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Giovanna Elisiana Carpagnano, Roberto Sabato, Donato Lacedonia, Raffaella Di Gioia, Valerio Saliani, Umberto Vincenzi, Maria Pia Foschino-Barbaro

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New non invasive ventilator strategy applied to COPD patients in acute ventilator failure

Giovanna Elisiana Carpagnano, Roberto Sabato, Donato Lacedonia, *Raffaella Di Gioia, Valerio Saliani, *Umberto Vincenzi, Maria Pia Foschino-Barbaro

Department of Medical and Surgical Sciences, Institute of Respiratory Diseases, University of Foggia – Italy, *Intermediate Intensive Respiratory Disease Unit, D'Avanzo Hospital, Foggia – Italy.

Address for correspondence and reprints:

Giovanna Elisiana Carpagnano

Department of Medical and Surgical Sciences, Institute of Respiratory Diseases, University of Foggia

71100 - Foggia, viale degli Aviatori

Tel. +39 (0)881 733084

Fax +39 (0)881 733040

E-mail: giovannaelisiana.carpagnano@unifg.it

Running title: Combined pressure ventilation in COPD

Abstract

Introduction: There is no evidence in the literature regarding the combined use of positive ventilation with negative ventilation. A recent study reported that the two techniques can be combined in patients with ARDS, who undergo ventilatory support for severe acute respiratory failure (ARF). There is experience of non-invasive ventilation in patients with chronic respiratory diseases and ARF.

The aim of this study was to test the efficacy of a non-invasive ventilatory strategy based on the combined use of negative (N) and positive ventilation (P) in bi-level mode (PN).

Methods: We enrolled 8 patients with severe COPD exacerbations and exacerbated chronic respiratory failure admitted in a monitored setting of an intermediate-intensive respiratory Unit.

Results: Patients underwent combined positive/negative ventilation and at different times, in place of the two singular ventilation modes (P and N).

After each cycle, in the combined P/N ventilatory mode, gas exchanges were significantly increased compared to the two singular P/N mode: pH (7.42 vs 7.40 and 7.40); PCO2 (85.01 vs 72.05 and 66.81 mmHg); FiO2/PO2 (488.75 vs 352.62 and 327.87).

All patients well tolerated the application of the double ventilation mode.

Conclusions: In conclusion, the use of dual mode ventilation appears well tolerated and superior to the individual modes in patients with COPD exacerbations and ARF.

Keywords: NIV, NPPV, ARDS, COPD.

List of abbreviations

ARDS: Acute Respiratory Distress Syndrome

NIV: Non-invasive Ventilation

COPD: Chronic Obstructive Pulmonary Disease

NPPV: Non-invasive Positive Pressure Ventilation

Bi-level PAP: Bi-level Positive Airway Pressure

ARF: Acute Respiratory Failure

CRF: Chronic Respiratory Failure

NPV: Negative Pressure Ventilation

PEEP: positive end expiratory pressure

PS: Pressure Support

PSV: Pressure Support Ventilation

PaO_2/FiO_2 (P/F)

$PaCO_2$: Carbon monoxide arterial partial pressure

Introduction

Non-invasive ventilation (NIV) refers to the administration of ventilatory support without using an invasive artificial airway (endotracheal tube or tracheostomy tube). The use of non-invasive ventilation has markedly increased over the past two decades, and non-invasive ventilation has now become an integral tool in the management of both acute and chronic respiratory failure. The key to the successful application of non-invasive ventilation is in recognizing its capabilities and limitations. This also requires identification of the appropriate patient and setting for the application of non-invasive ventilation (NIV). Non-invasive ventilation effectively unloads the respiratory muscles, increasing tidal volume, decreasing the respiratory rate, and decreasing the diaphragmatic work of breathing, which translates to an improvement in oxygenation, a reduction in hypercapnia, and an improvement in dyspnea[1].

Patients with underlying chronic obstructive pulmonary disease (COPD), who present acute respiratory failure (ARF), are the group most likely to be successfully treated with non-invasive ventilation (NIV) usually with positive pressure (NPPV). COPD is an ideal condition for non-invasive ventilation, given the rapid reversibility with treatment and added support that can be provided by non-invasive ventilation. Most of the experience with non-invasive ventilation has accrued with bi-level positive airway pressure (BiPAP). Although a variety of ventilatory modes are available in COPD in ARF, most centres now use bi-level positive airway pressure ventilation (Bi-level PAP), although many of the principles encompassed are applicable to other forms of NPPV.

Negative-pressure ventilation (NPV) can be defined as a type of ventilation in which the surface of the thorax is exposed to sub-atmospheric pressure (*i.e.* negative pressure) during inspiration. This sub-atmospheric pressure causes thoracic expansion and an expected decrease in pleural and alveolar pressures, thereby creating a pressure gradient for air to move from the airway opening into the alveoli. When the pressure surrounding the thorax increases and becomes atmospheric (or greater than atmospheric), expiration occurs passively owing to the elastic recoil of the lung and chest wall [2]. As with other modalities of non-invasive mechanical ventilation, the major advantage of NPV is the avoidance of endotracheal intubation and its related complications, while physiological functions are preserved, such as speech, coughing, swallowing and feeding. Moreover, therapeutic and diagnostic manoeuvres by fibre-optic bronchoscopy are easily performed during NPV [3]. Continuous external negative-pressure ventilation improves oxygenation under more physiological conditions with lower transpulmonary, airway, and intra-abdominal pressures than with NPPV [4, 5]. Studies of NPV have shown that COPD patients with severe respiratory acidosis, severe illness and hypercapnic encephalopathy may be successfully treated with this technique [6, 8].

A recent study reported that the positive and negative pressure ventilation can be combined advantageously in patients with acute respiratory stress disease, undergoing ventilatory support for severe acute respiratory failure. The aim of the study was to test the effectiveness of a new non-invasive therapeutic strategy, the combination of negative with positive pressure ventilation in the bilevel mode, in COPD patients with acute or chronic respiratory failure, in an intermediate intensive respiratory care-setting.

Methods

Patients and ventilatory strategies applied

We selected consecutively 8 COPD patients that came from the Emergency/Urgency Department (DEA) to the Intermediate Intensive Respiratory Disease Unit of the D'Avanzo Hospital of Foggia from October 2015 to February 2016. All COPD patients enrolled showed heart failure and chronic global respiratory failure exacerbation at enrollment. All patients were on long term domiciliary oxygen therapy for chronic lung failure. We excluded patients with OSAS, emphysema, and asthma. All subjects enrolled accepted to undergo the new combined ventilatory strategy proposed.

The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients signed an informed consent before being subjected to different procedures, and the study was approved by our Institutional Ethics Committee of Foggia.

Each patient underwent the following NIV cycles: positive-negative ventilation, positive pressure ventilation, negative pressure ventilation. A basic arterial blood gas analysis was performed before each ventilatory mode with or without the addition of oxygen flow, and then they underwent non-invasive mechanical ventilation for one hour after which the blood gas analysis was repeated. The three ventilation modes were performed at a later time with at least a three hour time interval. All patients were treated with medical therapy according to the lung diseases and oxygen therapy for lung failure.

Positive pressure ventilation: was performed with a Multilevel fan (DIMA-ITALY) in Bi-level mode with the following parameters: IPAP (between 18 to 28 cm H_2O in order to generate a tidal volume of 6-7 ml/kg); EPAP (4 to 6 cm H_2O); a respiratory rate of 18 breaths per minute and ventilatory support set to assisted /controlled. Negative pressure ventilation: was performed using the PEGASO fan (DIMA-ITALY) by means of an armor that creates a ventilation room around the chest and provided with a soft sheath so as to ensure maximum comfort for the patient and to ensure low losses. A negative pressure mode or intermittent negative inspiratory and passive expiratory modes were used for all patients. The inspiratory pressure value applied to all patients was equal to

-33 cm H_2O except for the I.F. patient, suffering from COPD syndrome and obesity, which was set to a value equal to -38 cm H_2O. Ventilation at positive and negative pressure was achieved, simply, by subjecting the patients at the same time to both ventilatory modes indicated (Figure 1). The fans at positive and negative pressure were connected to each other so as to operate in a synchronous manner and by means of the bi-level, either by creating a negative pressure around the chest through the armor, while during exhalation the bi-level continued to provide a positive pressure of lower entity than that of the inspiratory negative pressure.

Figure 1: Patient in double positive - negative ventilation.

Statistical analysis

The paired t-test was used for comparison of the results between the two groups with different NIV (non-invasive mechanical ventilation); the values were expressed as mean +/- standard deviation.

Results

Anthropometric, clinical and functional characteristics of patients are summarized in Table 1.

Patients n	**8**
Age (Years)	74±8.6
Male/female	6/2
BMI	27±1.7
Lung diseases:	
COPD	6
COPD/PF	1
COPD/OBESITY	1
Lung function:	
FEV1	50±5
FVC	73±6
FEV1/FVC	67.5±3
ABA	
pH	7.31 ± 0.05
$PaCO_2$ mmHg	85.01 ± 12.25
PaO_2 mmHg	64.2 ± 15.78
HCO_3^-	36.45 ± 2.87
Ventilatory strategy	Positive+Negative

Table 1: Patients' characteristics

All patients underwent combined positive and negative pressure ventilation without any side effects. All reported good tolerance to the new strategy after intervention.

To evaluate the effectiveness of the new ventilatory intervention of combined positive and negative pressure we analysed the pH, the $PaCO_2$ and FiO_2/PaO_2 before (T0) and after each NIV cycle (T1). We found a significant increase of pH after the positive-negative ventilation (PN) (pH To vs T1: 7.31 vs 7.42, p= 0.0008) compared to positive ventilation (P) (pH To vs T: 7.38 vs 7.40, p= NS) and negative (N) (pH T0 vs T1: 7.36 vs 7.40, p= NS) (Figure 2).

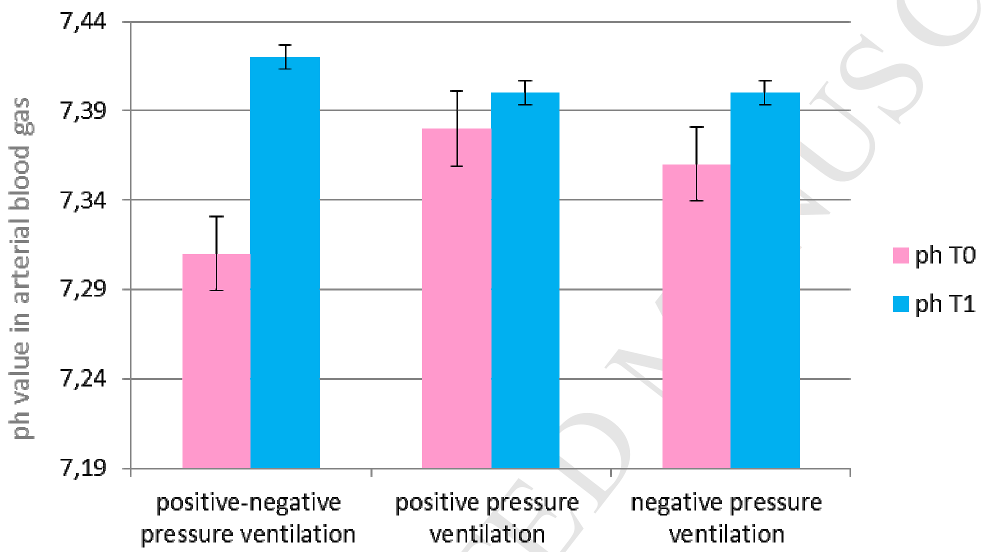

Figure 2: pH values before and after each cycle NIV.

As regards the $PaCO_2$, we observed a reduction after each ventilation cycle, but the reduction was greater after the positive-negative-pressure ventilation (PN), ($PaCO_2$ T0 vs T1: 85.01 vs 61.93 mmHg, p= 0.002) compared to the positive pressure ventilation (P) ($PaCO_2$ T0 vs T1: 72.05 vs 66.81 mmHg, p= 0.02) and to the negative one (N) ($PaCO_2$ T0 vs T1: 71.90 vs 71.53 mmHg, p= NS).

Similarly the reduction of $PaCO_2$ with the double NIV was statistically significant compared to that obtained with the negative ventilation, while there was only a trend toward a reduction when compared with the positive ventilation: ($PaCO_2$-PN vs N: 61.93 vs 71.53 mmHg, p= 0.01; $PaCO_2$-PN vs P: 61.93 vs 66.8 mmHg, p= 0.03), (Figure 3).

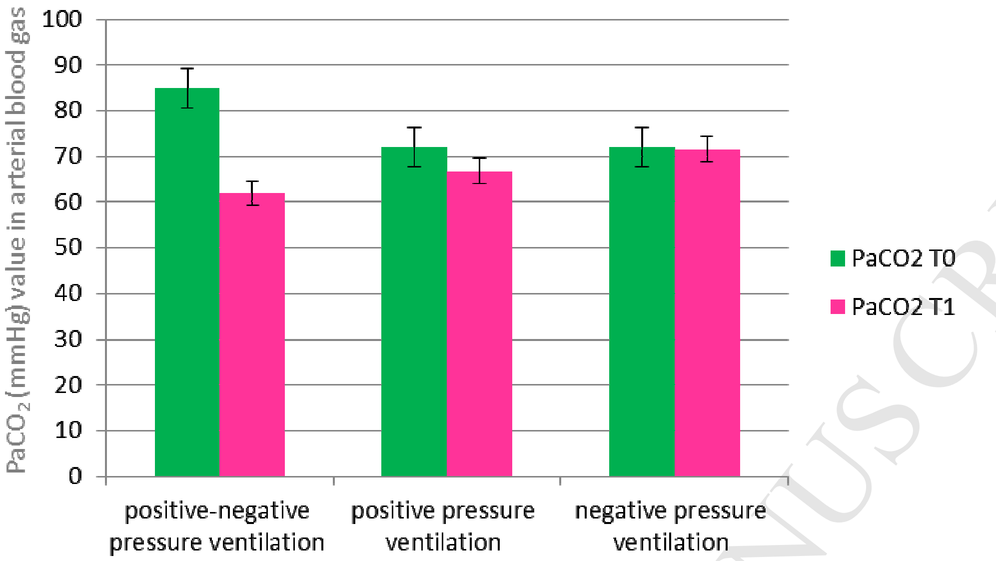

Figure 3: $PaCO_2$ values before and after each cycle NIV.

The application of each cycle NIV led to an increase in PaO_2/FiO_2 ratio (T1) from baseline (T0) that was higher with double ventilation: (PaO_2/FiO_2 PN T0 vs T1: 354.62 vs 488.75, p= NS) compared to positive pressure ventilation (PaO_2/FiO_2 P T0 vs T1: 337.12 vs 352.62, p= NS) and the negative one (PaO_2/FiO_2 N T0 vs T1: 346.75 vs 327.87, p= NS) (Figure 4).

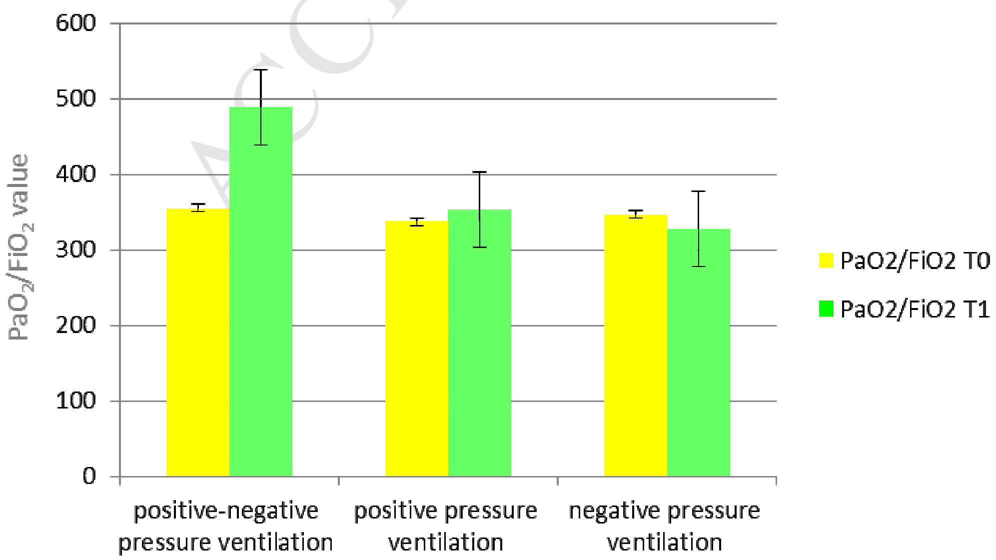

Figure 4: PaO_2/FiO_2 values before and after each cycle NIV.

Discussion

In this study we tested the possibility of effectively applying a double non-ventilation, as an innovative ventilatory strategy, in patients affected by COPD with severe acute or chronic respiratory failure.

We found that combined positive and negative pressure ventilation significantly improves arterial blood gases exchange determining a significant increase of pH, a reduction of $PaCO_2$, and an increment of the PaO_2/FiO_2 ratio compared to NIV with singular positive pressure or negative pressure.

The non-invasive positive pressure ventilation (NPPV) is still the standard treatment method for COPD patients with respiratory failure and excessive respiratory load, although several studies have shown that it can aggravate lung injury bringing to multi organ failure. This damage, called ventilator-induced lung injury (VILI), depends on several mechanisms including the cyclical alternation of distension and alveolar collapse associated with the tidal breathing generated by the fan. The damage from over-distension, or "volutrauma", is caused by an excessive end-inspiratory alveolar volume. It results from excessive stress at the end of inspiration, where for stress we mean the force applied to the alveolar walls at the end of inspiration, presumably due to an excessive transpulmonary pressure. It consists of damage to the epithelial and lung capillaries with the passage of fluids at the alveolar level. The "atelectrauma" is instead caused by the repeated opening and closing of alveolar units at end expiration, presumably induced from positive end-expiratory pressure (PEEP) inadequate to prevent the closure of alveolar units. The positive pressure ventilation could then force the opening of some alveoli collapsing during expiration, this leads to damage of the alveolar surfactant with impaired permeability of the alveolar-capillary membrane that facilitate the passage of the abnormal protein and solutes. Finally, mechanical damage would lead to the release of biological mediators that can further damage the lungs and the other organs. This type of damage has been defined biotrauma [9].

The positive pressure ventilation has however also a “protective” effect limiting the stress: it reduces the current volume reducing the force acting on the alveoli. Furthermore, the positive pressure ventilation significantly reduces the still high mortality rate for lung failure in COPD [10].

Decades ago negative pressure ventilation was widely used to improve oxygenation under more physiological conditions. This type of ventilation does not interfere with the cardiovascular system and does not appear devoid of disadvantages: it is allowed in patient “non-responders”, patients with ab-ingestis, with possible anatomical incompatibilities, obesity, or in need of much nursing assistance Sauret et al. tested NPV in acute hypercapnic respiratory failure due to intercurrent bronchial infection and showed, 1 h after the end of NPV, a better degree of oxygenation compared to that observed at baseline, while the improvement of $PaCO_2$ and pH obtained during NPV remained unchanged [11]. Also Gorini et al. reported that NPV is able to improve ventilatory patterns and arterial blood gases and to unload inspiratory muscles in patients with acute exacerbation of COPD [12]. Furthermore several studies demonstrated that the treatment of COPD patients by NPV might improve survival [13]. Although both NIV with positive and negative ventilation have several advantages in the managing of respiratory failure in COPD, no one, except in a case report of a man that developed ARDS after abscess drainage, investigated the possibility to use combined double pressure ventilation in a clinical setting. This new ventilatory strategy procedure cannot be easily managed in an ordinary Respiratory Unit, but requires an adequate location in an Intermediate Intensive Respiratory Disease Unit, medical / nursing staff and monitoring resources [14], and the eventual intubation (or invasive treatment) in the ICU on failure.

With this study we tried to achieve a new and effective therapeutic strategy in the field of non-invasive ventilation; carrying out a positive-negative pressure ventilation, respectively, then positive pressure ventilation and finally negative pressure ventilation. We showed that the separate use of positive and negative pressure ventilation in the same patient did not have substantial differences in terms of arterial blood gas analysis. The combined use of the negative and positive pressure ventilation was instead able to recruit and ensure effective lung volume, as indicated by the persistent better oxygenation in all cases studied with PaO_2/FiO_2 ratio at values higher than 350 mmHg.

These effects can be obtained from the complementary effects of the combined ventilation that act determining the distension of the lungs more effectively, maintaining lung volumes and acting, on a wide thoracic abdominal surface.

During the negative pressure ventilation substantially different pressure gradients were developed in the pleura compared to those with positive pressure ventilation. In addition, the pulmonary trans pressures (TPP: alveolar pressure less esophageal pressure), involved in both modes of ventilation, should be cumulative when the negative pressure ventilation is associated with the positive pressure. Furthermore, the distribution of ventilation is much more effective with this combination, resulting in alveolar recruitment and stabilization of lung volume, even in the most severe cases; these effects are likely to have contributed to the favorable result in terms of improving arterial blood gas parameters with an important reduction of hypercapnia, best oxygenation and gas exchange.

The main limit of this study is the small population. However, this is only a preliminary study where we aimed to test, for the first time in a clinical context the efficacy of the combined positive/negative ventilation. We are planning a new, larger study where we will also enroll COPD patients without long term domiciliary oxygen.

Furthermore, another limitation of this study is represented by the occasional inability to provide adequate PS + PEEP to ensure an acceptable oxygenation to patients with critical acute respiratory failure, independently from the flow and concentration of additional oxygen.

Conclusions

The present study shows that this new ventilatory technique can be used successfully in patients with excessive respiratory load and acute respiratory failure secondary COPD demonstrating clinical positive effect of the combined positive/negative pressure NIV and supporting it as a new therapeutic option that can influence the quality of life of patients and their prognosis.

We believe that this new ventilator strategy, whether it will be confirmed in terms of efficacy on a larger and selected COPD population with acute/chronic respiratory failure, could be proposed in an intermedium/ semi intensive ward based setting .

This is only a preliminary study where we tested patients with acute/chronic lung failure but we know that this approach could be very interesting in an emergency setting in ARDS patients that can benefit more from this new ventilatory strategy.

Therefore, in consideration of positive preliminary results, we are now planning a new study where we aim to explore the clinical utility of double positive-negative ventilation in a larger group of patients with chronic lung diseases and in a group of patients with acute lung failure. In this new study we will apply different ventilator strategies starting in a group of patients with positive pressure and in the parallel one with negative pressure and then comparing between parallel groups. With this strategy we aim to avoid that the positive critical effect of the first 4 hours of treatment for pH changes could influence the efficacy of one or the other ventilator mode.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

GEC and RDG designed the study, collected data, analysed data, wrote the manuscript. DL and VS analysed data and did statistical analysis. RS, UV and MPFB contributed to critical review and final approval of the manuscript. All authors read and approved the final manuscript.

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