Non-invasive ventilation at the pulmonary infection control window versus spontaneous breathing trials as weaning strategies in acute exacerbation of chronic obstructive pulmonary disease.

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Abstract: Introduction: Applying non-invasive positive pressure ventilation (NPPV) has been used for years in clinical practice during weaning of mechanically ventilated patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), in order to avoid complications of invasive ventilation. Nevertheless, the choice of the optimal timing to apply NPPV in exacerbations caused by pulmonary infections, and whether its use would provide benefit over conventional weaning strategies, remain an issue requiring further investigations. **Aim of the work**: To examine the efficacy of implementing Pulmonary Infection Control (PIC) window as the optimum switching point to wean invasive mechanical ventilation (IMV) in intubated patients for AECOPD with pulmonary infection, compared to conventional weaning strategies implementing the use of Spontaneous Breathing Trials (SBT). Methods: In our prospective randomized controlled study, we enrolled the included patients to two groups, where Group A patients were extubated at the PIC window and immediately received NPPV, while Group B patients were weaned according to the conventional criteria for weaning and were granted an SBT then were extubated and received venturi oxygen therapy. All patients were monitored for forty eight hours post-extubation through assessment and documentation of certain parameters at specific checkpoints, and accordingly the success and failure rates of both weaning strategies were decided, along with the predetermined secondary outcomes of the study. **Results:** 65 patients who were enrolled in the study. Of the 31 patients (47.7 %) who represent Group A, 27 patients (87%) were successfully weaned, and 4 patients (13%) developed respiratory distress within the 48 hourspost-extubation and were re-intubated. Two of these patients were diagnosed with ventilator-associated pneumonia (VAP). Of the other 34 patients (52.3%) representing Group B, 15 patients (44 %) experienced successful weaning, while the other 19 patients (56 %) developed respiratory distress and received NPPV. 8 patients were diagnosed with VAP and 7 of them failed to respond to NPPV within the 48 hours post-extubation, and were re-intubated. **Conclusion:** Based on the higher rate of successful weaning, shorter duration of invasive ventilation, shorter ICU length of stay and lower incidence of VAP, implementation of the PIC window as an optimal switching point for application of NPPV during weaning of IMV, has proven to be a more promising weaning modality than conventional weaning strategies.

[Sherif Wadie Nashed Sargious, Noha Sayed Hussein Ahmed, Dalia Fahmy Imam Aly and Michael T. G. Tawfik. **Non-invasive ventilation at the pulmonary infection control window versus spontaneous breathing trials as weaning strategies in acute exacerbation of chronic obstructive pulmonary disease.** *Nat Sci* 2019;17(6):115-124]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 15. doi:10.7537/marsnsj170619.15.

Keywords: Chronic obstructive pulmonary disease, Acute exacerbations**,** Acute respiratory failure, Invasive mechanical ventilation, Non invasive positive pressure ventilation**,** Pulmonary infection.

1. Introduction

Pulmonary infection is considered a very common condition in patients with chronic obstructive pulmonary disease (COPD). And the most common form encountered is community-acquired pneumonia (CAP). Many COPD patients with medical co-morbidities such as hypertension, diabetes and cardiovascular disease, are susceptible to pneumonia. Acute respiratory failure (ARF) precipitated by pulmonary infection can result in acute exacerbation of COPD through bronchial infections, bronchospasm, left ventricular failure, pneumonia, pneumothorax, or thromboembolic events. Once this condition occurs, in-patient mortality rate increases significantly to 50% among the elderly and 11% -26% among intensive care unit patients.

Endotracheal intubation and mechanical ventilation (MV) can help in clearance or suction of secretions and reduce the burden on the respiratory tract, partially or even completely, so as to control pulmonary infection. While respiratory muscle exhaustion, pulmonary hyperinflation, and malnutrition are common symptoms in patients with COPD, which may require mechanical ventilation for long periods of time. Prolonged MV has been associated for with the development of complications, for example, upper respiratory tract infections, sinusitis, and ventilator-associated pneumonia (VAP). VAP results in increased morbidity and mortality in

the intensive care unit, which reaches 30% or higher. Therefore, reducing the duration of mechanical ventilation is an important objective of critical care.

Accordingly, to reduce complications associated with prolonged MV, the use of non-invasive positive pressure ventilation (NPPV), which is the transition from invasive support to non-invasive support, has been studied in patients who are prepared to breathe spontaneously after removal of the tracheal tube, yet they are still not eligible to maintain respiratory effort without mechanical support. The studies aimed to examine the benefits of switching to non-invasive ventilation in reducing the duration of invasive mechanical ventilation (IMV), rates of VAP, and mortality.

In the meantime, the choice of the optimal timing for the use of NPPV is a key factor in successful treatment of ARF associated with acute exacerbation in patients with COPD. Early withdrawal of the tracheal tube and the immediate application of NPPV will result in loss of protection of the airway, increased stress and fatigue of the respiratory muscles, as well as imbalance in the optimal exchange of gases, while delayed use of non-invasive support may increase the risk of adverse complications. Optimal timing should therefore be carefully chosen to balance the potential risks associated with early removal of IMV and delay in the application of NPPV.

Through clinical practice, the Pulmonary Infection Control (PIC) window has become the switching point for transition from invasive to non-invasive mechanical ventilation, making it possible to determine the optimal timing for early withdrawal of the tracheal tube more accurately. The timely removal of the tube followed by NPPV immediately after the identification of the PIC window can provide respiratory support for muscle fatigue while avoiding the complications caused by long-term IMV.

Therefore, the objective of this study was to examine the efficacy of applying the PIC window as an optimal switching point for withdrawal of IMV in patients who were intubated due to acute exacerbation of COPD caused by pulmonary infection, compared to conventional weaning strategies that implement the use of spontaneous breathing trials (SBT) based on the daily examination of weaning parameters that predict successful extubation.

2. Patients and methods

This prospective randomized controlled study was performed in a 13-bed intensive care unit of AbuQir Specialized Hospital from December 2017 to May 2018. The study was approved by the hospital's Ethics Committee, meeting criteria of the Helsinki declaration, and following informed consents of the patient's first degree relatives.

Patients

Eligibility requirements were as follows: participants were aged ≥18 years old, male/female. All patients were diagnosed with COPD according to the diagnostic criteria of the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Revised 2011; Updated 2016), in whom bronchopulmonary infection was the major cause of acute exacerbation, requiring endotracheal intubation and mechanical ventilation (MV).

Methods

Eighty intubated COPD patients for acute exacerbation who were enrolled in the study. All patients included in the study were subjected to the necessary medical treatment (antibiotics and comprehensive therapy) according to international and local guidelines of management, and were mechanically ventilated and received full invasive ventilatory support using Synchronized Intermittent Mandatory Ventilation (SIMV) mode. Included patients were randomly divided into two groups using their medical record number (MRN) such that patients with even MRN's who fulfilled the criteria of the Pulmonary Infection Control (PIC) window were enrolled to the study group (Group A), and patients with odd MRN's who fulfilled the conventional weaning parameters were enrolled to the control group (Group B). Over the course of the study period, and with careful implementation of the pre-determined exclusion criteria, a total of 65 patients continued to be involved in the study divided among both designated groups, while the remaining portion of the patients pool were excluded.

Group A, the Study Group

Patients who fulfilled the criteria of the PIC Window, were timely extubated and Non-invasive Positive Pressure Ventilation (NPPV) was immediately applied according to a fixed protocol that was applied to all patients subjected to the strategy.

Changes in respiratory and hemodynamic parameters in Group A patients were monitored and recorded at baseline following extubation and at different fixed time intervals i.e. 2 hours, 12-hours, 24-hours and 48-hours checkpoints.

However, when these patients developed any of the pre-determined criteria of respiratory distress while on NPPV and were in need for re-intubation, invasive mechanical ventilation (IMV) was resumed and the event was calculated as failure of the weaning procedure.

Discharge from the ICU to another general ward was authorized when the clinical status remained stable for at least 48 hours after extubation.

Criteria applied to study procedure.

Identification of pulmonary infection:(Yingying Lv, 2017) • Significant infiltrates in chest X-rays • Changes in sputum (i.e. increased volume, thickened, yellow and purulent) • *Plus one or more of the following:* • Body temperature >37.5°C • WBC > 10×10^9/L, or N > 80%
Criteria of the PIC Window:(Yingying Lv, 2017) • Significantly dissipated lung radiographic infiltrates • Significant changes in sputum (less amount, density and lighter color) • The mode of mechanical ventilation adjusted to SIMV at 10-12 times/min and to pressure support ventilation (PSV) at a range of 10-12 cm H_2O. • *Plus one or more of the following:* • Body temperature <37.5°C • WBC < 10×10^9/L, or WBC decreased by 2×10^9/L
Criteria for re-intubation:(Zujin Luo, 2014) *If any of the following criteria were met:* • Respiratory or cardiac arrest • RR persistently >40 breaths/min or <8 breaths/min • Arterial pH ≤ 7.20 with a progressive increase in $PaCO_2$ • Serious hypoxia; PaO_2< 50 mmHg despite the use of a high FiO_2 • Clinical signs suggestive of severely decreased consciousness (e.g. coma, stupor, delirium).
Criteria of SBT failure:(Boles JM, 2007) *If any of the following criteria were met:* • Arterial pH < 7.32 • Increase in $PaCO_2$ ≥ 10 mmHg • RR > 35 breaths/min or ≥50% higher than baseline • SpO_2< 88% or PaO_2 ≤ 60 mmHg at FiO_2 ≥ 0.4 • HR > 140 beats/min or ≥20% higher/lower than baseline • SBP > 180 or <90 mmHg or ≥20% higher/lower than baseline • Use of accessory respiratory muscles, or thoracic-abdominal paradoxical movement • Decreased consciousness, agitation, or diaphoresis

Group B, the Control Group

Patients who fulfilled the conventional criteria of readiness for a weaning trial were subjected to a Spontaneous Breathing Trial (SBT) using Continuous Positive Pressure Ventilation (CPAP) and Pressure Support (PS) ventilation for 30 minutes according to a predetermined protocol applied to all patients.

Patients who showed no sign of respiratory distress; i.e. SBT was successful, were extubated and Venturi oxygen therapy was applied. During venturi oxygen therapy, FiO_2 was adjusted to obtain an SpO_2 of 88%–92%. Patients were monitored closely for physiological variables related to ventilation status, oxygenation and hemodynamics.

Patients were meticulously observed and received brief periods of NIPPV at fixed time intervals for the purpose of measurements and recordings. These intervals represented the same checkpoints applied to Group A patients (i.e. 2 hours, 12-hours, 24-hours and 48-hours checkpoints) to facilitate the comparison between the efficacy of the two strategies.

Discharge from the intensive care unit (ICU) to another general ward was authorized when a patient's clinical status remained stable for at least 48 h after extubation.

Failure of weaning was defined as development of respiratory distress following extubation, detected according to pre-determined measurable and clinical criteria.

NPPV was applied if patients showed respiratory distress after extubation (same protocol applied to group A). Patients who responded to NPPV followed the same fore-mentioned algorithm as for Group A and were discharged to the ward following 48 hours of stability.

Re-intubation was performed in case of failure to respond to NPPV and consequently failure of the SBT. IMV was resumed with full ventilatory support, and the event was calculated as failure of the weaning procedure.

Data collection

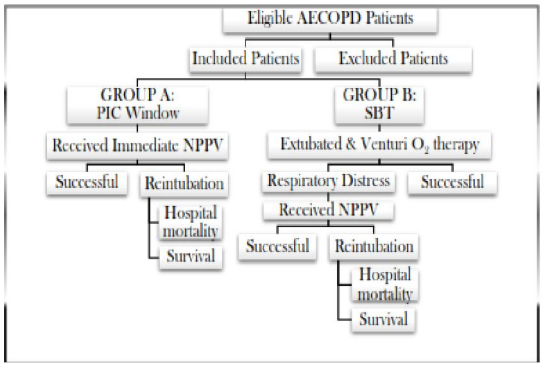


Figure 1: Flowchart of the study procedure.

Table 1. Baseline characteristics of patients of both groups before start of weaning

Baseline characteristics	Group A (n = 31)	Group B (n = 34)	*P* value
Demographic data			
Age (years)	59.76 ± 7.59	59.91 ± 7.82	0.483
Gender (male/female)	28/3	32/2	0.652
Course of COPD (years)	12.91 ± 4.33	11.85 ± 4.05	0.137
Smoking Index	509.09 ± 200.04	475 ± 181.79	0.216
APACHE II score	7.3 ± 0.58	7.33 ± 0.63	0.405
Hemodynamic parameters			
HR (beats/min)	85.64 ± 9.91	82.78 ± 11.04	0.132
SBP (mmHg)	133.03 ± 16.53	131.67 ± 17.78	0.398
MAP (mmHg)	84.97 ± 11.90	85.97 ± 12.08	0.432
Respiratory parameters			
RR (breaths/min)	15.03 ± 3.17	15.94 ± 3.4	0.134
V_T (L)	0.53 ± 0.10	0.61 ± 0.10	0.061
V_m (L/min)	8.05 ± 2.35	8.78 ± 2.65	0.362
Arterial pH	7.41 ± 0.03	7.41 ± 0.03	0.245
$PaCO_2$ (mmHg)	40.85 ± 2.41	40.08 ± 2.93	0.354
Hypoxic Index (mmHg)	255.61 ± 26.44	255.97 ± 24.30	0.466
SpO_2 (%)	89.85 ± 1.53	90.00 ± 1.52	0.336
PS level (cmH_2O)	11.12 ± 0.88	10.98 ± 0.83	0.134
PEEP level (cmH_2O)	5.82 ± 0.79	5.72 ± 0.76	0.302
Metabolic and Infection-related parameters			
HGB (g/dL)	13.30 ± 1.72	13.28 ± 1.73	0.476
Body Temperature (°C)	37.27 ± 0.19	37.22 ± 0.15	0.118
Sputum Volume (mL/day)	113.33 ± 41.21	118.28 ± 43.49	0.259
WBC ($\times 10^9$/L)	8.41 ± 1.69	8.71 ± 1.25	0.363
Neutrophils ratio (%)	87.09 ± 5.17	86.36 ± 4.89	0.309

Quantitative data are expressed as mean ± SD (Standard Deviation) for normally distributed data.
Qualitative data are expressed using number and percent.
COPD, chronic obstructive pulmonary disease; APACHE, acute physiology and chronic health evaluation; HR, heart rate; SBP, systolic blood pressure; MAP, mean arterial pressure; RR, respiratory rate; V_T, tidal volume; V_m, minute volume; $PaCO_2$, arterial carbon dioxide tension; SpO_2, arterial oxygen saturation measured by pulse oximetry; PS, pressure support; PEEP, positive end-expiratory pressure; HGB, hemoglobin; WBC, white blood cell counts.

Data were recorded and compared at three stages throughout the study; first stage entailed recordings of the baseline criteria of all patients before beginning the weaning procedure, and these criteria included descriptive data (age, gender, course of COPD, smoking Index and APACHE II score), hemodynamic parameters (heart rate, systolic blood pressure and mean arterial pressure), respiratory parameters (respiratory rate, tidal volume, minute volume, arterial pH, arterial carbon dioxide tension, hypoxic Index, arterial oxygen saturation, pressure support level and positive end-expiratory pressure) and metabolic and infection-related parameters (hemoglobin, body temperature, sputum volume, white blood cells count and neutrophils ratio). The second stage was the monitoring stage during the weaning procedure, where certain hemodynamic and respiratory parameters were carefully assessed and recorded for all patients of either of the two groups; A or B, at fixed time intervals over the 48-hours period post-extubation; namely at 2-hours, 12-hours, 24-hours and at 48-hours checkpoints. The third and final stage was specified to monitor the outcome of the study, where two outcome categories where monitored; primary outcome which was the observed rates of weaning success and failure for both strategies, and secondary outcomes which entailed: major complications related to IMV identified in both groups (namely ventilator-associated Pneumonia and ventilator-associated lung injury), number of days of invasive mechanical ventilation,

number of days of NPPV, total number of days of mechanical ventilation, rate of re-intubations and weaning failures, duration of ICU stay, duration of hospital stay and 30-days mortality rate.

AECOPD; acute exacerbation of chronic obstructive pulmonary disease, PIC; pulmonary infection control, SBT; spontaneous breathing trial, NPPV; non-invasive positive pressure ventilation.

3. Results

Patients enrolled to Group A in whom the criteria of the pulmonary infection control (PIC) window were detected, were 31 patients (47.7 %). On the other hand Group B patients who fulfilled the conventional criteria of weaning of invasive mechanical ventilation were 34 patients (52.3 %). Baseline characteristics that were recorded at the beginning of the weaning procedure are summarized in (Table 1).

Respiratory parameters during weaning

Parameters related to respiratory mechanics (Table 2)

Regarding the respiratory rate (RR), a statistically significant difference was found with a noted increased rate in Group B patients at the2-hours checkpoint, and persisted over the rest of the 48 hours duration.

Tidal volumes decreased significantly for Group B patients in comparison to Group A starting at the 12-hours checkpoint and continuously over the following recorded intervals. And simultaneously, minute ventilation values also started to show a statistically significant difference.

Table 2. Changes in respiratory parameters related to respiratory mechanics during weaning

Parameters		2-hours checkpoint		12-hours checkpoint		24-hours checkpoint		48-hours checkpoint	
		Gp. A	Gp. B	Gp. A	Gp. B	Gp. A	Gp. B	Gp. A	Gp. B
RR (breaths/min)	**Mean ± SD**	21.42±4.52	25.25±3.64	19.97±5.57	27.33±5.39	19.36±5.58	28.61±8.27	17.52±6.36	27.97±9.52
	***P* value**	0.001*		0.001*		0.001*		0.001*	
V_T (L)	**Mean ± SD**	0.42±0.09	0.40±0.11	0.44±0.10	0.38±0.13	0.46±0.12	0.37±0.13	0.48±0.13	0.36±0.13
	***P* value**	0.225		0.016		0.001*		0.0001*	
V_m (L/min)	**Mean ± SD**	8.62±1.78	8.94±1.55	8.48±2.11	8.91±1.89	8.61±2.22	9.49±1.41	7.86±2.08	9.10±1.71
	***P* value**	0.211		0.026		0.053		0.011	

Quantitative data are expressed as mean ± SD (Standard Deviation) for normally distributed data. RR, respiratory rate; V_T, tidal volume; L, Liter; V_m, minute volume.

Parameters related to blood gases (Table 3)

Arterial Blood gases indicated a statistically significant decrease in arterial pH in Group B patients but not in those of Group A by the 48-hour checkpoint. In relation, a statistically significant marginal increase in arterial CO2 tension was noted in Group B patients at the 24-hours checkpoint and more significantly by the 48-hours interval. Yet while observing these values by the 2-hours and 12-hours checkpoints, there was no statistically significant difference.

As regards oxygenation status, recordings of the hypoxic index started to show statistically significant difference by the 24-hours checkpoint, while values of the arterial oxygen saturation showed no statistically significant difference between both groups over the 48 hours.

Table 3. Changes in respiratory parameters related to blood gases during weaning

Parameters		2-hours checkpoint		12-hours checkpoint		24-hours checkpoint		48-hours checkpoint	
		Gp. A	Gp. B	Gp. A	Gp. B	Gp. A	Gp. B	Gp. A	Gp. B
Arterial pH	**Mean ± SD**	7.37±0.04	7.36±0.03	7.37±0.06	7.36±0.03	7.37±0.07	7.36±0.04	7.37±0.07	7.35±0.05
	***P* value**	0.026		0.024		0.025		0.019	
$PaCO_2$ (mmHg)	**Mean ± SD**	47.06±3.90	48.81±3.89	47.88±5.93	50.14±4.42	48.18±8.07	53.19±6.17	49.00±10.29	56.92±9.45
	***P* value**	0.213		0.157		0.049		0.001*	
Hypoxic Index (mmHg)	**Mean ± SD**	267.27±35.94	256.25±38.21	258.48±28.79	246.89±28.5	249.24±29.45	241.69±24.76	246.52±32.14	237.08±25.09
	***P* value**	0.098		0.052		0.029		0.004*	
SpO_2 (%)	**Mean ± SD**	91.91±3.69	90.56±3.79	90.09±3.22	89.81±3.39	89.79±2.33	88.42±2.86	89.39±2.93	87.98±3.18
	***P* value**	0.235		0.201		0.136		0.073	

Quantitative data are expressed as mean ± SD (Standard Deviation) for normally distributed data. $PaCO_2$, arterial carbon dioxide tension; mmHg; millimeter mercury; SpO_2, arterial oxygen saturation measured by pulse oximetry.

Hemodynamic parameters during weaning (Table 4)

Although recordings of heart rate (HR) showed some elevation clinically, data analysis did not prove any statistically significant difference between the two groups over the 48-hours duration.

Considering blood pressure changes, statistical study of recordings of systolic blood pressure (SBP) as well as mean arterial pressure (MAP) did not show significant difference exhibited by patients of both groups over the monitoring period.

Table 4. Changes in hemodynamic parameters during weaning

Parameters		2-hours checkpoint		12-hours checkpoint		24-hours checkpoint		48-hours checkpoint	
		Gp. A	Gp. B	Gp. A	Gp. B	Gp. A	Gp. B	Gp. A	Gp. B
HR (beats/min)	Mean ± SD	100.27±10.68	102.22±11.59	95.03±11.56	98.36±12.11	91.88±12.47	96.36±12.98	90.39±13.05	97.28±13.9
	P value	0.198		0.121		0.098		0.028	
SBP (mmHg)	Mean ± SD	134.09±23.73	138.56±28.94	124.85±18.76	132.61±23.73	124.55±14.32	134.17±18.91	127.88±17.36	136.67±25.90
	P value	0.177		0.105		0.089		0.032	
MAP (mmHg)	Mean ± SD	88.12±15.77	92.92±21.39	88.45±13.82	94.92±18.26	86.91±14.27	93.92±20.62	85.73±14.35	93.36±30.04
	P value	0.214		0.198		0.089		0.077	

Quantitative data are expressed as mean ± SD (Standard Deviation) for normally distributed data.
HR, heart rate; SBP, systolic blood pressure; MAP, mean arterial pressure.

Outcome

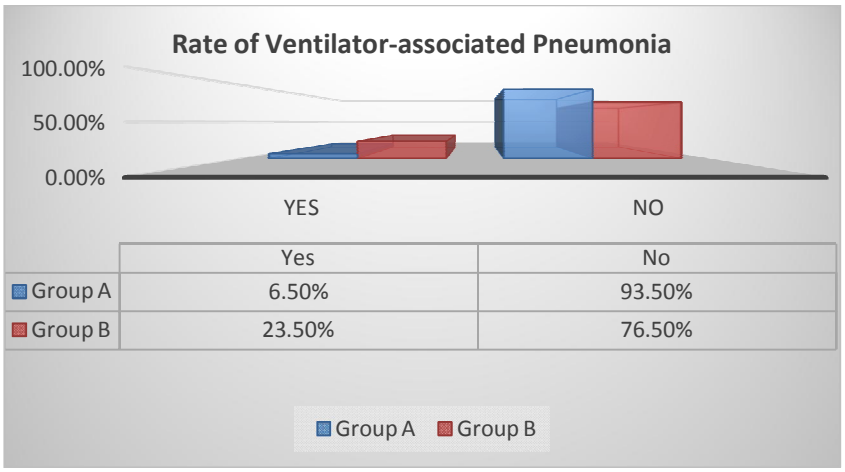
Detected rates of primary and secondary outcome parameters are summarized in (Table 5). Of the 31 patients (47.7 %) who represent Group A, 27 patients (87%) were successfully weaned and were later discharged to the in-patient ward. Four patients (13%) developed respiratory distress within the 48 hours post-extubation and were re-intubated according to the fore-mentioned criteria for re-intubation and resumed invasive mechanical ventilation according to the original ventilator settings that were used prior to the weaning procedure.

Two of these patients were diagnosed with VAP and were accordingly managed but one of them failed to respond to treatment and died. The remaining 3 patients were followed and assessed till achievement of the PIC window criteria and the weaning procedure was initiated once again and they were followed for a 48-hours period and they were successfully weaned and discharged to the in-patient ward.

Table 3. Observed primary and secondary outcomes of the two studied groups

Parameters	Group A (n = 31)	Group B (n = 34)	*P* value
Primary outcome			
Successful weaning rate	27/31 (87.1%)	15/34 (44.1%)	0.001*
Secondary outcome			
Diagnosed VAP rate	2/31 (6.5%)	8/34 (23.5%)	0.029*
Diagnosed VALI rate	0/31 (0.0%)	2/34 (5.9%)	0.088
Number of IMV days	3.30 ± 1.51	4.86 ± 2.01	0.0001*
Number of NPPV days	2.24 ± 0.60	2.39 ± 0.65	0.154
Total days of MV	5.39 ± 1.87	7.19 ± 2.20	0.001*
Duration of ICU stay (days)	6.76 ± 1.80	8.79 ± 2.18	0.001*
Duration of hospital stay (days)	7.12 ± 1.89	9.5 ± 2.25	0.0001*
Rate of re-intubations	4/31 (12.9%)	7/34 (20.6%)	0.209
30-days mortality rate	1/31 (3.3 %)	4/34 (11.8%)	0.101

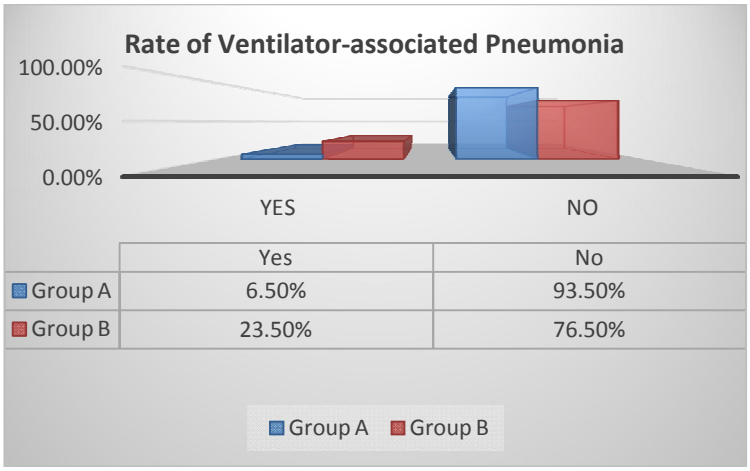
Quantitative data are expressed as mean ± SD (Standard Deviation) for normally distributed data.
Qualitative data are expressed using number and percent.
VAP, ventilator-associated pneumonia; VALI, ventilator-associated lung injury; IMV, invasive mechanical ventilation; NPPV, non-invasive positive pressure ventilation; MV, mechanical ventilation; ICU, intensive care unit.



Of the other 34 patients (52.3%) representing Group B, 15 patients (44 %) experienced successful weaning and were discharged to the in-patient ward, while the other 19 patients (56 %) developed respiratory distress and received NPPV over the 48-hours assessment period following the same protocol as Group A. 8 patients of them were diagnosed with VAP. Of the failed-weaning section of Group B, 7patients failed to respond to NPPV within the 48 hours post-extubation, and were re-intubated. Re-intubated patients resumed invasive mechanical ventilation according to their original ventilation settings and were followed for fulfilment of weaning criteria. Of the re-intubated patients, ventilator-associated acute lung injury (VALI) was detected in 2 patients, and collectively 4 patients of this group failed to show adequate response to their management plan and died. The remaining 3 patients were followed till fulfilment of criteria of the PIC window and were timely extubated and followed the same weaning strategy as Group A patients. They experienced successful weaning and were later discharged to the in-patient ward.

Regarding successful weaning rate, statistically significant difference was found between the two groups in favor of Group A.

Considering ventilator associated compli-cations, data analysis showed statistically significant difference regarding diagnosed VAP while there was no significant difference found regarding VALI.



Compared to patients of Group A, conventionally weaned patients of Group B experienced prolonged duration of invasive mechanical ventilation and total days of MV, along with total days of ICU stay and accordingly total duration of hospital stay. This was reflected by a statistically significant difference in data analysis, yet no difference has been shown regarding number of days of NPPV.

The reintubation rate within the 48 hours following extubation was comparable between Group A and Group B patients (12.9 % vs 20.6 %). Nevertheless, data analysis showed no statistically significant difference. Also comparison between both groups regarding mortality rate did not prove any statistically significant difference.

4. Discussion

Severe form of COPD usually causes a state of chronic respiratory muscle compromise attributed to the incomplete alveolar emptying at the end of expiration resulting in dynamic hyperinflation, intrinsic positive end-expiratory pressure (PEEPi), flattening of the diaphragm, recruitment of accessory respiratory muscles, and alterations in the shape of the rib cage ***(S.Hill, 2000)***. Mechanical ventilation is often life-saving when patients with COPD experience acute respiratory compromise and failure, but it also has its risks. There are adverse effects caused by PEEPi, including barotrauma risk, hemodynamic compromise, overload of inspiratory muscles, and weaning failure ***(Maria Tzoufi, 2005)***.

Weaning from MV is a process where MV is gradually withdrawn and the patient resumes spontaneous breathing efforts ***(Tobin MJ, 1990)***. If the weaning procedure is initiated early, it can often lead to cardiorespiratory failure. On the other hand, if its initiation is delayed, it can be unsuccessful due to respiratory muscle weakness caused by deconditioning and disrupted breathing regulation and accordingly delayed weaning adds a higher opportunity for developing ventilator-associated pneumonia (VAP) ***(Pierson, 1995)***.

In patients with COPD the weaning phase may account for as much as 59% of the time that the patient spends on a mechanical ventilator ***(Kuhlen R, 1998)***. Overall, the weaning procedures are unsuccessful in about 20% of the cases ***(Lemaire, 1993)***, whereas the initial weaning attempt in patients with COPD is reported to be unsuccessful in over 50% of the cases ***(Petrof BJ, 1990)***.

Early withdrawal of invasive MV (IMV) followed by noninvasive positive-pressure ventilation (NPPV) is a relatively new strategy for avoiding complications or reducing the duration of invasive mechanical support for intubated patients with respiratory failure. Choosing an appropriate time to transfer from IMV to NPPV is the key for performing sequential MV successfully. To miss or delay the switching point for sequential ventilation can certainly lose the optimal opportunity. However, the appropriate switching point has been controversial ***(C & Society, 2005)***.

In clinical practice, the pulmonary infection control (PIC) window has been the switch point for transferring from IMV to NPPV, so the time for early extubation can be more accurately judged. When the PIC window is achieved, a patient's condition will become stable and improved if ventilatory support is provided, and this applies especially for measures aiming to resolve fatigue of the respiratory muscles. Timely extubation followed by NPPV with the appearance of the PIC window could manage the problem of patient's fatigue involving respiratory muscles and ventilatory insufficiency simultaneously, thereby avoiding lower respiratory infection and VAP ***(Yingying Lv, 2017)***.

The present study shows that timely extubation and immediate application of NPPV once the PIC window is identified, appears to be a promising weaning modality for mechanically ventilated COPD patients in acute exacerbation precipitated by pulmonary infection.

In our prospective randomized controlled study, we enrolled the included patients to two groups, where Group A patients were extubated at the PIC window and immediately received NPPV, while Group B patients were weaned according to the conventional criteria for weaning and were granted a spontaneous breathing trial (SBT) then were extubated and received venturi oxygen therapy. All patients were monitored for 48 hours post-extubation through thorough assessment and documentation of certain parameters at specific checkpoints and accordingly the success and failure rates of both weaning strategies were decided, along with the predetermined secondary outcomes of the study.

Careful implementation of the previously mentioned inclusion and exclusion criteria ensured the selection of a homogenous pool of patients with almost similar baseline characteristics to guarantee the credibility of the study results.

As for the monitoring process during the weaning procedure using both strategies, the selection of fixed time-interval checkpoints for recording vital parameters facilitated the comparison of the efficacy of the weaning strategy between the two groups. Determination of specific measurable parameters, either respiratory, or hemodynamic, allowed for accurate recording of the progress and changes during the weaning procedure.

During acute decompensation of COPD, the goal is to reduce carbon dioxide levels by unloading the respiratory muscles and augmenting alveolar ventilation, thereby stabilizing arterial pH until the underlying etiology can be reversed ***(Organized jointly by the American Thoracic Society, 2001)***. NPPV achieves this by resting the respiratory muscles thus reducing their fatigue, improving the pattern of respiration and facilitating efficient gas exchange. Thus it may be beneficial in hypercapnic respiratory failure which is frequently encountered in COPD and in weaning failure ***(Mayank Mishra, 2014)***.

We found that the RR showed a significant increase in Group B patients who were extubated and received venturi oxygen therapy, and this increase was noted from as early as the 2-hours checkpoint, compared to patients who were receiving NPPV. This suggests that the respiratory distress after extubation

was not due to the recurrence of pulmonary infection, but rather to incomplete recovery of patients' capacity to breathe spontaneously. The respiratory muscle fatigue that caused this respiratory distress affected the other respiratory parameters at later check points, where VT and VM began to show decreased values for this group by the 12-hours checkpoint, hypoxic index dropped by the 24-hours checkpoint consistently with an increase in $PaCO_2$ tension, and eventually arterial pH showed a significant decrease by the 48-hours checkpoint.

Use of NPPV as an early weaning/extubation technique from invasive MV remains controversial and there are a few studies highlighting the role of NPPV in weaning patients with respiratory failure due to COPD. For instance, Nava et al. ***(Stefano Nava, 1998)***, found that NIPPV reduces weaning time, shortens the time of stay in the ICU, decreases the incidence of nosocomial pneumonia, and improves 60-day survival rates, thus concluding that NPPV is more effective than conventional PSV in weaning COPD patients from invasive MV.

Regarding the choice of the PIC window as an optimal switch point for starting NPPV, a comprehensive search for randomized controlled trials (RCTs) was concluded in a meta-analysis performed by Yingying et al. The trials were all parallel studies comparing the PIC window weaning strategy versus conventional weaning strategy in treatment of patients with respiratory failure due to COPD. The data obtained from these studies suggested that the PIC window reduced the need for intubation and mortality without increasing the risk of weaning failure in treatment of respiratory failure in COPD patients. Our study largely concurs with the findings of the previously mentioned studies regarding the favorable success rate as a weaning modality compared to conventional strategies, the shorter duration of ICU stay and the lower rate of diagnosed pneumonia as a complication of prolonged invasive ventilation.

Song et al. ***(Yuanlin Song, 2016)***differentiates between AECOPD patients with insignificant bronchopulmonary infection, for whom they suggest weaning by SBT assisted by NIV, and AECOPD patients with significant infection for whom they encourage replacement of IMV by NPPV at the PIC window. Their verdict was based on the recognition of a lower rate of VAP, shorter durations of IMV, ventilatory support, and ICU stay. And since we have limited our study to AECOPD patients in whom significant bronchopulmonary infection has been identified as a predisposing factor, we found our results in concordance with the findings of Song et al.

In contrast, Yan et al. ***(Yan HY, 2014)***conducted a study to investigate an optimal timing of sequential NPPV applied for patients with AECOPD, and concluded that a 2-hours SBT may be selected as the optimal timing for the use of NPPV, showing a high success rate of treatment and less need for re-intubation. However, those contradicting results to our study's findings could be explained by the fact that again our study was limited to patients with significant bronchopulmonary infection; an entity not addressed by the study in question of Yan et al.

Zujin et al. ***(Zujin Luo, 2014)***performed a study with more emphasis on AECOPD patients with bronchopulmonary infection. They found out that in such patients performing extubation to sequential NPPV at the time of SBT failure cannot guarantee that bronchopulmonary infection has been substantially controlled, and may increase the risk of reintubation despite immediate extubation to NPPV. On the other hand, the presence of the PIC window indicates that bronchopulmonary infection, the major cause of AECOPD, is under control, and thus drainage of airway secretion is not a major problem and the endotracheal tube may not be absolutely necessary; thus, timely extubation and switching to NPPV may not only provide ventilatory support and improve fatigue of respiratory muscle, but also shorten the duration of IMV to improve prognosis, regardless of whether the patients can afford respiratory loads independently.

According to these findings, Zujin et al. could provide experimental evidence that most AECOPD patients can breathe independently at the PIC window, yet the vast majority develop respiratory distress. And therefore, to avoid reintubation, NPPV had to be performed for all AECOPD patients, whether or not they had passed the SBT. Similar findings were evident in the results of our study, which proved a statistically significant difference in the group of patients who were extubated at the PIC window and received NPPV, compared to conventionally weaned patients, regarding successful weaning rate, duration of invasive mechanical ventilation, total days of ICU stay and accordingly total duration of hospital stay.

Increase in the duration of MV often leads to increased incidence of nosocomial pneumonia, mainly due to the fact that the presence of endotracheal tube predisposes to impaired cough reflex and mucociliary clearance. NPPV has been considered as one of the strategies to decrease the incidence of VAP. Present study also confirms the same, as our findings proved a statistically significant decrease in the rate of diagnosed VAP amongst the group of patients who were weaned at the PIC window using NPPV. These results were consistent with the findings of Shiva et al. and also same verdict was concluded in the meta-analysis including 16 trials performed by Yingying et al. NPPV also decreased the mortality in the post-extubation phase by avoiding sedation, tracheostomy,

and intubation and allowed swallowing, thereby decreasing gastro-oesophageal reflux, aspiration to the airways and consequently development of VAP.

Limitations to the study

Several limitations of this study must be taken into account. First, the analysis was based on a population of patients with AECOPD in whom bronchopulmonary infection was the major cause. However, one should note that bronchial pulmonary infection accounted for 50%–70% of acute exacerbation of COPD occurrences worldwide. Therefore, our results cannot be extrapolated to all AECOPD patients. Second, patients were monitored only during ICU stay, and no data were collected after patients were discharged from the ICU. Finally, the sample size was relatively small, although the primary outcomes were significant.

5. Conclusion

To conclude, based on the higher rate of successful weaning, shorter duration of invasive ventilation, shorter ICU length of stay and lower incidence of VAP, implementation of the PIC window as an optimal switching point for application of NPPV during weaning of IMV, has been shown in the present study to be a more promising weaning modality than conventional weaning methods through SBT. Therefore, this strategy should be encouraged as a more superior weaning strategy for COPD patients in acute respiratory failure under significant broncho-pulmonary infection.

Acknowledgements

The author would like to extend sincere gratitude to Dr. Bassem N. Bishay, MD, Assistant Professor of Critical Care Medicine, Alexandria University, Egypt, whose help and guidance provided indispensable support to the accomplishment of this study.

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4/23/2019