Pulmonary infection control window in treatment of severe respiratory failure of chronic obstructive pulmonary diseases: a prospective, randomized controlled, multi-centred study

Collaborating Research Group for Noninvasive Mechanical Ventilation of Chinese Respiratory Society

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Abstract:

Background Early withdraw from invasive mechanical ventilation (MV) followed by noninvasive MV is a new strategy for changing modes of treatment. This study was conducted to estimate the feasibility and the efficacy of early extubation and sequential noninvasive MV commenced at beginning of pulmonary infection control window in patients with exacerbated hypercapnic respiratory failure
caused by chronic obstructive pulmonary diseases (COPD).

**Methods** A prospective, randomized controlled study was conducted in eleven teaching hospitals’ respiratory or medical intensive care units in China. Ninety intubated COPD patients with severe hypercapnic respiratory failure triggered by pulmonary infection (pneumonia or purulent bronchitis) were involved in the study. When the pulmonary infection had been controlled by antibiotics and comprehensive therapy, the "pulmonary infection control window (PIC window)" has been reached. Each case was randomly assigned to study group (extubation and noninvasive MV via facial mask immediately) or control group (invasive MV was received continuously after PIC window by using conventional weaning technique).

**Results** Study group (n=47) and control group (n=43) had similar clinical characteristics initially and at the time of PIC window. Compared with control group, study group had shorter duration of invasive MV [(6.4±4.4) days vs (11.3±6.2) days. P=0.000], lower rate of ventilator associated pneumonia (VAP) (3/47 vs 12/43. P=0.014), fewer days in ICU [(12±8) days vs (16±11) days. P=0.047] and lower hospital mortality (1/47 vs 7/43. P=0.025).

**Conclusions** In COPD patients requiring intubation and invasive MV for hypercapnic respiratory failure, which is exacerbated by pulmonary infection, early extubation followed by noninvasive MV initiated at the start of PIC window may decrease significantly the duration of invasive MV, the risk of VAP and hospital mortality.

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Mechanical ventilation (MV) is effective in treatment of acute exacerbation of chronic obstructive pulmonary disease (COPD) with acute respiratory failure. Endotracheal intubation and MV can help to drain sputum and reduce the respiratory workload partially, or even completely, so as to control bronchial pulmonary infection rapidly and reduce the energy cost to patients' respiratory muscles. Hyperinflation, respiratory muscle fatigue and malnutrition, which are common in COPD patients, may require prolonged MV. During prolonged MV, due to implementation of an invasive artificial airway, ventilator associated pneumonia (VAP) requiring repeated treatment often occurs. [1,2] The mortality of VAP in ICU is about 30% or higher. The key to reduce VAP is to shorten the duration of artificial airway placement. [3] Recently, noninvasive positive pressure ventilation (NIPPV) has been used to treat acute exacerbation of COPD successfully. [4,5] The incidence of VAP can be reduced
remarkably during NIPPV because no invasive artificial airway is needed.

The sequential noninvasive MV, in COPD induced hypercapnic respiratory failure patients following short term invasive MV strategy, defined as early extubation, is conducted before conventional criteria for weaning are attained and followed by noninvasive MV immediately. The duration of invasive MV can be shortened and the side effects of invasive MV may be reduced with this ventilation strategy. Several controlled studies have demonstrated the safety of using sequential noninvasive following short term invasive MV strategy in exacerbated COPD patients. [6-8] In most of these studies sequential MV groups displayed lower incidence of VAP, shorter hospitalisation in ICU and higher successful weaning rate than that in conventional MV groups. However, the effect of our sequential MV on mortality is still controversial because of different results in these studies.

Choosing an appropriate time to transfer from invasive MV to noninvasive MV is the key to performing sequential MV successfully. So far no generally accepted boundary of standard switch point has been defined. However, using pulmonary infection control window (PIC window) as the switch point for transferring from invasive to noninvasive MV, the time for early extubation could be more accurately judged and improved therapy efficacy was achieved by Wand and coworkers. [8] The aim of our multicentred, randomized controlled study was to evaluate the effectiveness of sequential noninvasive MV following short term invasive MV in COPD patients complicated with hypercapnic respiratory failure, using PIC window as the switch point.

METHODS

Design
A multicentred, prospective, randomized controlled study was carried out in respiratory or medical intensive care units of eleven teaching hospitals in China. Beijing Institute of Respiratory Medicine, China, randomly recruited all patients.

Patients
From November 2000 to June 2003, hospitalized COPD patients were enrolled. Selection criteria were as follows: a) receiving invasive MV in ICU because of hypercapnic respiratory failure; b) ≤85 years; c) in accordance with the criteria of COPD guideline constituted by Chinese Medical Association in 1997; [9] d) capable of selfcare in the past year; e) COPD exacerbation due to bronchial pulmonary infection; f) PIC window appeared after antibiotic, MV and comprehensive therapy.

Excluding criteria were: a) severe cerebral, heart, hepatic and renal failure; b) severe malnutrition; c) severe water and electrolyte disturbance difficult to normalize; d) upper airway or face injury preventing mask ventilation; e) cough asthenia when PIC window appeared; f) intolerance to NIPPV.

Criteria of bronchial pulmonary infection: a) significant bronchial pulmonary infection displayed by chest X-rays and/or sputum increased, thickened and turned to yellow and purulent; b) at least one of the following symptoms: leukocyte count higher than 10×10^9 /L ; increased percentage of neutrophils ( more than 80%); body temperature higher than 37.5°C.
The standard of the PIC window was determined by the following items: a) significantly decreased radiographic infiltrations; b) significantly reduced quantity of sputum, thinning of sputum, decreased density of sputum to less than $\frac{1}{2}$; c) at least one of the following signs accompanied: body temperature decreased to less than 37.5°C, leukocyte count below $10 \times 10^9$ /L or $2 \times 10^9$ /L less than before; d) adjustment of ventilator settings to 10-12 times per minute for synchronous intermittent mechanical ventilation (SIMV) and 10 to 12 cmH2O (1 cmH2O=0.0198 kPa) for pressure support ventilation (PSV).

**Treatment**

Patients were ventilated using assistance controlled mechanical ventilation during the initial 4 hours to 12 hours of invasive MV, and then switched to have SIMV+PSV). Fraction concentration of inspired oxygen, tidal volume and respiratory rate of SIMV and the level of PSV were adjusted according to patient's ventilation, result of blood gas analysis and endurability. With the improvement of patient's condition and ventilation, the rate of SIMV and the level of PSV were decreased gradually to 10 to 12 times per minute and 10 to 12 cmH2O respectively. During MV, comprehensive therapy was performed, including administration of antibiotics, dissolution of sputum, drainage of airway secretion, dilatation of bronchi, recovery of electrolyte disturbance and nutrient support. Once the PIC window had appeared, each patient was randomly assigned to study group or control group.

The patients in study group were extubated, followed by noninvasive MV in bilevel positive airway pressure mode (BiPAP-Harmony, Respironic Co., USA). The levels of PSV and fraction concentration of inspired oxygen were adjusted so that the patient's respiratory rate was less than 28 times per minute, the partial pressure of oxygen in arterial blood ranged from 65 mmHg to 90 mmHg, the partial pressure of carbon dioxide in arterial blood was kept between 45 mmHg and 60 mmHg or maintained the same as that before extubation. All patients had the addition of 4 to 6 cmH2O of positive end expiratory pressure to reduce the increased inspiratory workload due to intrinsic positive end expiratory pressure. The patients were weaned from noninvasive MV when they met all the following criteria: the level of PSV was decreased gradually until the difference between inspiratory and expiratory positive airway pressures was $\leq 5$ cmH2O, and stable.

Before the PIC window appeared, the treatment in control group was the same as that in the study group. After the PIC window appeared, invasive MV continued in control group and the patients were weaned by using SIMV+PSV. The patients were weaned from MV when they met all the following criteria: the rate of SIMV was decreased gradually to 5 times per minute; the level of PSV was decreased to 5 to 7 cmH2O; the patient's condition remained stable for at least 4 hours.

**Observation items**

Observations did not end until the patients were discharged from hospital. Data collected were the incidence of VAP, the duration of invasive MV and total MV, the number of patients who met the criteria of intubation after weaning from invasive MV, hospital mortality, the days in ICU, the days in hospital and the cost of hospitalisation.

The diagnostic standards for VAP were: a) pneumonia occurred 48 hours or later following receiving invasive MV; b) newly occurred pulmonary infiltrations; c) signs of...
pulmonary consolidation and/or moist rales; d) accompanied by at least one of the following signs: leukocyte count higher than $10 \times 10^9 /L$ or less than $4 \times 10^9 /L$, with or without nuclear shift to left; a body temperature higher than 37.5°C; purulent or increased secretion of airway; and new pathogen isolated from bronchial secretion.

The criteria of intubation were: a) pH $\leq 7.20$ accompanied with progressive increase in PaCO$_2$ during treatment; or b) refractory hypoxia (PaO$_2$ < 50 mmHg even with sufficient oxygen supply); c) severe disturbance of consciousness (coma, stupor or delirium); d) respiratory or cardiac arrest; e) respiratory depression, bradypnea (respiratory rate < 8 times per minute); or severe dyspnoea (respiratory rate > 40 times per minute).

Statistical analysis
All parameters were expressed as the mean±standard deviation (SD). With the use of SPSS 10.0 software, groups were compared by unpaired t-test when normality assumptions were satisfied and by the Mann-Whitney test when normality assumptions were not satisfied. Frequency distributions were compared using the chi-square test. All statistical tests were two tailed. A P value less than 0.05 was considered statistically significant.

RESULTS
Ninety patients were involved in the study and randomly assigned to study group (47 cases) or control group (43 cases). Differences between the two groups in terms of general conditions before invasive MV and at the point of PIC window were not significant (Tables 1 and 2).

There were no significant differences in the main indices between the two groups during the first 24 hours of the random group division following PIC window appearing (Table 3). However, 24 hours after stopping ventilation the heart rate was faster in control group than in study group ($P<0.05$, Table 4), which suggested noninvasive ventilation could also provide effective respiratory support for patients in study group.

Compared with control group, study group had shorter duration of invasive MV [(6.4 ± 4.4) days vs (11.3 ± 6.2) days, $P=0.000$], even though the total durations of MV in the two groups were similar. Compared with control group, study group had lower incidence of VAP (3/47 vs 12/43, $P=0.014$), shorter hospitalisation in ICU [(12 ± 8) days vs (16 ± 11) days, $P=0.047$] and lower hospital mortality (1/47 vs 7/43, $P=0.025$). There was no statistical difference in the number of patients who meet the criteria of intubation after weaning from invasive MV for 10 days, days in hospital and the cost of hospitalisation between study and control groups (Table 5). One case in study group died because of exacerbation of COPD. Seven cases in control group died. Of the seven cases, four died of exacerbation of COPD and the other three died of circulatory failure due to coronary heart disease, acute myocardial infarction or apnoea due to airway sputum blockage respectively.

DISCUSSION
To our knowledge, in this study, it was the first time to use PIC window as the switch point of sequential MV. [8] Yet that was a historical matched cases controlled study in a single centre. This multicentred, prospective, randomized controlled study showed
that using PIC window, early extubation and sequential noninvasive MV in COPD with exacerbated hypercapnic respiratory failure could reduce the duration of invasive MV, the incidence of VAP and hospital mortality.

The value of noninvasive MV in treating exacerbated COPD patients has been widely proven. Some patients can avoid intubation by using noninvasive MV. The positive pressure ventilation can reduce the patients' respiratory workload and respiratory muscle fatigue. But noninvasive MV is not suitable when patients have severe bronchial pulmonary infection with a lot of sputum and have not enough strength to cough, and/or the patients are unconscious due to severe hypercapnia. In these circumstances, establishing an artificial airway is needed to facilitate sputum drainage and guarantee enough respiratory support. So the therapeutic effects of invasive MV can derive from two considerations: one is the effect of positive pressure ventilation, the other is the effect of artificial airway. Noninvasive MV has the same effect from positive pressure ventilation as that in invasive MV. By using noninvasive MV to treat acute respiratory failure, the benefits of positive pressure ventilation are obtained without intubation.

Using an endotracheal tube can result in harmful side effects, because bacteria may migrate into bronchi along the tube and the sediment upon the cuff may flow downwards. These disadvantages of the artificial airway can result in bronchial and pulmonary infection, which is called VAP. Once VAP occurs, the patient's condition will become worse, duration of MV will be prolonged and weaning will be difficult to perform. [2,3] VAP has even been referred to as artificial airway associated pneumonia because the endotracheal tube is a susceptible factor in the development of the respiratory infection. [11] In invasive MV, shortening the duration of the endotracheal intubation as much as possible can reduce the incidence of VAP. Therefore, sequential noninvasive MV becomes a favourable replacement.

In China, exacerbation of COPD occurs in about 80% to 90% of patients because of bronchial pulmonary infection. This study and a previous study [8] both indicate that usually by days 6-7 of invasive MV, sputum was well drained, the antibiotic was administrated reasonably, so the clinical indices of pulmonary infection improved as demonstrated by thinning and decrease in sputum, clearing of sputum cloudiness, decrease in body temperature, radiographic infiltrations and in leukocytes. We refer to the period of time when pulmonary infection is under control as the pulmonary control window (PIC window). If invasive MV continues after appearance of PIC window, VAP occurs due to the prolonged contact of the artificial airway. The appearance of the PIC window means that ventilatory insufficiency has become the patient's major problem, as drainage of sputum became a minor one. At this time, a patient's condition will become stable and improve if given ventilation support, especially provided by the measures to resolve fatigue of the respiratory muscles. In view of this, we suggest that timely extubation followed by noninvasive MV immediately upon appearance of the PIC window will resolve simultaneously the problem of patient's fatigue of respiratory muscles and ventilatory insufficiency and the risk of lower airway infection and VAP.

To ascertain the beginning of the PIC window accurately is the key point of this strategy for sequential MV. From the beginning of comprehensive treatment including invasive MV and anti-infection, one should look for the right opportunity for extubation.
and change to noninvasive MV. We need to understand the criteria for "window": if missed, VAP occurs, patient's condition relapse and the duration of MV prolonged, resulting in ventilator dependence and consequent failure to wean.

It is important to follow invasive MV with noninvasive MV immediately in order to support the patients by positive pressure ventilation continuously, otherwise the patients' conditions may get worse. In two recent studies, the patients who had respiratory distress within 48 hours after extubation and discontinuation of MV were randomized into noninvasive MV group and standard medical therapy group. Noninvasive positive pressure ventilation does not prevent the need for reintubation or reduce mortality. [12,13]

There was no significant difference in total days of MV between the two groups in this study while previous studies indicated sequential MV could reduce days of total MV. [6,8] This outcome might be attributed to the relative shorter duration of invasive MV in control group [(11.3±6.2) days] of our study.

Nava et al from Italy, [6] Girault et al [7] from France and Ferrer et al [14] from Spain reported similar research. In their studies, sequential MV can reduce the duration of invasive MV, incidence of VAP, and days in ICU. Nava's group [6] and Ferrer's group [14] also found early noninvasive MV could reduce hospital mortality. The main difference between our study and others is the selection of switching point from invasive to noninvasive MV. In Nava's and Girault's studies, patients who failed the T tube test after a short time of invasive MV accepted early extubation followed by noninvasive MV. In our opinion, spontaneous breath test may be used as switching point properly in patients who have no significant pulmonary infection. But in COPD patients exacerbated due to pulmonary infection, using PIC window as the switching point would be more efficient.

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