

Original Article

Noninvasive mechanical ventilation in the weaning of AECOPD patients with respiratory failure: modified glasgow coma scale score ≥ 13 as the switching point

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Abstract: *Background:* Sequential noninvasive ventilation improves the outcomes of weaning from invasive mechanical ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with respiratory failure. However, the optimal timing is still controversial. Herein, the efficacy and feasibility of using a modified Glasgow Coma Scale (GCS) score ≥ 13 points was investigated as the switching point. *Methods:* All 152 AECOPD patients who received invasive mechanical ventilation (IMV) between May 2015 and June 2017 in the intensive care units at 3 institutions were randomly assigned to a sequential noninvasive ventilation (NIV) or a control group (n = 76 for both groups). Modified GCS score ≥ 13 points and clinically stable condition for 3 hours was used as the criteria for initiation of weaning. *Results:* In the NIV group, there were no significant differences with respect to mean blood pressure, oxygenation index, respiratory rate, pH, arterial partial pressure of carbon dioxide and oxygen between the two time-points: before extubation and 3 hours after extubation. Compared with the control group, sequential NIV significantly decreased hospital mortality from 22.37% to 6.58% ($p = 0.06$), reduced the duration of IMV, and shortened the length of hospital stay. *Conclusions:* The application of a modified GCS score ≥ 13 as the switching point for sequential invasive-noninvasive ventilation may significantly improve prognosis of AECOPD patients with respiratory failure.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, respiratory failure, invasive mechanical ventilation, noninvasive ventilation, glasgow coma scale

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide with globally, approximately 3 million people dying yearly due to COPD [1]. An estimated 12-18% of patients are hospitalized due to acute exacerbation of chronic obstructive lung disease (AECOPD) and receive treatment in the intensive care unit (ICU) [2]. The mortality rate in these patients approaches 15% [3]. Despite the advent of noninvasive ventilation (NIV), invasive mechanical ventilation (IMV) is still required for 5.9-26.0% of AECOPD patients [4, 5]. However, IMV should be discontinued at the earliest to prevent complications of pro-

longed IMV, such as ventilator-associated pneumonia (VAP) and ventilator-induced lung injury (VILI) [6, 7].

Sequential invasive-noninvasive ventilation has been studied as a means to minimize complications among patients who are weaned off IMV. Moreover, several meta-analytic studies have shown that noninvasive weaning reduces the likelihood of mortality, endotracheal intubation, and pneumonia without a concomitant increase in the risk of reintubation [8, 9]. However, there is a need to determine optimal criteria for withdrawal of IMV. Spontaneous breathing trial (SBT), automated systems, or pulmonary infection control (PIC) window have all been applied

Modified GCS score to guide weaning from ventilation

in this regard [10-12]. Use of PIC as a criteria for initiation of sequential ventilation strategy has yielded excellent results [13]. However, the PIC relies on x-ray imaging and does not take into account the lag between clinical manifestations and radiological signs. Additionally, this approach overlooks other important factors apart from infection. It is worth noting that decreased level of consciousness has been identified as a risk factor for extubation failure [14, 15]. Furthermore, the modified Glasgow Coma Scale (GCS) score, which is a more objective and quantitative measure of the overall clinical condition of ventilated patients, has been used to evaluate the level of consciousness of intubated patients [16, 17]. In this study, a modified GCS score ≥ 13 was hypothesized to be the switching point for sequential invasive-noninvasive ventilation in patients with AECOPD.

Methods

Study design and participants

This was a prospective, randomized, controlled study. Patients with AECOPD, who were admitted to the ICUs at 3 institutions (Wenling Hospital Affiliated to Wenzhou Medical University, the First Affiliated Hospital of Wenzhou Medical University, and the Changsha Central Hospital). Patients were prospectively enrolled between May 2015 and June 2017. The inclusion criteria were: age ≥ 18 years; patients receiving IMV for respiratory failure; patients who qualified the COPD diagnostic criteria recommended by the Chinese Treatment Guidelines for Chronic Obstructive Pulmonary Disease (2007) [18]; oxygen partial pressure < 60 mmHg; and absence of any absolute contraindication to NIV. The exclusion criteria included acute stroke, acute pulmonary embolism, cardiogenic pulmonary edema, and other causes of acute respiratory failure; death within 3 days following admission; active upper gastrointestinal bleeding; treatment discontinuation; and admission to the ICU within < 3 months of study enrolment.

Subjects were randomly assigned to sequential NIV or control groups using the random number table method. The study protocol was approved by the Ethics Committee of the Wenling Hospital Affiliated to the Wenzhou Medical University and all subjects provided written informed consent prior to their enrolment.

Treatment protocols

All subjects received the following treatments: anti-infective agents, antispasmodics, glucocorticoids (methylprednisolone, 40-80 mg/day) and anti-inflammatory agents, expectorants, nutritional support, and sedatives. In addition, appropriate measures to maintain internal homeostasis were also implemented. Dexmedetomidine was the first-line sedative administered as an intravenous bolus infusion over 10 minutes at a dose of $1 \mu\text{g}/\text{kg}$, followed by $0.2\text{--}0.8 \mu\text{g}/\text{kg}/\text{h}$ using a micro-pump. The infusion rate was adjusted to maintain the Richmond Agitation-Sedation Score between -2 and $+1$. The neurological wake-up test was conducted daily as described. Patients were required to perform 3 tasks, i.e., opening eyes in response to verbal command, eye tracking, and shaking hands on instruction if the sedation was in the target range. If the above criteria were not met, the sedative dose was adjusted until the target was reached.

Weaning protocol

The parameters of mechanical ventilation were adjusted according to the results of arterial blood gas (ABG) analysis and change in illness state. In the NIV group, patients were ventilated with synchronized intermittent mandatory ventilation (SIMV) mode with the addition of pressure support ventilation (PSV) or assist/control (A/C) mode. The respiratory rate (RR) was set at 13-18 cycles/min and tidal volume (VT) at $8\text{--}10 \text{ mL}/\text{kg}$ to maintain the arterial partial pressure of carbon dioxide (PaCO_2) at $35\text{--}50$ mmHg. The inspired oxygen fraction (FiO_2) and positive end-expiratory pressure (PEEP) were adjusted to preserve arterial oxygen saturation (SpO_2) of $\geq 90\%$. The definition of the modified GCS score [19] is shown in **Table 1**. After the modified GCS score reached 13 points and remained stable for 3 hours, IMV was switched to NIV by using noninvasive ventilators (Philips Weikang Company, USA). Then, the spontaneous/timed (S/T) mode was used with an inspiratory positive airway pressure (IPAP) of $12\text{--}14 \text{ cmH}_2\text{O}$ and expiratory positive airway pressure (EPAP) of $5 \text{ cmH}_2\text{O}$, which were gradually increased to the appropriate level within 5-20 minutes of the switch to NIV. Patients in the control group received continued conventional invasive mechanical ventilation even at a modi-

Modified GCS score to guide weaning from ventilation

Table 1. Modified Glasgow Coma Scale

Score	Eye	Verbal	Motor
1	Does not open eyes	No response to speech	Makes no movements
2	Opens eyes in response to painful stimuli	Response to loudly call	Extension to painful stimuli
3	Opens eyes in response to voice	Understanding error	Abnormal flexion to painful stimuli
4	Opens eyes spontaneously	Slow understanding of speech	Flexion/withdrawal from painful stimuli
5	N/A	Correct understanding of speech	Localizes painful stimuli
6	N/A	N/A	Obeys commands

Notes: The modified GCS evaluated 3 parameters: eye, verbal, and motor responses. The scores of these 3 values separately as well as their combined score were considered. The lowest possible GCS (the sum) score was 3 (deep coma or death), whereas the highest was 15 (fully conscious person). N/A, not applicable.

fied GCS score of ≥ 13 points, and a combination of SIMV + PSV was used before weaning these patients off the ventilator. The frequency of SIMV was gradually reduced to 8-10 beats/min, and the pressure support was gradually decreased to 8-10 cmH₂O, FiO₂ \leq 0.4, and PEEP \leq 5 cmH₂O; these indices were maintained for up to 3 hours prior to extubation. Subsequently, oxygen inhalation through masks or nasal catheter was initiated.

Data collection and outcomes

Data pertaining to the baseline characteristics and indices at admission were collected and these included the Acute Physiology and Chronic Health Enquiry (APACHE II) score, modified GCS score, mean arterial blood pressure (MBP), and oxygenation index (OI). Indices such as the MBP, OI, RR, and the results of ABG analysis were also measured before weaning and 3 h after weaning to NIV. The primary outcome was hospital mortality. The secondary outcomes were incidence of VAP, re-intubation rate, duration of invasive ventilation, and length of hospital stay.

Statistical analysis and power analysis

All analyses were conducted using the SPSS 16.0 (for Windows; SPSS; Chicago, IL, USA). Continuous variables are expressed as mean \pm standard deviation (SD). Between-group differences with respect to continuous variables were evaluated using the Student's *t*-test. All categorical variables are expressed as ratios and analyzed using the Chi-square (χ^2) test. All statistical analyses were two-sided, and $p < 0.05$ was considered indicative of statistically significant difference.

The sample size for each group was determined according to the formula:

$$n = 2 [(\mu_{1-\alpha} + \mu_{1-\beta})\sigma/\delta]^2$$

Where n was the sample size of each group; α was one type of error; β was the second type of error; $1-\beta$ was the power; μ was the standard normal deviation value (calculated as $\mu_{1-\alpha}$ and $\mu_{1-\beta}$ corresponding to the single-side cutoff of $1-\alpha$ and $1-\beta$); σ was the overall SD, which was estimated by the sample SD (S); δ was the permissible error, which is the effect difference between the NIV and control groups. Therefore, if $\alpha = 0.025$ (unilateral) and $\beta = 0.1$, then $\mu_{1-\alpha} = 1.9600$ and $\mu_{1-\beta} = 1.2816$. According to the pre-experimental results, $S = 1.9$ -that is, $\sigma = 1.9$; $\delta = 1$, $n = 2 [(\mu_{1-\alpha} + \mu_{1-\beta})\sigma/\delta]^2 = 2 [(1.9600 + 1.2816) * 1.9/1]^2 = 75.87 \approx 76$. Thus, 76 patients are inferred to be required in each group for adequate statistical power.

Results

Baseline characteristics

A total of 152 patients (91 men and 61 women; mean age \pm SD, 55.3 \pm 9.1 [range, 31-86] years) qualified the patient-selection criteria and were randomly assigned to the NIV or control group ($n = 76$ for both groups). There were no significant between-group differences with respect to sex, age, or body mass index (BMI). There were no significant between-group differences with respect to concomitant diseases such as cardiovascular disease, cerebrovascular disease, diabetes, or chronic kidney disease. The between-group differences with respect to APACHE II score, modified GCS score, MBP, OI, or pH value at admission were also not statistically significant ($p > 0.05$; **Table 2**).

Safety of sequential NIV strategy guided by modified GCS score ≥ 13 points

In the NIV group, patients underwent extubation followed by sequential NIV if the modified GCS score was ≥ 13 points. The following indices measured prior to extubation showed no

Modified GCS score to guide weaning from ventilation

Table 2. Baseline characteristics of the study population

Variables	NIV group (n = 76)	Control group (n = 76)	t/ χ^2 value	p-value
Male (%)	47 (61.84%)	44 (57.89%)	0.246	0.620
Age (years)	55.05±15.66	56.27±13.56	0.514	0.608
BMI (kg/m ²)	20.71±2.49	21.08±3.85	0.706	0.481
APACHE II	24.51±2.19	23.86±3.79	1.297	0.197
Modified GCS	7.22±1.88	7.09±1.50	0.484	0.629
MBP (mmHg)	103.36±10.67	102.43±12.27	0.499	0.349
OI (mmHg)	158.62±10.91	161.66±14.03	1.488	0.139
pH value	7.20±1.49	7.24±1.87	0.145	0.885
Cardiovascular disease	12 (15.79%)	14 (18.42%)	0.186	0.667
Cerebrovascular disease	16 (21.05%)	11 (14.47%)	1.126	0.289
Diabetes	10 (13.16%)	14 (18.42%)	0.792	0.374
Chronic kidney disease	6 (7.89%)	4 (5.26%)	0.428	0.513

Abbreviations: APACHE, Acute Physiology and Chronic Health Enquiry (APACHE II) score; BMI, body mass index; GCS, Glasgow Coma Scale; MBP, mean blood pressure; NIV, noninvasive ventilation; OI, oxygenation index.

Table 3. Indices before and 3 hours after extubation in the sequential NIV group

Variables	Before extubation	3 hours after extubation and NIV	t value	p-value
MBP (mmHg)	108.58±12.70	106.51±10.60	1.089	0.278
OI (mmHg)	218.75±18.21	219.64±23.09	0.264	0.792
RR (breaths/min)	19.97±2.52	20.56±3.81	1.137	0.257
pH value	7.34±1.57	7.29±1.65	0.196	0.845
PaO ₂ (mmHg)	89.85±16.52	86.86±11.99	1.278	0.203
PaCO ₂ (mmHg)	44.86±18.39	49.33±13.50	1.689	0.093

Abbreviations: MBP, mean blood pressure; NIV, noninvasive ventilation; OI, oxygenation index; PaO₂, partial pressure of oxygen; PaCO₂, partial pressure of carbon dioxide.

significant difference from those measured at 3 hours after extubation: MBP, OI, RR, pH, PaO₂, and PaCO₂ ($p > 0.05$; **Table 3**).

Primary and secondary outcomes

Compared to the control group, sequential NIV significantly decreased hospital mortality from 22.37% to 6.58% ($p = 0.06$; **Table 4**). The incidence rates of re-intubation and VAP in the NIV group were significantly lower ($p = 0.07$ and 0.008 , respectively) than those in the control group. Furthermore, sequential NIV significantly decreased the duration of IMV and the length of hospital stay.

Discussion

In the present study, application of a modified GCS score ≥ 13 as the criteria for switching to

sequential NIV after extubation improved the prognosis of ICU patients with AECOPD-induced respiratory failure. Sequential NIV stabilized the vital signs and the results of ABG post-extubation. Moreover, sequential NIV decreased the in-hospital mortality and the incidence of re-intubation and VAP, and shortened the duration of IMV and length of hospital stay.

Despite the development of protective lung ventilation strategies and optimal management of respiratory failure, the incidence of AECOPD-induced respiratory failure continues to be relatively high (24.5%) [20]. Studies have shown that prolonged endotracheal intubation can cause lower respiratory tract infection and VAP and exacerbate respiratory distress. This may extend the duration of invasive ventilation and cause difficulties in weaning patients off ventilation [6, 7]. Prolonged endotracheal intubation can also lead to airway injury, tracheoesophageal fistula, and other complications.

Failure to calibrate the mechanical ventilation in a timely manner may extend the duration of endotracheal intubation leading to poor quality of life and worse prognosis. Therefore, this study attempted to facilitate early removal of endotracheal intubation, followed by sequential NIV. The aim was to minimize the duration of IMV and to avoid the deleterious effects of prolonged IMV.

Identification of an optimal switching point is the key for an effective sequential ventilation strategy. In China, the switching point is mainly the PIC window, as proposed by the Beijing Institute of Respiratory Diseases; in other countries, a 48-hour window is considered. However, both these criteria have certain limitations. The former overlooks the time-lag between clinical and radiological manifestations

Modified GCS score to guide weaning from ventilation

Table 4. Primary and secondary outcomes

Variables	NIV group (n = 76)	Control group (n = 76)	t/ χ^2 value	p-value
Hospital mortality (n, %)	5 (6.58%)	17 (22.37%)	7.653	0.006
Re-intubation (n, %)	4 (5.26%)	15 (19.74%)	7.278	0.007
Incidence of VAP (n, %)	3 (3.95%)	13 (17.11%)	6.985	0.008
Duration of IMV (days)	3.31±0.72	9.87±1.70	30.99	< 0.001
Length of hospital stay (days)	16.65±2.20	22.78±2.27	16.911	< 0.0001

Abbreviations: IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; VAP, ventilator-associated pneumonia.

and the role of non-infective factors, while the latter overlooks inter-individual differences among patients.

The application of sequential NIV should qualify 3 conditions: a high level of consciousness, a certain degree of cooperation, and appropriate compliance; therefore, change in consciousness is an essential criterion to determine noninvasive respiratory support. AECOPD-induced respiratory failure is mainly due to pulmonary infection, ventilatory insufficiency, respiratory muscle fatigue, or other factors. Therefore, the level of consciousness tends to vary over the disease course in patients with COPD. The GCS score is widely applied for the assessment of awareness. It represents an objective measure of the dynamic changes in the overall clinical condition of COPD patients with severe respiratory failure. Patients with endotracheal intubation cannot speak even if they are conscious. Therefore, the GCS scoring system was modified to improve the sensitivity and accuracy by incorporating patient responses in lieu of speech. Zheng et al. [21] used a GCS score of 15 as a switching point for sequential invasive-noninvasive strategy, which significantly improved the prognosis of patients with COPD and respiratory failure. However, there may be a delayed effect if 15 points, as the highest GCS score, is used as a switching point for sequential therapy. In this study, the modified GCS score ≥ 13 and clinical stability for 3 hours as the criteria for initiation of sequential NIV. The vital signs and results of ABG were stable after 3 hours of sequential NIV. Our results indicate the safety and feasibility of our strategy for initiation of sequential NIV. Use of this strategy decreased the in-hospital mortality rate and incidence of re-intubation and VAP, and shortened the duration of

IMV and length of hospital stay. The sequential ventilation strategy reduced the discomfort, restlessness, and pain induced by intubation, and increased patient trust and coordination, resulting in a higher rate of successful weaning and lower incidence of re-intubation.

Some limitations of this study should be noted. First, different thresholds of modified GCS (e.g., 10 or 15 points) were not compared as the switching point. Second, the modified GCS score may vary in tandem with improvement or deterioration of hypoxemia and hypercapnia. However, the relationship between these factors and the specified study endpoints was not evaluated.

Conclusion

A modified GCS score ≥ 13 points as the switching point for sequential invasive-noninvasive ventilation can significantly improve the prognosis of AECOPD patients with respiratory failure.

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Disclosure of conflict of interest

None.

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Modified GCS score to guide weaning from ventilation

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