a trend toward a lower proportion of patients remaining on mechanical ventilation after 30 days in the NIV group ($P = 0.056$). Stratifying the 64 cases according to the NIV outcome, we found no difference between the 40 patients who received endotracheal intubation after NIV had failed and the 64 controls who received ETMV as first ventilatory

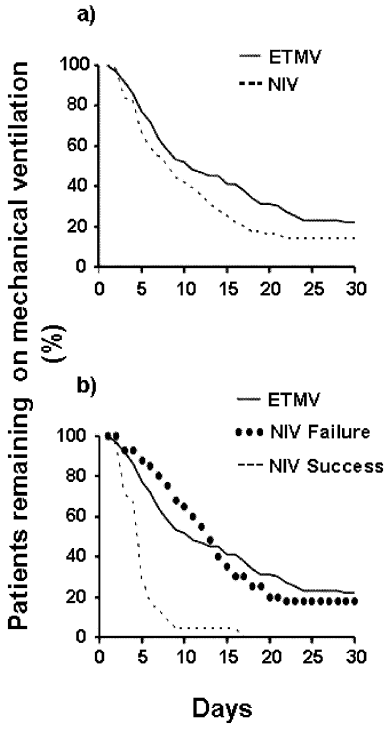

Fig. 1a,b Kaplan-Meier curves for percentages of patients remaining on mechanical ventilation. **a** Comparison between cases (NIV, *n*=64) and controls (ETMV, *n*=64). Although a significant difference was not found, there was a trend toward a lower proportion of patients remaining on mechanical ventilation after 30 days in the NIV group ($P = 0.056$); **b** Comparison between NIV success (*n*=24), NIV failures (*n*=40), and ETMV (*n*=64). The patients successfully treated with NIV received mechanical ventilation for a shorter period of time than those who were treated with conventional invasive ventilation as first intervention ($P <0.001$) and after NIV failure ($P <0.001$). NIV indicates patients receiving noninvasive ventilation as first ventilatory treatment (cases). ETMV, indicates patients receiving invasive mechanical ventilation as first ventilatory treatment (controls). NIV success indicates patients treated with noninvasive ventilation who avoided endotracheal intubation. NIV failure indicates patients who failed noninvasive ventilation and then received endotracheal intubation and invasive ventilation

treatment. The 24 patients successfully treated with NIV received mechanical ventilation for a shorter period of time than both the 64 controls ($P <0.001$) and the 40 NIV failures ($P <0.001$), as depicted in Fig. 1b.

To assess whether delaying intubation and conventional invasive ventilation harmed the patients who failed NIV, we compared the outcomes of the 40 patients who underwent ETMV after NIV failure with those of the 64 controls receiving ETMV as a first intervention (Table 3). Patients' characteristics were comparable overall, although in the subgroup of patients who failed NIV the $PaCO_2$ was slightly, but significantly, higher and there was a trend toward a longer length of pre-ICU hospital stay. The clinical outcomes were no different between the 40 patients who were intubated after NIV failure and the

Table 3 Comparison between patients who failed noninvasive ventilation and controls. Data are presented as mean ± SD unless otherwise stated. [*NIV* failure indicates patients who failed noninvasive ventilation and then received endotracheal intubation and invasive ventilation, *ETMV* indicates patients receiving invasive mechanical ventilation as first ventilatory treatment (controls), FEV_1 indicates forced expiratory volume in one second, *VC* vital capacity, *ICU* Intensive Care Unit, *ARF* acute respiratory failure, *CAP* community-acquired pneumonia, *SAPS II* Simplified Acute Physiology Scale]

	NIV Failure (*n*=40)	ETMV (*n*=64)	*P* value
CHARACTERISTICS			
Age, years	69 (6)	69 (5)	.58
Male/ Female, *n*	29/11	44/20	.83
FEV_1, % of predicted	34 (6)	34 (6)	.62
VC, % of predicted	55 (4)	58 (10)	.14
Cause of ARF			
Exacerbation, *n* (%)	28 (70)	45 (70)	
CAP, *n* (%)	12 (30)	19 (30)	.99
Pre-ICU hospital stay, days	7 (4)	5 (4)	.06
SAPS II score	37 (7)	35 (6)	.47
pH before ventilation	7.17 (0.05)	7.18 (0.06)	.28
PaO_2 before ventilation, torr	42 (9)	44 (8)	.26
$PaCO_2$ before ventilation, torr	107 (14)	100 (13)	.01
HCO_3 before ventilation; mmol/L	39 (5)	38 (4)	.15
Body mass index (kg/m^2)	23.3 (3.7)	23.1 (3.4)	.78
OUTCOMES			
ICU mortality, *n* (%)	5 (13)	11 (17)	.59
Post-ICU hospital mortality, *n* (%)	4 (10)	5 (8)	.73
Duration of ventilation, days	13 (4)	12 (3)	.11
ICU stay, days	16 (3)	15 (3)	.13
Post-ICU hospital stay, days	11 (3)	11 (4)	.50
Patients with serious complications, *n*(%)	23 (57)	42 (66)	.41

64 controls who received ETMV as first ventilatory treatment. In the subgroup of patients in whom NIV failed, both $PaCO_2$ and pH were significantly improved both at the first arterial blood gas assessment and at the time of intubation, compared to the baseline values obtained before NIV institution (Fig. 2). The number of serious complications was not different between patients immediately intubated and patients who underwent endotracheal intubation (ET) after NIV failure.

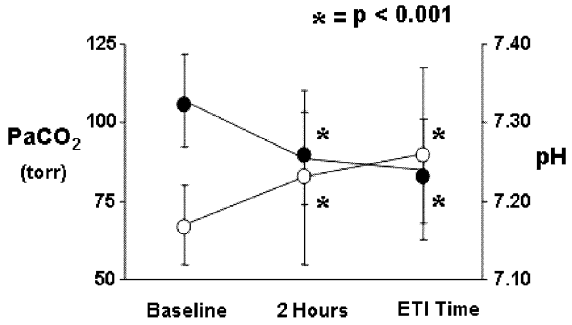

Fig. 2 Changes in pH and $PaCO_2$ over time in the subgroup of patients who failed non-invasive ventilation (NIV). Mean (SD) pH (*empty circles*) and $PaCO_2$ (*filled circles*) are shown at ICU admission (prior to NIV institution), after 2 h of NIV, and before endotracheal intubation (ETI), from left to right, respectively. On average, compared to the baseline values, pH and $PaCO_2$ were significantly improved both after 2 h of NIV and at the time of intubation

Compared to the 104 patients who received ETI (controls + NIV failures), the 24 patients who were successfully treated with NIV had lower ICU mortality (P = 0.04), fewer complications (P =.0005), shorter time spent on mechanical ventilation (P <.0001), shorter ICU (P <.0001) and post-ICU (P =.008) lengths of stay (Table 4).

Discussion

The main finding of this study was that in COPD patients with severe ARF, compared to conventional invasive ventilation through an endotracheal tube, NIV had a high rate of failure and did not produce significant differences in mortality rate, duration of mechanical ventilation, and length of ICU and post-ICU hospital stay, but resulted in fewer serious complications and showed a trend toward a faster process of weaning off mechanical ventilation. The clinical outcomes in the subgroup of 40 patients who were intubated after NIV failure were similar to the 64 controls who received ETMV as first ventilatory treatment.

The major criticism of the present study arises from the design adopted. A case-control study, as opposed to a randomized trial, is biased toward an overestimation of the positive effects in the treatment group [29]. The lim-

Table 4 Outcomes comparison between NIV success and all intubated patients [*NIV* success indicates patients treated with noninvasive ventilation who avoided endotracheal intubation, *All ETI* indicates all patients who received endotracheal intubation (controls + NIV failures), *ICU* indicates Intensive Care Unit]

	NIV success (*n*=24)	All ETI (*n*=104)	*P* value
ICU mortality, *n* (%)[a]	0 (0)	16 (15)	.04
Post-ICU hospital mortality, *n* (%)	2 (8)	9 (9)	.99
Duration of ventilation, days, mean (SD)	5 (3)	13 (3)0	<.0001
ICU stay, days, mean (SD)	8 (4)	15 (3)0	<.0001
Post-ICU hospital stay, days, mean (SD)	9 (3)	11 (4)	.008
Patients with serious complications, *n* (%)	4 (17)	60 (58)	.0005

[a] Since one value in comparison was zero, 0.5 was added to both values to make calculations possible

ited value of case-control studies, as compared to randomized trials, has been partially reappraised by recent systematic reviews of the literature [30, 31] concluding that well-designed observational studies, which avoid or consistently reduce confounding factors, are likely to provide valid results. To avoid the risk of discrepancies in severity between cases and controls we used an extremely careful matching process, made possible by a large and complete database of patients. By matching prior pulmonary function tests, obtained during the stable phase of COPD, we aimed to study cases and controls with comparable severity of the underlying ventilatory deficit. The severity of the acute phase on ICU admission was also comparable between cases and controls both with regard to overall severity, as assessed by SAPS II, and acuteness of respiratory failure, as assessed by pH. The other (unmatched) characteristics were also not significantly different between the two groups. Another limitation of the studies comparing patients treated in different periods may be that variations in the medical therapy can occur over time. However, in the time window considered in this study, no variations in respect to both the drugs utilized and their doses had been introduced into the treatment protocols.

Patients who received NIV as first ventilatory treatment showed a lower rate of complications and a trend toward a faster weaning process. However, mortality rate, duration of mechanical ventilation, and lengths of ICU and post-ICU hospital stays were not different between cases and controls. Compared to the studies where NIV was used at an earlier stage to avoid ETMV rather than as an alternative to it [1, 2, 3, 4, 6], in our study NIV was prone to a higher rate of failure and produced less positive results. However, these findings are in accordance with the results obtained by Conti et al. in a patient population of comparable severity [13].

In contrast with all previous studies [1, 2, 3, 4, 6, 13], we also included patients whose precipitating cause of ARF was CAP. Ambrosino et al. reported that in COPD patients with ARF the presence of pneumonia was correlated with a less favorable NIV outcome [32], but they did not discriminate between CAP and nosocomial pneumonia. More recently, Confalonieri et al. found that NIV had a 100% success rate in avoiding endotracheal intubation in a small subgroup of COPD patients with CAP and mild to moderate ARF [5]. We found that the rate of NIV failure in the subgroup of 21 COPD patients who had CAP as precipitating cause of ARF was 52%, as opposed to 65% for the 43 patients with COPD exacerbation (P=0.59). Two patients with CAP (9%) and four with exacerbation (9%) died (P = 0.99); days spent on mechanical ventilation (P = 0.58) and serious complications (P = 0.99) were also not significantly different between these two subgroups.

To assess whether postponing ETMV harmed the patients who failed NIV, we compared the outcomes of the 40 patients who received endotracheal intubation and invasive ventilation following NIV failure with the 64 controls who received ETMV as first ventilatory treatment and found no difference in any outcome variable (Table 3). Of note, baseline characteristics between these two groups were comparable, with the exception of the $PaCO_2$ values before institution of mechanical ventilation, which were slightly but significantly higher in the 40 patients who failed NIV. A large multicentre cohort study recently reported that the rate of ICU mortality was no different between patients intubated after a failed attempt of NIV and patients treated with ETMV as first ventilatory treatment [18]. In this regard, it is worth noting that in our study the 40 patients who failed NIV showed on average a significant improvement in arterial blood gases both after the first 2 h of NIV and immediately before endotracheal intubation, compared to the baseline values obtained prior to NIV institution (Fig. 2). It is important to remark in this regard that, with respect to the baseline values, at the time of intubation arterial blood gases had deteriorated only in seven patients, were unchanged in eight patients, and had improved to some extent in the remaining 25 patients. Fifteen (37.5%) patients failed NIV because of mask intolerance and discomfort, a reason which is recognized as one of the most common for NIV failure [15] and probably held particular importance in our study where the patients needed continuous support. However, regardless of the causes, the elevated rate of patients who fail NIV and necessitate ETI indicates that NIV should be applied in an appropriate setting where endotracheal intubation can be immediately performed when required.

Several studies have shown NIV to be effective in decreasing mortality rate, duration of mechanical ventilation, and ICU and hospital lengths of stay, possibly by averting side-effects and complications related to the endotracheal tube [3, 6, 13, 14]. In keeping with previous results [3, 7, 9, 10, 12, 33, 34], in our study none of the patients who succeeded NIV and avoided endotracheal intubation died and, in addition, they had shorter ICU and hospital lengths of stay, fewer complications, and did not develop nosocomial pneumonia at all.

In conclusion, our findings confirm that in COPD patients with severe ARF, deemed to require ventilatory assistance, NIV is prone to a high rate of failure, but, nevertheless, provides some advantages compared to conventional invasive ventilation. In addition, this study shows that the patients who fail NIV are not harmed by the delayed institution of ETI, while those who avoid ETI have a clear-cut benefit. Overall, these results indicate that in COPD patients with advanced ARF it is worthwhile to attempt a trial of NIV prior to moving on to endotracheal intubation.

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