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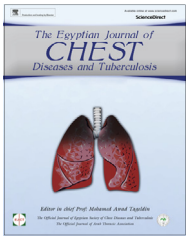

ORIGINAL ARTICLE

Role of bronchoscopy during non invasive ventilation in hypercapnic respiratory failure

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Abstract *Introduction:* Non invasive positive pressure ventilation (NIPPV) is the first line treatment for hypercapnic acute respiratory failure (ARF) secondary to COPD exacerbation in selected patients. Limited data exist supporting the use of fiberoptic bronchoscopy (FOB) during this clinical setting. The aim of this study is to assess the role of FOB during NIPPV in patients with decompensated COPD acute exacerbation.

Methods: This study is a randomized prospective case control pilot study carried out on 50 patients - admitted to critical care units at Alexandria University Hospital, Egypt - suffering from hypercapnic ARF secondary to COPD exacerbation with Kelly Matthay Score from 2 to 4. All patients received NIPPV. Patients were divided randomly into 2 equal groups: group I (cases) (25 patients) was subjected to additional intervention of early FOB during the first 6–12 h from admission while group II (control) (25 patients) received the conventional treatment and NIPPV only. Outcome parameters measured were changes in ABG data, duration of NIPPV, rate of its success, ICU stay and mortality as well as the safety of FOB and possible complications.

Results: No significant difference was detected between the 2 groups regarding the baseline characteristics. No serious complications happened from FOB, and Oxygen desaturation happened in 4/25 patients (16%), Tachycardia in 2/25 patients (8%). In group I, 23 patients (92%) were successfully weaned from NIPPV versus 16 patients (64%) in group II ($p = 0.037$). Total duration of NIPPV was 28.52 h in group I versus 56.25 h in group II ($p = 0.001$). Length of ICU stay was 4.84 days in group I versus 8.68 days in group II ($p = 0.001$). Only 1 patient died in group I versus 3 patients in group II ($p = 0.609$).

Conclusion: The early application of FOB during NIPPV in patients with ARF due to COPD exacerbation was shown to be safe. Significant improvement in the outcome of patients who underwent FOB was noticed in terms of improved ABG data, shorter duration of NIPPV, higher percentage of success and shorter ICU stay while no significant difference was detected in mortality.

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Introduction

The American Thoracic Society, European Respiratory Society, and the British Thoracic Society have each defined COPD using slightly different wordings and approaches over the past 15 years.The Global Initiative for Chronic Obstructive Lung Disease (GOLD) a report produced by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) defines COPD as a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases [1].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) – a report produced by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) – defines an exacerbation of chronic obstructive pulmonary disease (COPD) as an acute increase in symptoms beyond normal day-to-day variation .This generally includes an acute increase in one or more of the following cardinal symptoms: cough increases in frequency and severity, sputum production increases in volume and/or changes character, and dyspnea increases [2].

It is estimated that 50–60 percent of exacerbations are due to respiratory infections (mostly bacterial like *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and Enterobacteriaceae and viral like rhinoviruses. Influenza, parainfluenza, coronavirus, and adenovirus), 10 percent are due to environmental pollution, and 30 percent are of unknown etiology [3].

Some COPD exacerbations of unknown etiology may be related to other medical conditions, such as myocardial ischemia, heart failure, aspiration, or pulmonary embolism [4]. Patients with COPD who present to the hospital with acute worsening of dyspnea should be evaluated for potential alternative diagnoses, such as heart failure, pulmonary thromboembolism, and pneumonia. This was illustrated in an autopsy study of 43 patients with COPD who died within 24 h of admission for a COPD exacerbation .The primary causes of death were heart failure, pneumonia, pulmonary thromboembolism, and COPD in 37, 28, 21, and 14 percent, respectively [2].

Noninvasive positive pressure ventilation (NIPPV) refers to mechanical ventilation delivered through a noninvasive interface, such as a face mask, nasal mask, or nasal prongs; it is more comfortable allowing expectoration, eating, speech and prevents rebreathing than full face mask. The face mask is generally preferred over a nasal mask or nasal prongs during the initiation of NIV for several reasons. Most patients with acute respiratory failure are mouth breathers; therefore, NIV delivered by a nasal mask results in a large air leak through the mouth and a worse outcome. The nasal air passages offer significant resistance to airflow, which can mitigate the beneficial effects of NIPPV if a low level of positive airway pressure is used. There are two principal forms used: Pressure support ventilation (PSV) and bilevel positive airway pressure (BiPAP). PSV is the most common mode chosen by clinicians who want to maximize patient comfort and synchrony. Both provide positive airway pressure during the respiratory cycle, but BiPAP offers pressure in a biphasic manner, with higher pressures during inspiration than expiration. Studies in patients with obstructive lung disease indicate that low-level CPAP offsets the detrimental effects of auto-positive end-expiratory pressure, which are caused by gas trapped in alveoli at end expiration and decreases inspiratory work of breathing. The addition of inspiratory pressure support to CPAP (or BiPAP) generally improves tidal volume in proportion to the amount of pressure applied .Both CPAP and BiPAP have been used as an alternative to intubation in patients with a variety of respiratory conditions, including congestive heart failure with pulmonary edema and COPD, avoiding the complications associated with endotracheal intubation. It improves numerous clinical outcomes and is the preferred method of ventilatory support in many patients with an acute exacerbation of COPD complicated by hypercapnic acidosis [5,6].

NIPPV has physiologic benefits. Respiratory mechanics measured after the initiation of NIPPV demonstrate a decreased respiratory rate, an increased tidal volume, and increased minute ventilation. In addition, the arterial oxygen tension (PaO2) tends to increase as the PaCO2 decreases. The pressure support level should be increased until patient's respiratory rate is below 30 breaths per min because this respiratory rate indicates that the inspiratory effort has been reduced to a reasonable level. However, the expiratory effort of patients with COPD may increase when the pressure support is increased, which makes selection of the optimal pressure support level difficult [7].

Flexible fiberoptic bronchoscopy (FOB) has become an indispensable tool in the optimal management of intensive care unit (ICU) patients with both diagnostic and therapeutic goals. Its safety and usefulness, in well-trained hands with appropriate precautions, have led to its increasing use even in unstable and mechanically ventilated patients. Currently, rigid bronchoscopes are not often used except for the management of massive hemoptysis, removal of tracheobronchial foreign bodies, laser photoresection for obstructing endobronchial tumours, dilatation of tracheobronchial strictures and placement of airway stents [8,9].

In bronchoalveolar lavage (BAL), the FOB is wedged into a subsegmental bronchus and multiple aliquots (20–50 ml) of saline are instilled into that lung segment and then withdrawn by suction. The centrifuged BAL fluid is stained for opportunistic pathogens and cultured. Although 200 ml was once considered the maximum, recent literature demonstrates that lavage volumes of up to 300 ml are well tolerated. Patients should not eat or drink anything 6–12 h before procedure. Also you to try avoid any aspirin, ibuprofen, or other blood-thinning drugs before procedure. After procedure, your gag reflex will return. However, until it does, patients should not eat or drink anything. To test if the gag reflex has returned, place a spoon on the back of your tongue for a few seconds with light pressure. If patient does not gag, wait 15 min and try it again [10].

So, the aim of this work is to assess the role of early fiberoptic bronchoscopy during non invasive ventilation in acute exacerbation of COPD patients in terms of effectiveness and safety.

Patients

This prospective case control study was carried out on 50 patients, suffering from hypercapneic acute respiratory failure as a result of acute exacerbation of chronic obstructive pul-

monary disease (COPD), receiving non invasive mechanical ventilation admitted consecutively to critical care units at Alexandria university main hospital.

Patients were divided into two groups:

- Group I (cases): 20 patients received conventional medical treatment plus early fiberoptic bronchoscopy during non invasive ventilation.
- Group II (controls): 20 patients received only conventional medical treatment and noninvasive ventilation.

The inclusion criteria

All COPD patients met all the following criteria while breathing oxygen via a venturi mask.

a) pH less than 7.33 and ($PaCO_2$) above 55 mmHg.
b) (PaO_2)/(FiO_2) ratio less than 200.
c) Dyspnea at rest with respiratory rate (RR) above 25 breaths/min.
d) Use of accessory respiratory muscles.
e) Mild hypercapneic encephalopathy Kelly Matthay score [11] between 2 & 4.
f) Inability to spontaneously clear airways from excessive secretions, as expressed by the lowest score of an arbitrary cough efficiency scale evaluated by the nurses on the basis of the volume of the expelled sputum after three hard coughing efforts (1 = less than 2 ml; 2 = between 2 and 6 ml and; 3 = more than6 ml).

Methods

Patients were divided into two groups:

- Group I (cases): 25 patients received medical treatment and early fiberoptic bronchoscopy within 12 h of starting non invasive ventilation.
- Group II (control): 25 patients received only medical treatment and non invasive ventilation.

Medical therapy

All patients received medical therapy consisting of:

1) Controlled oxygen therapy.
2) Nebulized bronchodilator (salbutamol and anticholinergic drugs).
3) Intravenous corticosteroids.
4) Antibiotic strategy was based on empirical intravenous administration of levofloxacin plus β-lactam (for penicillin-allergic patients: levofloxacin plus aztreonam or carbapenem), unless some risk factors for *Pseudomonas aeruginosa* were identified (ciprofloxacin plus anti-pseudomonal β-lactam). Antibiotic-therapy was later adjusted according to the results of bacterial cultures [12].
5) Subcutaneous low-molecular weight heparin; and therapy for comorbidities if necessary.
6) Anti stress ulcer.

Before fiberoptic bronchoscopy (FOB)

Non invasive ventilation was delivered in a pressure support (PS) mode with positive end-expiratory pressure (PEEP) or pressure controlled mode (BiPAP) via a well-fitting full-face mask with the addition of a heated humidifier [13]. PS or inspiratory positive airway pressure (IPAP) was initially set at 10 cm H_2O and then titrated up to achieve an expiratory tidal volume of 8–10 ml/kg and a respiratory rate below 25 breaths/min to a maximum of 25 cm H_2O depending on clinical and arterial blood gases (ABGs) response and patient tolerance. PEEP or expiratory positive airway pressure (EPAP) was always set at 5 up to 10 cm H_2O to achieve optimal ventilation and oxygenation. Back-up RR is set at a 14–18 breaths/min. FiO_2 was initially set at 0.50–0.60 then titrated down till reaching 0.30 or arterial oxygen saturation ranging between 90% and 92%. The time from initiation of NIV to the bronchoscopy procedure was recorded. Following bronchoscopy all patients remained on noninvasive ventilatory support for at least two hours.

During FOB bronchoscopy procedure

Before, during and after bronchoscopy, level of conscious, the electrocardiogram, arterial blood pressure, pulse oximeter and ventilatory parameters (FiO_2, ventilator mode, inspiratory and expiratory pressures, tidal volume, and respiratory rate) were continuously monitored. Arterial samples were drawn for blood gas analysis from the arterial line at baseline, before and 2 h after procedure. Ventilator settings were adjusted to optimize ventilatory support. The fraction of inspired oxygen (FiO_2) was increased to 100% just before and throughout the procedure. FOB was performed after the patients had adapted to NIPPV. A swivel connector (T-adapter) was inserted between the ventilator tubing and the mask to allow the insertion of the bronchoscope. Sedation was achieved in all cases using midazolam ranging from 2.5 mg up to 10 mg in incremental doses to achieve conscious sedation, before and after the insertion of the bronchoscope and can be repeated every three to five minutes according to patient tolerance. Topical anesthesia of the nasopharynx (10% lidocaine spray solution) and larynx (5 ml of 2% lidocaine hydrochloride were instilled via the bronchoscope channel to the laryngeal, tracheal and bronchial mucosa, not exceeding an overall dose of 200 mg) was performed before advancing the bronchoscope into the tracheobronchial tree. Firstly, a careful suction of bronchial secretions was performed to fully clear airways. Then, the tip of the FOB was wedged into the bronchial sub segment. Bronchoalveolar lavage (BAL) was performed by sequential instillation of five aliquots of 20 mL saline solution at room temperature. The retrieved fluid was sent immediately to the microbiology laboratory for microscopic analysis and culturing. The isolated bacteria with a count of 10^4 CFU/mL or more of the BAL fluid were considered as etiological agents of infection. The duration of bronchoscopy was defined as the time from insertion until removal of the bronchoscope from the tracheobronchial tree [14,15].

After FOB

After the bronchoscopic procedures, the FiO_2 decreased in order to maintain arterial oxygen saturation measured by the pulse oximetry (SpO_2) at 90–92%. Routine chest physiotherapy was done to facilitate expectoration. Electrocardiogram, SpO_2, and noninvasive blood pressure were monitored continuously. ABGs were sampled as follows: at baseline, before, and at the end of FBO; and subsequently as clinically indicated.

Weaning

NIPPV was applied continuously at least during the first 12–24 h. Once clinical status and ABGs had improved, NIPPV was administered intermittently with sessions lasting two to six hours three times daily. Then PS or IPAP was reduced progressively. NIPPV weaning was considered successful within three days of ventilation or more when all the following criteria are met for longer than 24 h while breathing with oxygen (FiO_2 0.28): pH above 7.35, SpO_2 above 90%, RR less than 20 breaths/min, fully conscious, efficient cough with a significant amount of sputum, radiographic improvement of chest infection and stable hemodynamic status [15].

Failure of NIPPV trial was considered if at least one of the following criteria for intubation was met: cardiac arrest or severe hemodynamic instability; respiratory arrest or gasping; and/or worsening of ABGs or worsening of sensorium level during NIPPV.

Comparison between the two groups of the study regarding the ABG data, the success of NIPPV in avoiding invasive mechanical ventilation, the duration of NIPPV, length of ICU stay and mortality were recorded and analyzed statistically using appropriate statistical tests.

Results

This comparative case control prospective study was conducted on 50 patients admitted to the Critical Care Medicine Department &Respiratory Intensive Care Unit in Alexandria Main University Hospital by acute exacerbation of chronic obstructive pulmonary disease (COPD) and fulfilling the criteria for application of non invasive positive pressure ventilation (NIPPV).

Patients were randomly assigned into two equal groups by allocated randomization:

- Group I (cases): 25 patients received conventional medical treatment plus early fiberoptic bronchoscopy during non invasive ventilation.
- Group II (controls): 25 patients received only conventional medical treatment and noninvasive ventilation.

Comparison between the two studied groups according to arterial blood gases at different periods

At admission, patients were initially managed with repeated sittings of bronchodilator nebulizer through a face mask with O2 flow 5–10 L/min, pH in group I ranged between 7.23 and 7.32 with a mean value of 7.27 ± 0.03 while in group II, pH ranged between 7.22 and 7.32 with a mean value of 7.28 ± 0.03 with no statistical difference between both groups (p 0.059). Six to twelve hours from admission during NIV (before Bronchoscopy), pH in group I ranged between 7.25 and 7.34 with a mean value of 7.30 ± 0.03 while in group II, pH ranged from 7.10 to 7.36 with a mean value of 7.29 ± 0.08 with no significant statistical difference between both groups (p 0.561). 8–14 h from admission during NIV (2 h after bronchoscopy in group I), Improvement of pH in group I ranged between 7.33 and 7.46 with a mean value of 7.38 ± 0.04 which was significantly better than values in group II, as pH ranged from 7.31 to 7.38 with a mean value of 7.36 ± 0.02 (p 0.015).

At admission on face mask with O2 flow 5–10 L/min, PCO2 in group I ranged between 64.0 and 92.0 mmHg with a mean value of 77.24 ± 08.42 mmHg while in group II, PCO2 ranged between 60.0 and 92.0 mmHg with a mean value of 72.76 ± 09.04 mmHg with no statistical difference between both groups (p 0.076). Six to twelve hours from admission during NIV (before bronchoscopy), PCO2 in group I ranged between 52.0 and 76.0 mmHg with a mean value of 70.12 ± 7.41 mmHg while in group II, PCO2 ranged from 52.0 to 112.0 mmHg with a mean value of 71.72 ± 16.43 mmHg with no significant statistical difference between both groups (p 0.659). 8–14 h from admission during NIV (2 h after bronchoscopy in group I), PCO2 in group I ranged between 40.0 and 67.0 mmHg with a mean value of 55.68 ± 7.76 mmHg while in group II, PCO2 ranged from 56.0 to 71.0 mmHg with a mean value of 63.63 ± 5.11 mmHg with significant statistical lower values of PCO2 in group I (p 0.001).

At admission on face mask with O2 flow 5–10 L/min, O2 index in group I ranged between 135.0 and 162.0 with a mean value of 149.64 ± 07.97 while in group II, O2 index ranged between 122.0 and 170.0 with a mean value of 147.64 ± 10.60 with no statistical difference between both groups (p 0.455). Six to twelve hours from admission during NIV (before bronchoscopy), O2 index in group I ranged between 140.0 and 205.5 with a mean value of 169.16 ± 19.51 while in group II, O2 index ranged from 72.0 to 227.0 with a mean value of 159.52 ± 53.98 with no significant statistical values between both groups (p 0.408). 8–14 h from admission during NIV (2 h after bronchoscopy in group I), O2 index in group I ranged between 180.0 and 300.0 with a mean value of 242.24 ± 039.27 while in group II, O2 index ranged from 190.0 to 245.0 with a mean value of 221.94 ± 17.61 with a significant statistical higher value in group I (p 0.030).

Incidence of complications during FOB

Few complications developed during FOB procedure. Desaturation of arterial blood (SaO2 less than 88%) displayed on the monitor occurred in 4/25 patients (16%). Increased heart rate more than 120 beats/minute occurred only in 2/25 cases (8%).

Ventilator settings before and after FOB among group I

Inspiratory positive airway pressure (IPAP) before FOB ranged between 15.0 and 22.0 cm H_2O with a mean value of 19.56 ± 2.08 while after FOB, it ranged between 10.0 and 20.0 with a mean value of 14.60 ± 3.48 with a significant statistical difference ($p < 0.001$). Expiratory positive airway pressure (EPAP) before FOB was ranging from 7.0 to 10.0 cm H_2O

Table 1 Neurologic status score.

Grade No.	Description
1	Alert, follows complex three-step command (i.e., take a sheet of paper, tear it into four pieces and place three pieces in one pile)
2	Alert, follows simple commands (show me two fingers)
3	Lethargic, but arousable and follows simple commands
4	Stuporous, i.e., only intermittently follow simple command even with vigorous attempts to arouse patient
5	Comatose, brain stem intact
6	Comatose with brain stem dysfunction

Table 2 Comparison between the two studied groups according to APACHE II score and Kelly Matthay score.

	Group I (n = 25)		Group II (n = 25)		p
	No.	%	No.	%	
APACHE II score					
Min.–Max.	7.0–21.0		11.0–20.0		0.432
Mean ± SD	15.24 ± 3.03		15.88 ± 2.67		
Median	16.0		15.0		
Kelly Matthay score					
2	7	28.0	8	32.0	–
3	16	64.0	13	52.0	
4	2	8.0	4	16.0	
Min.–Max.	2.0–4.0		2.0–4.0		0.825
Mean ± SD	2.80 ± 0.58		2.84 ± 0.69		
Median	3.0		3.0		

p: p value for Student t-test.

with a mean value of 7.60 ± 1.15 while after FOB, it was significantly less as it ranged between 5.0 and 7.0 with a mean value of 5.80 ± 1.0 ($p < 0.001$). Frequency before FOB was ranging between 20 and 25 breaths per minute with a mean value of 24.68 ± 1.14 which was significantly less after FOB, as it ranged between 12 and 22 with a mean value of 16.52 ± 2.25 ($p < 0.001$). Also fraction of inspired oxygen (FiO_2) showed a significant decrease after the bronchoscopy as it was ranging from 40% to 50% with a mean value of 42.40 ± 4.36 before FOB versus 35–40% with a mean value of 37.20 ± 2.53 after FOB ($p < 0.001$).

Outcome

Outcome was evaluated as regards success of weaning from NIV, total duration of NIV in succeeded cases, length of ICU stay, and mortality rate during hospitalization.

In group I, 23 cases (92%) have been successfully weaned from NIPPV while only 2 cases(8%) failed on NIPPV and intubated while in group II ,16 cases (64%) have been successfully weaned from NIPPV while 9 cases (36%) failed on NIPPV and intubated with a significant statistical difference in favor of group I ($p = 0.037$). Total duration of NIV in succeeded cases in group I ranged between15.0 and 48.0 h with a mean value of 28.52 ± 10.63 while in group II, it ranged from 24.0 to 96.0 h with a mean value of 56.25 ± 21.34 with a significant statistical value between both groups (p 0.001). As regards the length of Intensive care unit (ICU) stay in group I, it ranged between 2.0 and 25.0 days with a mean value of 4.84 ± 4.51 while in group II it ranged from 4.0 to 35.0 days with a mean value of 8.68 ± 7.18 with a significant statistical value between both groups (p 0.001). Only one case (4%) in group I died versus 3 cases (12%) in group II with no significant statistical value between both groups ($p = 0.609$).

Table 3 Comparison between the two studied groups according to PH at different periods of follow up.

	Group I (n = 25)	Group II (n = 25)	p
At admission (pre NIPPV)			
Min.–Max.	7.23–7.32	7.22–7.32	0.059
Mean ± SD	7.27 ± 0.03	7.28 ± 0.03	
Median	7.26	7.28	
6–12 h later During NIPPV (pre FOB)			
Min.–Max.	7.25–7.34	7.10–7.36	0.561
Mean ± SD	7.30 ± 0.03	7.29 ± 0.08	
Median	7.30	7.30	
8–14 h from admission (Post FOB in group I)			
Min.–Max.	7.33–7.46	7.31–7.38	< 0.001*
Mean ± SD	7.38 ± 0.04	7.33 ± 0.02	
Median	7.37	7.36	

p: p value for Student t-test *: Statistically significant at $p \leqslant 0.05$.

Table 4 Comparison between the two studied groups according to PCO_2 at different periods of follow up.

	Group I (n = 25)	Group II (n = 25)	p
At admission (pre NIPPV)			
Min.–Max.	64.0–92.0	60.0–92.0	0.552
Mean ± SD	74.24 ± 8.42	72.76 ± 9.04	
Median	76.0	71.0	
6–12 h later During NIPPV (pre FOB)			
Min.–Max.	52.0–76.0	52.0–112.0	0.659
Mean ± SD	70.12 ± 7.41	71.72 ± 16.43	
Median	69.0	69.0	
8–14 h from admission (Post FOB in group I)			
Min.–Max.	40.0–67.0	56.0–71.0	0.001*
Mean ± SD	55.68 ± 7.76	63.63 ± 5.11	
Median	56.0	63.50	

Table 5 Comparison between the two studied groups according to O2 index at different periods of follow up.

	Group I (n = 25)	Group II (n = 25)	p
At admission (pre NIPPV)			
Min.–Max.	135.0–162.0	122.0–170.0	0.455
Mean ± SD	149.64 ± 7.97	147.64 ± 10.60	
Median	150.0	147.0	
6–12 h later During NIPPV(pre FOB)			
Min.–Max.	140.0–205.0	72.0–227.0	0.408
Mean ± SD	169.16 ± 19.51	159.52 ± 53.98	
Median	167.0	175.0	
8–14 h from admission (Post FOB in group I)			
Min.–Max.	180.0–300.0	190.0–245.0	0.030*
Mean ± SD	242.24 ± 39.27	221.94 ± 17.61	
Median	243.0	221.0	

p: p value for Student t-test *: Statistically significant at $p \leqslant 0.05$.

Table 6 Incidence of complications during FOB.

	No.	%
Desaturation (SaO_2 < 88%)	4	16.0
Sinus tachycardia > 120 b/m	2	8.0
Gag and vomiting	0	0.0
Bronchospasm	0	0.0
Pneumothorax	0	0.0
Trauma	0	0.0
Fever	0	0.0

Table 7 Comparison between ventilator settings before and after FOB among group I.

	Before FOB	2 h after FOB	p
IPAP(PS above PEEP)			
Min.–Max.	15.0–22.0	10.0–20.0	< 0.001*
Mean ± SD	19.56 ± 2.08	14.60 ± 3.48	
Median	20.0	14.0	
EPAP			
Min.–Max.	7.0–10.0	5.0–7.0	< 0.001*
Mean ± SD	7.60 ± 1.15	5.80 ± 1.0	
Median	7.0	5.0	
RR			
Min.–Max.	20.0–25.0	12.0–22.0	< 0.001*
Mean ± SD	24.68 ± 1.14	16.52 ± 2.28	
Median	25.0	16.0	
FiO_2			
Min.–Max.	40.0–50.0	35.0–40.0	< 0.001*
Mean ± SD	42.40 ± 4.36	37.20 ± 2.53	
Median	40.0	35.0	

p: p value for Paired t-test *: Statistically significant at $p \leqslant 0.05$.

Table 8 Comparison between the two studied groups according to outcome.

	Group I (n = 25)		Group II (n = 25)		Test of sig.
	No.	%	No.	%	
Weaning					
Failed	2	8.0	9	36.0	FE p = 0.037*
Succeeded	23	92.0	16	64.0	
Total duration of NIV in succeeded cases (hours)					
Min.–Max.	15.0–48.0		24.0–96.0		p < 0.001*
Mean ± SD	28.52 ± 10.63		56.25 ± 21.34		
Median	26.0		48.0		
ICU stay (days)					
Min.–Max.	2.0–25.0		4.0–35.0		p < 0.001*
Mean ± SD	4.84 ± 4.51		8.68 ± 7.18		
Median	4.0		6.0		
Mortality during ICU stay					
Survived	24	96.0	22	88.0	FE p = 0.609
Died	1	4.0	3	12.0	

FE p: p value for Fisher Exact test.
p: p value for Mann Whitney test.
*: Statistically significant at $p \leqslant 0.05$.

Table 9 Distribution of the studied cases according to BAL bacteriology among group I.

	No.	%
BAL bacteriology		
No growth	14	56.0
Organism	11	44.0
Staph aureus	3	12
Pseudomonas	3	12
Candida	2	8
E. coli	1	4
Proteus	1	4
Klebsiella	1	4

BAL bacteriology results in group I

Bacteriological study of the BAL revealed no growth in 14/25 cases (56%) while 11/2 cases (44%) had positive findings. *Staphylococcus auerus* in 3 cases, *Pseudomonas aeuroginosa* was found in 3 cases while candida was found in 2 cases. *Escherichia coli*, Proteus, and Klebsiella were found only once in 3 different patients.

Discussion

Arterial blood gases' analysis showed an almost similar baseline pH with a mean value of 7.27 ± 0.03 in group I versus 7.28 ± 0.03 (p 0.059) in group II. Relative improvement in the pH was noticed in a similar pattern in both groups after the application of NIPPV (before bronchoscopy) as mean value of pH in group I improved to 7.30 ± 0.03 while in group II, the mean value became 7.29 ± 0.08 with no significant statistical difference between both groups ($p = 0.153$). Significant difference in pH was noticed in favor of group I after the bronchoscopy as the mean value of pH was 7.38 ± 0.04 which was significantly better than values in group II, as pH mean value was 7.33 ± 0.02 ($p = 0.015$). These changes in pH after the application of the bronchoscopy are comparable to the study done by Scala et al. [16] as pH was initially 7.27 improved to 7.29 after application to NIPPV, it remained 7.29 during bronchoscopy and improved significantly to 7.37 after bronchoscopy ($p < 0.05$). Scala et al.'s study was the first study performed to assess the role of FOB during NIPPV in patients with decompensated COPD while the main difference that the control group in that study was patients on invasive mechanical ventilation and community acquired pneumonia was the etiology of decompensation in both studied groups.

Similar changes were noticed in the PCO2 as the initial mean value in mmHg was 74.24 ± 8.42 improved to 70.12 ± 7.41 after application of NIPPV, with significant further improvement after the bronchoscopy to 55.68 ± 7.76 in group I while in group II the readings were 72.76 ± 9.04, 71.72 ± 16.43 and 63.63 ± 5.11, respectively. Significant difference was detected only in the third readings (after doing the bronchoscopy in group I and nearly at the same time in group II) with $p = 0.001^{*}$. Comparing these results with Scala et al.'s [16] results, we can observe a similarity in the two studies in the trend of PCO2 in mmHg as it was 76, 75 and 60 in the initial setting, during NIPPV and after fiberoptic bronchoscopy, respectively.

The Oxygenation index was low in both groups at the baseline with mean values of 149.64 ± 07.97 and 147.64 ± 10.60 in group I and II, respectively, and then it started to show some improvement in both groups after the application of the NIPPV. Significant improvement in oxygenation was seen in group I compared to group II after doing bronchoscopy in group I as the mean value was 242.24 ± 39.27 in group I versus 221.94 ± 17.61 in group II (p 0.030). The baseline readings are comparable to Scala et al.'s [16] study as it was 163 then increased to 211 during NIPPV, but in contrast to the present study PaO2/FiO2 dropped after bronchoscopy to 200. This can be explained by the different timing of sampling post bronchoscopy in the two studies as we preferred to postpone the sampling in the current study 2 h post bronchoscopy as long as no significant drop in oxygen saturation was recorded by oximetry to avoid recording the immediate relative desaturation which is expected after bronchoscopy which may mask the real improvement in oxygenation after clearing the secretions from the lung during bronchoalveolar lavage. Besides the etiology of decompensation in scala study was community acquired pneumonia while in my study was different factors including upper and lower respiratory tract infections, environmental factors, atopy, discontinuation of maintenance medical treatment, and another medical illness.

Considering the limited data on the application of FOB during NIPPV in COPD patients, it was very important to record the complications related to FOB in group I of the study to validate the safety of the procedure in this specific setting and compare it to overall rates of FBO related complications in other studies. Few complications developed during FOB procedure. Desaturation of arterial blood (SaO2 less than 88%) displayed on the monitor occurred in 4/25 patients (16%) but it was not clinically significant to prevent the completion of the procedure and it was temporary for few minutes and easily manageable through temporary increase in PS or IPAP on NIPPV and enhancing the procedure. Another complication was encountered in the form of increased heart rate more than 120 beats /minute which occur in only 2/25 cases (8%) and it was mostly related to the light sedation as it disappeared with the administration of extra doses of sedative drugs. However, no significant side effects as vomiting, cardiovascular events, pneumothorax and bronchospasm happened during the procedure. The lack of major complications is consistent with previous reports, which clearly demonstrated the feasibility and safety of FBO plus BAL performed under the assistance of NIPPV in patients with severe hypoxemic and hypercapnic ARF who should have to be otherwise intubated to allow such invasive procedures [17–21]. This was also in agreement with a feasibility study done by Hans Jörg Baumann et al. [22] to assess the safety of FOB in patients with acute hypoxemic respiratory failure requiring NIPPV, the average duration of bronchoscopy was 7.8 ± 5.5 min (range 3.5–37.0 min). In all cases bronchoscopy was completed without subsequent complications. Two patients developed transient SaO2 values below 90% during the procedure, the minimum SaO2 was 84% (Tables 1–6).

The application of FOB in group I patients provided an additional benefit apart from the drainage of copious secretions and clearing the airway which is the provision of early accurate sampling of tracheal and alveolar secretions for microbiological examination. This analysis was greatly helpful to reach an accurate diagnosis and started a targeted antibiotic

strategy guided by the culture and sensitivity results, while in group II, there was a real problem to get a good sputum sample from the lower airway not contaminated from the oral flora. Bacteriological study of the BAL obtained in group I of the study revealed no growth in 14/25 cases (56%) while 11/25 cases (44%) had positive findings. *Staphylococcus auerus* in 3 cases, *Pseudomonas aeuroginosa* was found in 3 cases while candida was found in 2 cases. *E. coli*, Proteus, Klebsiella were found only once in 3 different patients. Comparing our microbiological data with Scala et al. [16] study where the BAL results on 15 patients revealed *Streptococcus pneumonia* in 5 patients (33.3%), *Pseudomonas aeuroginosa* was found in 4 patients (26.7%) and *Staphylococcus auerus* in 2 cases (13.3%), we can notice that the same organisms were isolated from both studies with the only exception of the *Streptococcus pneumonia* which was not isolated from the current study although it is known to be the first causative organism for community acquired pneumonia and the second common organism in acute exacerbation after *Haemophilus influenza* bacteria. This finding might be explained as a high proportion of patients in the present study were initially admitted to the hospital in the medical wards and shifted to critical care areas after developing decompensated respiratory failure and they might have got gram negative hospital acquired infections during their stay in addition to the preceding intake of oral antibiotic before admission which may alter classical pattern of microorganisms.

Analysis of the NIPPV settings before and after the application of FOB showed significant improvement in all parameters after the procedure in the form of decrease in EPAP, IPAP, respiratory rate and FiO_2 (Table 7) with p value < 0.001 for all parameters. These findings demonstrate the clear benefit of the FOB as a synergetic tool with NIPPV to minimize the work of breathing and oxygen requirement which was subsequently reflected in the form of lower ventilator setting. This beneficial effect was mainly due to clearance of secretions and also due to recruiting the partially atelectatic alveoli by washing of mucous plugs.

In group II, 16 cases (64%) have been successfully weaned from NIPPV while 9 cases (36%) failed and required intubation and mechanical ventilation. Most of them failed due to accumulation of secretions with subsequent deterioration of the ABG findings and depressed consciousness level. Comparing this failure rate (36%) with another study also done by Raffaele Scala et al. [23] in 2005 on 80 patients with acute respiratory failure, NIPPV failed in 23 of 80 patients (28.8%) which is near to our study. In another study done by Carlucci A et al. [24] studying Noninvasive versus Conventional Mechanical Ventilation, 43 patients out of 108 patients (40% of all NIV patients) eventually required endotracheal intubation while in group I of the present study, the failure rate on NIPPV is significantly less than group II as only 2 patients failed out of 25 patients (8%). In Scala et al.'s [16] study which is the only study done to assess the effect of early FBO during NIPPV, the technique failed in 3 of 15 patients (20%). The discrepancy between the ratios in the two studies cannot be explained due to the small number of patients which make any statistical analysis or correlation unreliable. Besides the etiology of decompensation in scala study was community acquired pneumonia while in my study was different factors which were less medically serious than pneumonia. The total duration of NIV in succeeded cases in group I (23 patients) ranged between 15.0 and 48.0 h with a mean value of 28.52 ± 10.63 while in group II (16 patients), it ranged from 24.0 to 96.0 h with a mean value of 56.25 ± 21.34 with a significant statistical value between both groups (p 0.001) denoting the possible beneficial effect of FOB in facilitation of faster weaning after removing the secretions and improvement of blood gases. The duration of NIPPV in group II is more or less comparable to Raffaele Scala et al.'s [23] study as NPPV was delivered for a median duration of 40.75 h (21.63 to 73 h) (mean duration for the first day, 12.3 h [SD, 6.7 h]) for a median duration of 5.0 days. In another study done by Carlucci Aetal [24] the mean length of NIV according to the reason for mechanical ventilation was 6.3 days (range: 1–29 days) in hypoxemic ARF, 5.6 days (range: 1–24 days) in hypercapnic ARF, and 2.4 days (range: 1–6 days) in pulmonary edema (Tables 8 and 9).

The length of Intensive Care Unit (ICU) stay in group I was significantly shorter in group I compared to group II (p 0.001). This is explained by the faster improvement in patients of group I and less incidence of intubation and mechanical ventilation which definitely lead to the prolongation of ICU stay in group II .Comparing the length of ICU stay in group II where we apply NIPPV without FOB with another similar matching group of NIPPV in Carlucci A et al. [24] study, a high degree of similarity exists as the length of stay in the present study was ranging from 4.0 to 35.0 days with a mean value of 8.68 ± 7.18 days while it was $8.\ 6 \pm 6.3$ days in the NIPPV group in the other study.

Only one case (4%) in group I died versus 3 cases (12%) in group II with no significant statistical difference between both groups ($p = 0.609$). Comparing the mortality in group I to the mortality in Scala et al.'s [16] study, where 3 out of 15 patients (20%) died, it was found that it is much less in our study. This can be attributed to the etiology of decompensation in scala study was community acquired pneumonia while in my study was different factors less in severity. However, the interpretation of data in this limited number of patients is unreliable. The mortality in group II (12%) came in agreement with most of the studies applied on NIPPV for hypercapnic respiratory failure, as an example the mortality in Carlucci A et al. [24] study was 10% (5 out of 50 patients). Minor change in this percentage of mortality between different studies can be understood in the light of different levels of care and experience in different centers as well as different baseline characteristics of the studied groups of patients.

Finally, it is obvious that the application of FOB was safe and beneficial for patients in the present study in terms of outcome and also in reducing the economic burden of patient care by reducing the number of patients who need invasive mechanical ventilation as well as shorter stay in ICU. However, the selection of patients -managed by NIPPV in whom application of FBO will be beneficial remains a clinical decision to be done by the treating physician based on the overall clinical condition of the patient and his initial response to treatment on NIPPV and also the available resources and the skills of the physician in the provision of FOB with minimal risk of complications. With the application of more randomized clinical trials on the role of bronchoscopy in the setting of AHRF, a clear consensus and precise guidelines might develop in the future emphasizing its application as a standard of care during NIPPV.

The limitations of the study are related mainly to the limited sample size of 50 patients (25 cases and 25 controls). However, this can be explained by the difficult recruitment of

patients fulfilling the matching criteria to be involved in the study as the 50 patients were recruited over a period of 18 months, considering also the novelty of the research as it was the first time – to the best of our knowledge – to investigate the role of FBO during NIPPV in AECOPD patients as Scala et al.'s [16] study published in 2010 did not compare between two groups of patients of NIPPV as we did. The control group in Scala et al.'s [16] study was patients on invasive ventilation. We totally agree that this study was very important and a pioneer but we are claiming that our study design and objectives are more reasonable and the results we reached in our pilot study can be considered a preliminary cornerstone and starting point for further investigations in the same topic through a multicenter study to provide adequate sample size in a reasonable duration.

Another limitation is related to some technical difficulties in the early provision of FBO during the course of NIPPV as we were planning to do the procedure within the first 6 h from the patient admission. However, the unavailability of skilled personnel to do the bronchoscopy in a safe way in many times delayed the procedure to 2–6 h more than the initial plan, all patients who underwent bronchoscopy later than 12 h from admission were omitted from the study. In another study done by Hans Jörg et al. [22] on the role of the FOB in patients with acutehypoxemic respiratory failure requiring NIPPV the median duration of continuous NIV prior to bronchoscopy was 10.5 h.

The last considered limitation in the present study is the unavailability of the sedative drug dexmedetomidine (precedex) in the Egyptian market which would be definitely a better choice to provide adequate and safe sedation during FOB without compromising the respiration or cardiovascular stability of the patients. However, with the provision of titrated sedation of midazolam under the supervision of highly experienced intensivists, we were able to provide adequate sedation during bronchoscopy with no serious complications [25,26].

Conflict of interest

None.

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