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Raffaele Scala
Stefano Nava
Giorgio Conti
Massimo Antonelli
Mario Naldi
Ivano Archinucci
Giovanni Coniglio
Nicholas S. Hill

Noninvasive versus conventional ventilation to treat hypercapnic encephalopathy in chronic obstructive pulmonary disease

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R. Scala (✉) · M. Naldi · I. Archinucci · G. Coniglio
Unità Operativa di Pneumologia e Unità di Terapia Semi-Intensiva Respiratoria, Arezzo, Italy
e-mail: raffaele_scala@hotmail.com
Tel.: +39-0575-254541
Fax: +39-0575-254545

S. Nava
Fondazione S. Maugeri, Respiratory Intensive Care Unit, Pavia, Italy

G. Conti · M. Antonelli
Università Cattolica, Intensive Care Unit and Anesthesiology, Rome, Italy

N. S. Hill
Tufts-New England Medical Center, Division of Pulmonary, Critical Care and Sleep Medicine, Boston, Mass., USA

Abstract *Objective:* We recently reported a high success rate using noninvasive positive pressure ventilation (NPPV) to treat COPD exacerbations with hypercapnic encephalopathy. This study compared the hospital outcomes of NPPV vs. conventional mechanical ventilation (CMV) in COPD exacerbations with moderate to severe hypercapnic encephalopathy, defined by a Kelly score of 3 or higher. *Design and setting:* A 3-year prospective matched case-control study in a respiratory semi-intensive care unit (RSICU) and intensive care unit (ICU). *Patients and participants:* From 103 consecutive patients the study included 20 undergoing NPPV and 20 CMV, matched for age, simplified acute physiology score II, and baseline arterial blood gases. *Measurements and results:* ABG significantly improved in both groups after 2 h. The rate of complications was lower in the NPPV group than in the CMV group due to fewer cases of nosocomial pneumonia and sepsis. In-hospital mortality, 1-year mortality, and tracheostomy rates were similar in the two groups. Fewer patients remained on ventilation after 30 days in NPPV group. The NPPV group showed a shorter duration of ventilation. *Conclusions:* In COPD exacerbations with moderate to severe hypercapnic encephalopathy, the use of NPPV performed by an experienced team compared to CMV leads to similar short and long-term survivals with a reduced nosocomial infection rate and duration of ventilation.

Keywords Acute respiratory failure · Chronic obstructive pulmonary disease · Conventional ventilation · Endotracheal intubation · Hypercapnic encephalopathy · Noninvasive ventilation

Introduction

Hypercapnic encephalopathy (HE) has been considered a relative contraindication to noninvasive positive pressure ventilation (NPPV) because of the perceived risk of pulmonary aspiration and lack of cooperation [1–4]. This was because most randomized controlled trials of NPPV for acute respiratory failure (ARF) have excluded HE patients. However, several uncontrolled studies suggest that noninvasive ventilatory techniques are highly successful in avoiding endotracheal intubation (ETI) in patients with hypercapnic ARF and severely impaired consciousness [5–9]. Moreover, two recent randomized controlled trials including about 50% of patients with severe HE (Kelly score > 3) [10] demonstrated the potential advantages of using NPPV as an alternative to conventional mechanical ventilation (CMV) in severe hypercapnic ARF [11, 12]. In addition, two case-control studies [13, 14] have clearly shown that NPPV is feasible and avoids ETI in most ARF patients with HE, even those with frank coma. In particular, NPPV failure and hospital mortality were similar in COPD patients with and without HE [13, 14]. Despite the accumulating evidence to support the use of NPPV in HE patients CMV is still the recommended

gold-standard ventilatory treatment for ARF patients with potentially life-threatening HE [1]. This is because the role of NPPV as an alternative to CMV in HE remains unsettled due to the lack of comparative studies between the two ventilatory techniques.

The present case-control study compared the efficacy of NPPV administered in a respiratory semi-intensive care unit (RSICU) with that of CMV provided in an intensive care unit (ICU) to treat patients with COPD exacerbations and moderate–severe HE.

Methods

Study design

This prospective case-control study was performed between January 2002 and January 2005 in two centers: a 3-bed RSICU in the Respiratory Division of S. Donato Hospital, Arezzo, and the 18-bed general ICU of the Catholic University of Rome. The study protocol was approved by the ethics committees of both institutions, and informed written consent was obtained from the proxy.

Cases (NPPV)

All 55 COPD patients with ARF due to either acute exacerbation or community-acquired pneumonia [15, 16] and with sensorium impairment admitted to the RSICU over the observed period were considered eligible for the study. The study included 20 patients who met all the following criteria while breathing oxygen via a venturi mask: (a) pH below 7.35 and $PaCO_2$ higher than 50 mmHg; (b) PaO_2 fraction of inspired oxygen (FIO_2) less than 300; (c) dyspnea at rest with respiratory rate (RR) more than 25 or fewer than 12 breaths/min; (d) use of accessory respiratory muscles or paradoxical abdominal breathing; (e) Kelly score between 3 and 5 (3 = lethargic, but arousable and follows simple commands; 4 = stuporous, i.e., only intermittently follows simple command even with vigorous attempts to arouse patient; 5 = comatose, brainstem intact). We employed the Kelly–Matthay scale [10] as it is easily administered and is sensitive to minor changes in mental status in mechanically ventilated patients. Exclusion criteria were: (a) refusal of NPPV; (b) facial deformity sufficient to preclude mask fitting; (c) preexisting psychiatric and/or neurological disorders unrelated to HE; (d) upper gastrointestinal bleeding; (e) upper airway obstruction; (f) acute coronary syndromes; (g) tracheostomy or ETI before admission; (h) need for urgent ETI due to cardiac or respiratory arrest or psychomotor agitation, severe hemodynamic instability [17].

NPPV was provided in RSICU by nurses and physicians adequately trained in this technique. The mean nurse:patient ratio in the overall respiratory division was 1:6.5, with one nurse for each shift usually dedicated to the RSICU [14]. Electrocardiogram, pulse-oximetry (SpO_2), and noninvasive blood pressure were monitored continuously. Arterial blood gases (ABGs) were sampled before and after 2 and 4 h of NPPV and subsequently as clinically indicated. Nasogastric tubes were inserted only in patients who developed gastric distension. ETI and transfer to the ICU were promptly available if NPPV failed. NPPV (Vela, Viasys, Loma Linda, Calif., USA) was delivered in pressure support (PS) mode with positive end-expiratory pressure (PEEP) via a well fitting full-face mask (Mirage, ResMed). PS was initially set at 10 cmH_2O and then titrated to achieve an expiratory tidal volume of 8–10 ml/kg and a RR less than 25 breaths/min until a maximum of 25 cmH_2O depending on clinical ABGs response and patient tolerance. PEEP was always set at 5 cmH_2O [18]. Back-up RR was set at a 14–18 breaths/min, lower than the patient's spontaneous RR. FIO_2 was adjusted to keep SpO_2 at 90–94%. All patients received standard medical therapy consisting of controlled oxygen therapy during NPPV-free periods; salbutamol and anticholinergic drugs during NPPV via a spacer; intravenous aminophylline, corticosteroids, antibiotics; subcutaneous low-molecular weight heparin; and therapy for comorbidities if necessary. No pharmacological sedation was administered. NPPV was applied continuously at least during the first 12–24 h. Once clinical status, Kelly score, and ABGs improved, NPPV was administered intermittently with sessions lasting 2–6 h three times daily [14]. Then PS was reduced progressively twice a day by 3 cmH_2O until a level of 8 cmH_2O or less was reached. NPPV weaning was considered successful after 3 days of ventilation or more when all the following criteria were met for longer than 24 h while on breathing with oxygen (FIO_2 0.28): pH higher than 7.35, SpO_2 above 90%, RR less than 30 breaths/min, Kelly score 1, and stable hemodynamic status [14]. Home mechanical ventilation (HMV) via facial or nasal mask was considered if the patient remained partially dependent on NPPV ($\geq$ 8 h/day) after 10 days.

NPPV was considered to have failed if at least one of the following criteria for ETI was met: (a) cardiac arrest or severe hemodynamic instability; (b) respiratory arrest or gasping; (c) mask intolerance; (d) difficulty in clearing bronchial secretions; (e) worsening of ABGs or of sensorium level during NPPV [17]. If the patient and/or proxy refused CMV, NPPV was considered to have failed when the a priori ETI criteria were met. Tracheostomy was performed in intubated patients after NPPV failure when the weaning process was prolonged for more than 12 days.

Controls (CMV)

From the 48 COPD patients consecutively admitted to the ICU during the same period who received CMV according

Table 1 Matching criteria between noninvasive positive pressure ventilation (*NPPV*) and conventional mechanical ventilation (*CMV*) groups (*SAPS*, simplified acute physiology score)

	NPPV ($n = 20$)	CMV ($n = 20$)	p
Age (years)	75 ± 5	73 ± 4	0.29
pH baseline	7.22 ± 0.02	7.22 ± 0.05	0.66
PaO_2/FIO_2 baseline	162 ± 33	161 ± 32	0.94
$PaCO_2$ baseline (mmHg)	88 ± 15	90 ± 10	0.75
SAPS II score	34 ± 7	36 ± 6	0.35
Kelly–Matthay score	3.4 ± 0.6	3.4 ± 0.6	1.00

to the same inclusion criteria used for NPPV group, and whose data were prospectively collected we selected 20 to serve as controls. The decision to intubate these patients without attempting a trial of NPPV was taken by the physician in charge at the emergency room before ICU admission. CMV patients showing any of NPPV group exclusion criteria except for points a and b were not included in the study to prevent a potential bias of selection. Exclusion criteria were the same as those applied to NPPV group [17] as well as inclusion in previous studies and ETI after failure of an initial NPPV trial. The matching of controls was performed manually according to the following criteria: age ($\pm$ 5 years); PaO_2/FIO_2 ($\pm$ 10), $PaCO_2$ ($\pm$ 5 mmHg), and pH ($\pm$ 0.03) before mechanical ventilation (MV); simplified acute physiology score (SAPS) II [19] ($\pm$ 5points) assessed within the first 24 h after the admission. When more than one potential control was present, the best matched subject was selected. After careful matching (100% for all parameters) 20 patients from each group were selected (Table 1); cases and controls did not differ significantly on any the variables used for matching.

The standard therapy protocol was the same as that described for NPPV group [14] except that controls were sedated at the time of intubation (2 mg/kg propofol intravenously followed by a continuous infusion at 0.5–3 mg/kg per hour usually lasting for 24–36 h); no paralyzing drugs were used. The ICU nurse:patient ratio was 1:3. CMV was delivered via an ICU ventilator (Siemens 300 or Puritan Bennett 840) in assist-control mode (tidal volume 8–10 ml/kg; back-up RR 10–14 breaths/min; FIO_2 0.35; PEEP 5 cmH_2O). When spontaneous breathing reappeared (usually $\geq$ 24 h), the ventilator mode was changed to PS [11] following the same criteria used for NPPV group. Extubation was performed if the patient was able to tolerate a 2 h T-piece trial with FIO_2 0.28 ($pH > 7.35$, $SpO_2 > 90\%$, $RR < 30$ breaths/min, normal sensorium, stable hemodynamic status). If after 12 days the patient was still intubated and ventilated, tracheostomy was performed according to the physician in charge judgement; then weaning was resumed following the above protocol. HMV via tracheostomy was considered if the patient was still ventilator-dependent after 30 days [11]. The number of invasive devices per patient was significantly greater in the CMV than the NPPV group (Table 2).

Data collection and end-points

In addition to the matching variables, other parameters were collected: gender, body mass index, spirometry in a stable status within the previous 6 months, comorbidities as assessed by the Charlson score [20], RR, heart rate, hospital-stay before MV, number of invasive devices, PS, need for de-novo long-term oxygen-therapy (LTOT) and HMV. The primary endpoint was the rate of major complications [11]: septic complications and nosocomial pneumonia were diagnosed using strict criteria [21, 22]. Assuming a power of 80% with an α-error of 0.05,

Table 2 Characteristics of noninvasive positive pressure ventilation (*NPPV*) and conventional mechanical ventilation (*CMV*) groups according to nonmatching criteria (*BMI*, body mass index; FEV_1, forced expiratory volume in the first second; *CAP*, community-acquired pneumonia; *RR*, respiratory rate; *HR*, heart rate; *MV*, mechanical ventilation; *PS*, pressure support; *IQR*, interquartile range)

	NPPV ($n = 20$)	CMV ($n = 20$)	p
Males	14 (70%)	15 (75%)	0.63
BMI	25 ± 5	27 ± 6	0.54
FEV_1 (% of predicted)	30 ± 8	34 ± 10	0.38
Charlson score (IQR)	1.25 (0–2)	0.40 (0–2)	0.06
RR (bpm)	36 ± 6	35 ± 3	0.48
HR (bpm)	111 ± 26	101.5 ± 20.9	0.24
CAP	5 (25%)	5 (25%)	1.00
pre-MV hospital days (IQR)	1 (1–1)	1 (1–2)	0.61
PaO_2 baseline (mmHg)	47 ± 11	53 ± 14	0.10
PS (cmH_2O)	19 ± 5	19 ± 4	0.91
Invasive devices/patient	1.3 ± 1.3	4.1 ± 0.9	0.01

a sample size of 67 patients was calculated on the basis of the reported finding of major complications in NPPV vs. CMV-treated ARF patients (36% vs. 60%) [11, 22]. Secondary endpoints were: ABG changes, in-hospital and 1-year mortality, tracheostomy, percentage of weaning from MV at 30 days, length of hospital stay and of MV.

Statistical analysis

The Kolmogorov–Smirnov test was used to verify whether all recorded variables were normally distributed ($p > 0.05$). Continuous data are expressed as mean (± standard deviation) if distributed normally or as median (interquartile range) if not; categorical data are presented as frequency. Continuous variables were compared with the two-tailed unpaired Student's t test (parametric data) or the Mann–Whitney U test (nonparametric data). Categorical data were compared using the χ^2 or, when appropriate, Fisher's exact test. A p value less than 0.05 was considered statistically significant. Differences in the probability of remaining on MV over 30 days between cases and controls were investigated by means of Kaplan–Meier curves. Analyses were performed using version 10.0 of SPSS software (SPSS, Chicago Ill., USA).

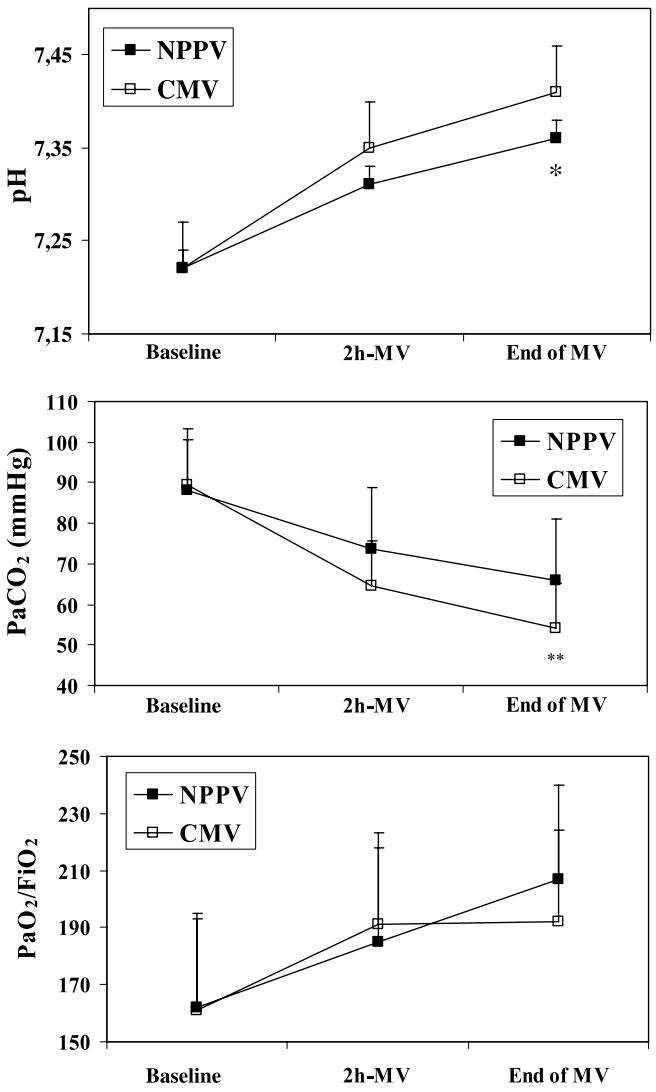

Fig. 1 Arterial blood gases before, after 2 h and at the end of mechanical ventilation in the noninvasive positive pressure ventilation (*NPPV*) and the conventional mechanical ventilation (*CMV*) groups. Values are expressed as mean ± SD; $*p < 0.05$, $**p < 0.005$ between groups

Results

Compared to baseline ABGs had improved similarly in NPPV and CMV groups after 2 h ($p < 0.05$). By the end of MV pH was higher and $PaCO_2$ lower in the CMV group than the NPPV group ($p < 0.05$; Fig. 1). The sensorium level significantly improved within 24 h in the NPPV group (Fig. 2); neurological evaluation was not possible in the CMV group for the administration of sedation. The complication rate was significantly higher with CMV than with NPPV due to a greater occurrence of infectious events. Hospital and 1-year mortality rates, tracheostomies, and de-novo initiations of LTOT and HMV were similar in the two groups (Table 3).

NPPV failed in 7 of 20 patients (35%) after 4.9 ± 7.2 days and a total of 55.1 ± 81.0 h of ventilation due to worsening of ABGs ($n = 5$), mask intolerance ($n = 4$), secretion retention ($n = 3$), or worsening level of consciousness ($n = 2$). Patients who failed NPPV showed a lower pH after the first 2 h of ventilation than those who succeeded (7.26 ± 0.05 vs. 7.34 ± 0.06, $p = 0.005$). Nasogastric tubes were needed in three patients for gastric distension that proved to be fully reversible. Mild facial skin erythema occurred in four patients. Four patients were not intubated after NPPV failure because ETI was

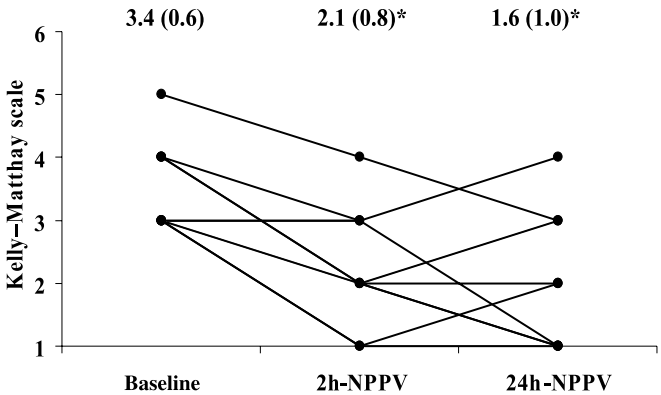

Fig. 2 Kelly–Matthay score in noninvasive ventilation group at baseline ($n = 20$), after 2 h ($n = 20$) and 24 h ($n = 18$) of mechanical ventilation. *NPPV*, Noninvasive positive pressure ventilation. Values are expressed as mean ± SD; $*p < 0.0001$ vs. baseline

Table 3 Hospital mortality, 1-year mortality, tracheostomy rate, and complications in noninvasive positive pressure ventilation (*NPPV*) and conventional mechanical ventilation (*CMV*) groups (*MV*, mechanical ventilation; *LTOT*, long-term oxygen therapy; *HMV*, home mechanical ventilation)

	NPPV ($n = 20$)	CMV ($n = 20$)	p
In-hospital mortality	5 (25%)	5 (25%)	1.00
One-year mortality	9 (45%)	10 (50%)	0.75
Tracheostomy	2 (10%)	6 (30%)	0.23
Patients with complications	6 (30%)	13 (65%)	0.02
Patients with lethal complications	3 (15%)	5 (25%)	0.40
Complications	7	23	0.01
Sepsis and septic shock	2 (10%)	9 (45%)	0.02
Nosocomial pneumonia	0 (0%)	7 (35%)	0.01
Acute renal failure	2 (10%)	2 (10%)	1.00
Gastrointestinal bleeding	0 (0%)	1 (5%)	1.00
Urinary tract infections	0 (0%)	2 (10%)	0.49
Cardiovascular complications	3 (15%)	2 (10%)	1.00
Length of hospitalization (days; IQR)	5.0 (1.0–9.5)[a]	21.5 (6.0–21.5)[b]	0.02
Length of MV (days)	13.7 ± 6.1[a]	26.5 ± 22.3[b]	0.04
De novo LTOT	5 (25%)	6 (30%)	1.00
De novo HMV	3 (15%)[c]	2 (10%)[d]	1.00

[a]NPPV patients who avoided ETI ($n = 13$)
[b]CMV patients who survived to discharge ($n = 15$)
[c]HMV via nasal or facial mask
[d]HMV via tracheostomy

refused, and they died from septic shock ($n = 1$), cardiac arrest ($n = 1$), or progression of ARF ($n = 2$). Two of the three intubated patients were discharged alive, one of them with a tracheostomy; the third patient died of septic shock after being tracheostomized. Causes of in-hospital death in CMV group were septic shock ($n = 3$), acute renal failure ($n = 1$), and cardiac arrest ($n = 1$), three of them after tracheostomy.

Kaplan–Meier analysis showed that the percentage of patients unweanable from MV at 30 days, with the inclusion of those who died while on ventilation, was significantly lower in the NPPV than the CMV group (Fig. 3). Overall durations of MV and hospitalization were significantly shorter in the 13 of 20 NPPV patients who avoided ETI than in the 15 of 20 CMV patients who survived to discharge. Intention-to-treat analysis showed MV length to be significantly shorter in the NPPV than the CMV group (5.5 ± 3.3–11.5 vs. 21.5 ± 6.0–25.6 days, $p = 0.009$). No significant differences in any endpoints merged between pneumonia and exacerbations of COPD patients between the groups.

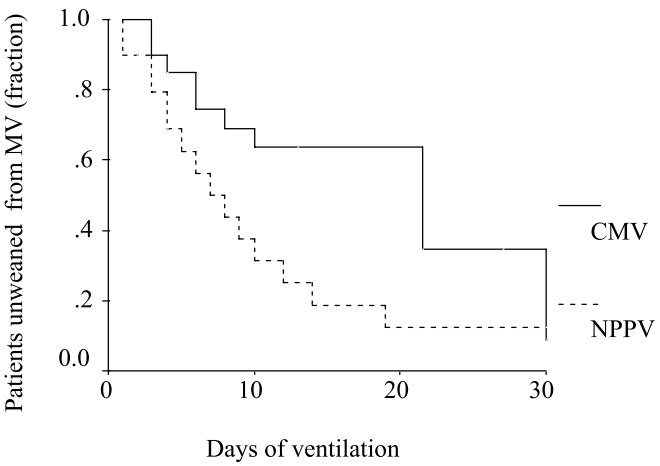

Fig. 3 Kaplan–Meier curves showing that the percentage of patients unweaned from mechanical ventilation (MV) at 30 days was significantly lower with noninvasive pressure ventilation (*NPPV*) than with conventional mechanical ventilation (*CMV*; log-rank 5.33, $p = 0.02$). Patients who died while on mechanical ventilation were considered unweaned off the ventilator

Discussion

This is the first study to directly compare outcomes of NPPV and CMV in COPD patients with HE due to severe ARF. Improvements in ABGs as well as 1-year mortality and tracheostomy rates were similar between NPPV and CMV groups. Interestingly, NPPV significantly reduced serious infectious complications and shortened the durations of MV and hospitalization compared to CMV.

The main limitation of the present study is the case-control design and lack of randomization, which may bias results in favor of the therapy under investigation. Both cases and controls were prospectively enrolled during the same period, but unfortunately we could not perform a randomized controlled trial because CMV could be applied only in the ICU, and the unpredictability of bed availability in different units located in different hospitals made randomization impossible. On the other hand, well-designed observational studies may yield reliable results provided that cases and controls are well balanced by careful match-

ing, and the interference of confounding factors is minimized [23]. In our study cases were similar to controls not only for the matching criteria (age, ABGs, SAPS II score) but also for other historical-clinical-physiological features.

Another concern regarding the study design is the different setting where the two groups were treated. The lower intensity of care in RSICU than in ICU (e.g., nurse:patient ratio) could have contributed to a higher rate of NPPV failures. However, the application of the same inclusion and exclusion criteria as well as the same standard therapies in the two units should have minimized this bias. Nevertheless, we cannot exclude the possibility that potential differences in pharmacotherapy, prevalence of nosocomial infections, intensity of monitoring, and characteristics of patients admitted to the two units contributed to differences in outcomes. It should also be emphasized that our RSICU has extensive experience with the management of HE using NPPV [14], with the capability of promptly intubating failing patients. Thus our findings may not be reproducible in units less experienced in NPPV.

Another potential limitation of our study is the low statistical power, with a recruited population ($n = 40$) smaller than the calculated sample size. Logistic reasons impeded a larger enrollment and achieving the recruitment target would have required an additional 2–3 years at the prior accrual rate, with a further bias due to the very long period of enrollment. However, we believe very unlikely that the twofold higher rate of complications found in CMV group could be due to casualty alone.

Consistent with recent reports [9, 11–14], our study confirms that NPPV has a high success rate when applied in patients with hypercapnic ARF and markedly reduced levels of consciousness. The major concern about the use of NPPV in HE patients, i.e., inability to cooperate [24–29], appears to be unfounded. In fact, the hypercapnia often has a narcotic effect—reducing the need for sedation and promoting cooperation—at least until $PaCO_2$ drops and the patient becomes more alert. In the present study mask intolerance led to NPPV failure in only 15% of cases. This is in agreement with previous studies [6, 9, 14] showing that compliance with NPPV was as good in patients with as in those without HE.

Another important concern with HE is that the depressed sensorium increases the likelihood of aspiration pneumonia. Consequently we excluded patients with a Kelly score of 6. However, once again, our results counter this concern and suggest that, if anything, that the risk of nosocomial infection is much less with NPPV. The postulated risk of aspiration pneumonia due to the lack of upper airways protection in patients with a depressed cough reflex and copious secretions [1–4] was minimized by the NPPV-induced rapid improvement in neurological status [5–7, 9, 13]. In our study the Kelly score dropped significantly after 1–2 h in the NPPV group, associated with a significant improvement in ABGs. In this scenario the avoidance of sedation during NPPV is one of the main advantages over CMV. In the present study worsening of the Kelly score led to NPPV failure in only 10% of patients, and nosocomial pneumonia never developed in any cases. Accordingly, numerous other studies [7, 11, 16, 17, 22, 24, 28–34] have clearly demonstrated that NPPV to treat ARF markedly reduces infectious complications compared to CMV, especially nosocomial pneumonia.

Another important observation is that fewer invasive devices were used in the RSICU group than the ICU group, undoubtedly related to the less aggressive monitoring with NPPV management. This almost certainly contributed to the lower occurrence of septic complications associated with NPPV and parallels the earlier findings of Girou et al. [33], who showed that ARF patients treated with NPPV exhibited a lower rate of catheter-related infections, ventilator-associated pneumonia, and urinary infections than matched-controls treated with CMV. Two recent trials comparing NPPV vs. CMV in COPD patients with severe hypercapnic ARF [11, 22] reported significantly faster weaning in patients successfully treated with NPPV than those treated with CMV. The quick recovery of a normal level of consciousness together with the prevention of pneumonia played an important role in reducing the length of MV and hospitalization [24]. The NPPV-failure group had a higher rate of tracheostomy than the CMV group. This difference was not statistically significant, and the relatively small sample size renders the interpretation difficult. The greater rate of complications (100% vs. 50%) in tracheostomized CMV patients probably explained the 50% mortality rate found in this group.

Some caveats are worth considering when interpreting our results. Patients with severe COPD exacerbations and HE are critically ill and warrant close observation in a skilled unit with the means to promptly intubate the patient readily at hand if necessary. Thus the use of NPPV to treat severe ARF should be reserved for centers where all staff members have acquired sufficient experience with these kinds of patients [35].

In conclusion, we have shown that during an episode of COPD exacerbation with moderate–severe HE, the use of NPPV vs. CMV is associated with similar short- and long-term survivals, fewer nosocomial infections, and shorter durations of MV and of hospitalization in patients who succeed with NPPV. We advocate an initial cautious NPPV trial in patients with COPD exacerbations and HE as long as there are no other contraindications, and the technique is provided by experienced caregivers in a closely monitored setting where ETI is always readily available. Larger randomized controlled trials comparing NPPV to CMV among COPD patients with acute exacerbations presenting with different levels of consciousness and managed in a similar setting are necessary to confirm our results.

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