Physiologic Effects of Negative Pressure Ventilation in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

MASSIMO GORINI, ANTONIO CORRADO, GIUSEPPE VILLELLA, ROBERTA GINANNI, ANNIKE AUGUSTYNEN, and DONATELLA TOZZI

Respiratory Intensive Care Unit, Careggi Hospital, Florence, Italy

To assess the physiologic effects of continuous negative expiratory pressure (CNEP), negative pressure ventilation (NPV), and negative expiratory end-expiratory pressure (NEEP) added to NPV in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), we measured in seven patients ventilatory pattern, arterial blood gases, respiratory mechanics, and pressure-time product of the diaphragm (PTPdi) under four conditions: (1) spontaneous breathing (SB); (2) CNEP (−5 cm H₂O); (3) NPV (4) NPV plus NEEP. CNEP and NEEP pressures were provided by a microprocessor-based iron lung capable of thermistor-triggering. Compared with SB, CNEP improved slightly but significantly Paco₂ and pH, and decreased PTPdi (388 ± 59 versus 302 ± 43 cm H₂O s, respectively, p < 0.05) and dynamic intrinsic positive end-expiratory pressure (PEEPi) (4.6 ± 0.5 versus 2.1 ± 0.3 cm H₂O, respectively, p < 0.001). NPV increased minute ventilation (Ve), improved arterial blood gases, and decreased PTPdi to 34% of value during SB (p < 0.001). NEEP added to NPV further slightly decreased PTPdi and improved patient-ventilator interaction by reducing dynamic PEEPi and nontriggering inspiratory efforts. We conclude that CNEP and NPV, provided by microprocessor-based iron lung, are able to improve ventilatory pattern and arterial blood gases, and to unload inspiratory muscles in patients with acute exacerbation of COPD.

Randomized controlled trials have clearly shown that, compared with standard medical treatment, noninvasive positive pressure ventilation reduces the need of endotracheal intubation (1–3) and hospital mortality (1–4) in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). Noninvasive positive pressure ventilation, however, is not without its problems, and failure rates of 7 to 50% have been reported (5). Severe respiratory acidosis (6) and illness at presentation (6, 7), excessive airway secretions (7), and inability to minimize the amount of air leakage (7) are major factors associated with failure of noninvasive positive pressure ventilation. Noninvasive mechanical ventilation can also be provided by negative pressure ventilators (8), and some recent studies suggest that negative pressure ventilation (NPV) provided by iron lung can be successful in patients with severe acute respiratory failure due to COPD (9, 10). Negative pressure ventilators, however, are not widely used for several reasons (11), including the paucity of data on the physiologic effects of NPV in patients with acute exacerbations of COPD. Although many studies have investigated ventilation, gas exchange, and respiratory muscle function during NPV in patients with stable COPD (12–17), to our knowledge, data on the effects of different types of NPV on respiratory muscle effort in patients with acute exacerbations of COPD are lacking.

Thus, the present studies were undertaken to investigate whether the application of continuous negative expiratory pressure (CNEP), NPV, and negative expiratory end-expiratory pressure (NEEP) added to NPV could improve ventilatory pattern and arterial blood gases, and unload inspiratory muscles in patients with acute respiratory failure due to COPD.

METHODS

Seven male patients with severe COPD treated with NPV for acute on chronic respiratory failure were studied within 72 h of admission to Respiratory Intensive Care Unit. All subjects gave informed consent to the procedures as approved by the human studies committee of our institution. Airflow was measured with a no. 2 Fleisch pneumotachograph (Guerra, Florence, Italy) connected to a face mask, and a Validyne pressure transducer (Validyne Corp., Northridge, CA), and flow signal was integrated into volume (18).

Mouth pressure (Pm) and tank pressure (Ptank) were measured using differential pressure transducers (Validyne). Total lung resistance (26) and dynamic lung compliance (Cdyn) were measured, and changes in the end-expiratory lung volume (EELV) were obtained as the product of Cdyn and change in end-expiratory volume (27, 28). In three patients surface electromyographic activity of parasternal muscles (Eps) was recorded and processed, as previously described (29).

NPV was provided by a microprocessor-based iron lung (Coppa, Biella, Italy) with wide flexibility in setting pressures and timing, and capable of providing CNEP and assist/control NPV by using a thermistor triggering. All signals were acquired at 100 Hz, using an analog/digital data acquisition system, and stored in a personal computer for analysis.

Subjects were studied in supine position, enclosed in the tank ventilator with an airtight facial mask (Gibeck Respiration AB, Upplands-Vasby, Sweden). The thermistor triggering was placed at the free way line of the pneumotachograph connected to the face mask. The level of negative pressure (ranging from −15 to −25 cm H₂O) had previously been titrated by the attending physician. The backup frequency was set at 6 cycles/min such that every breath was subject-initiated, and trigger sensitivity was set at 75 to 80% of maximum. Oxygen administration was maintained constant throughout the study.

Data were recorded during a 10-min period in control condition, i.e., while the subject breathed spontaneously (SB) through the face mask with iron lung off. Three trials were performed afterward randomly in each subject: (1) application of CNEP (−5 cm H₂O); (2) application of NPV; (3) application of −5 cm H₂O negative expiratory end-expiratory pressure during NPV (NPV-NEEP). Between each experimental condition the patients returned to SB for 15 min. Data were recorded during a 5-min period after a 20-min period in each experimental condition. Mean values of variables were com-

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Correspondence and requests for reprints should be addressed to Dr. Massimo Gorini, UTIIP-Fisioterapia Toracica, Careggi Hospital, Villa D’Ognaissanti, Viale Pieraccini, 24, 50134 Firenze, Italy. E-mail: mgorini@qbisoft.it

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pared with analysis of variance for repeated measures, and Scheffé test of multiple comparisons when appropriate. A p value of \( < 0.05 \) was considered statistically significant. Results are presented as mean \( \pm \) SE. For additional information on patient characteristics and experimental methodology, see the online data supplement.

RESULTS

The effects of the application of CNEP, NPV, and NEEP added to NPV in a representative patient are shown in Figure 1. Continuous negative extrathoracic pressure caused an improvement in ventilatory pattern, with increase in tidal volume (\( V_t \)) and decrease in respiratory frequency (\( f \)), without substantial change in transdiaphragmatic pressure swing. NPV resulted in a further increase in \( V_t \) associated with a marked decrease in inspiratory volume without any change in minute ventilation (\( V_e \)) (Table 1). In contrast, NPV caused a significant increase in \( V_e \), which was essentially the result of a further increase in \( V_t \). The ventilatory pattern did not change with NEEP added to NPV (Table 1). Dynamic PEEPi did not change significantly during NPV compared with SB, but it was significantly reduced both during CNEP compared with SB, and during NPV-NEEP compared with NPV (Table 1). Changes in EELV throughout the experimental procedures were small and not significant (Table 1). As shown in Table 2, Pa\(_{CO_2}\) and pH improved slightly but significantly with CNEP compared with SB, and they further improved with the application of NPV. Furthermore, NPV caused a significant increase in Pa\(_{O_2}\) compared with both CNEP and SB. There was no further change in arterial blood gases when NEEP was added to NPV (Table 2).

PTPdi/br did not change during CNEP compared with SB, but it decreased markedly during NPV (\( p < 0.0001 \)) (Table 1). PTPdi/min, however, decreased progressively with CNEP and NPV compared with SB (Table 1). As a mean, the reduction in PTPdi/min was 21.8 (\( p < 0.05 \)) and 66.3% (\( p < 0.001 \)) during CNEP and NPV, respectively. The association of NEEP to NPV resulted in slight, nonsignificant, reduction in both PTPdi/br (14.3%) and PTPdi/min (16.9%) compared with NPV alone (Table 1). In the three patients studied, changes in peak (Eps) and rate of rise (Eps/Ti) of electromyographic activity of parasternal muscles had a trend similar to those observed for the indexes of diaphragm effort (Table 1).

Nontriggering inspiratory efforts, defined as inspiratory attempts (decrease in pleural pressure [Ppl]$^-$1 cm H\(_2\)O with simultaneous change in flow) that failed to start an assisted breath, were observed in five of the seven patients during NPV (Figure 2). Compared with NPV alone, the association of NEEP with NPV resulted in a significant decrease in nontriggering inspiratory efforts (6.8 \( \pm \) 1.1% of total breaths versus 4.1 \( \pm \) 0.2%, respectively, \( p < 0.05 \)).

DISCUSSION

This is the first physiologic study to evaluate the effects of different types of NPV provided by a microprocessor-based iron lung in patients with acute exacerbation of COPD. The main findings can be summarized as follows: (1) compared with SB, the application of CNEP resulted in slight improvement in arterial blood gases associated with significant decrease in dynamic PEEPi and inspiratory muscle effort; (2) NPV caused significant improvement in ventilatory pattern associated with

### Table 1. Breath Components, Lung Mechanics, Pressure–Time Product of the Diaphragm, and Electromyographic Activity of Parasternal Muscles during Spontaneous Breathing and Different Types of NPV\(^*\)

<table>
<thead>
<tr>
<th></th>
<th>SB</th>
<th>CNEP</th>
<th>NPV</th>
<th>NPV - NEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_t ), L/min</td>
<td>7.41 ( \pm ) 0.14</td>
<td>7.49 ( \pm ) 0.25</td>
<td>8.49 ( \pm ) 0.62(^\dagger)</td>
<td>9.00 ( \pm ) 0.55(^\dagger)</td>
</tr>
<tr>
<td>( V_t ), L</td>
<td>0.39 ( \pm ) 0.01</td>
<td>0.50 ( \pm ) 0.03</td>
<td>0.62 ( \pm ) 0.06(^\dagger)</td>
<td>0.64 ( \pm ) 0.05(^\dagger)</td>
</tr>
<tr>
<td>T/f/Ttot</td>
<td>18.9 ( \pm ) 0.6</td>
<td>15.1 ( \pm ) 0.9(^\dagger)</td>
<td>14.6 ( \pm ) 0.9(^\dagger)</td>
<td>14.4 ( \pm ) 1.0(^\dagger)</td>
</tr>
<tr>
<td>PTPdi/br, cm H(_2)O</td>
<td>0.31 ( \pm ) 0.02</td>
<td>0.32 ( \pm ) 0.02</td>
<td>0.33 ( \pm ) 0.02</td>
<td>0.35 ( \pm ) 0.02</td>
</tr>
<tr>
<td>PTPdi/min, cm H(_2)O ( \cdot ) s</td>
<td>0.40 ( \pm ) 0.02</td>
<td>0.40 ( \pm ) 0.02</td>
<td>0.46 ( \pm ) 0.04</td>
<td>0.43 ( \pm ) 0.03</td>
</tr>
<tr>
<td>PEEPi dyn, cm H(_2)O</td>
<td>4.6 ( \pm ) 0.5</td>
<td>2.1 ( \pm ) 0.3(^\dagger)</td>
<td>4.1 ( \pm ) 0.4</td>
<td>2.2 ( \pm ) 0.3(^\dagger)</td>
</tr>
<tr>
<td>R(_e), cm H(_2)O/L/s</td>
<td>25.2 ( \pm ) 3.2</td>
<td>25.1 ( \pm ) 3.1</td>
<td>24.6 ( \pm ) 3.4</td>
<td>24.9 ( \pm ) 3.2</td>
</tr>
<tr>
<td>SELVL, L</td>
<td>0.10 ( \pm ) 0.05</td>
<td>0.10 ( \pm ) 0.05</td>
<td>0.07 ( \pm ) 0.03</td>
<td>0.05 ( \pm ) 0.06</td>
</tr>
<tr>
<td>PTPdi/br, cm H(_2)O</td>
<td>20.7 ( \pm ) 2.7</td>
<td>20.5 ( \pm ) 2.6</td>
<td>9.1 ( \pm ) 1.5(^\dagger)</td>
<td>7.8 ( \pm ) 1.2(^\dagger)</td>
</tr>
<tr>
<td>PTPdi/min, cm H(_2)O ( \cdot ) s/min</td>
<td>386 ( \pm ) 59</td>
<td>302 ( \pm ) 44(^\dagger)</td>
<td>130 ( \pm ) 23(^\dagger)</td>
<td>108 ( \pm ) 15(^\dagger)</td>
</tr>
<tr>
<td>Eps, % SB</td>
<td>100 ( \pm ) 0</td>
<td>91.3 ( \pm ) 2.2</td>
<td>53.3 ( \pm ) 4.3(^\dagger)</td>
<td>48.1 ( \pm ) 3.8(^\dagger)</td>
</tr>
<tr>
<td>Eps/Ti, % SB</td>
<td>100 ( \pm ) 0</td>
<td>72.3 ( \pm ) 1.0(^\dagger)</td>
<td>36.7 ( \pm ) 1.0(^\dagger)</td>
<td>29.7 ( \pm ) 1.9(^\dagger)</td>
</tr>
</tbody>
</table>

\(^\dagger\) Data recorded in three patients.

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**Definition of abbreviations:** \( \triangle EELV \) = change in end-expiratory lung volume compared with SB; Eps and Eps/Ti = peak and rate of rise of electromyographic activity of parasternal muscles, respectively; PEEPi dyn = dynamic intrinsic positive end-expiratory alveolar pressure; R\(_e\) = total lung resistance; SB = spontaneous breathing; Ti/Ttot = fractional inspiratory time; \( V_t/Ti \) = mean inspiratory flow.

\(^*\) Values are expressed as mean \( \pm \) SE.

\(^\dagger\) \( p < 0.05 \), treatment versus SB.

\(^\ddagger\) \( p < 0.001 \), treatment versus SB.

\(^\dagger\) \( p < 0.001 \), treatment versus SB.

\(^\dagger\dagger\) Data recorded in three patients.
Further improvement in arterial blood gases and marked reduction in inspiratory muscle effort; (3) NEEP added to NPV improved patient–ventilator interaction, reducing dynamic PEEPi and nontriggering inspiratory efforts.

In the present study the effects of different types of NPV on inspiratory muscle function were analyzed by measuring Pdi and PTPdi. In line with several studies on the physiologic effects of both positive (17, 21, 30–33) and negative (15, 17) pressure ventilation, PTPdi was used as an index of inspiratory muscle effort because it has been found to be correlated with the oxygen consumption of respiratory muscles (34, 35). Furthermore, it has been shown in normal subjects and patients with stable COPD that there is a significant relationship between changes in PTPdi and electromyographic activity of diaphragm during both positive and negative pressure ventilation, and that this relationship is similar with the two ventilatory techniques (17). This suggests clearly that during both positive and negative pressure ventilation changes in PTPdi really reflect changes in diaphragm activation. Finally, the present data showing that changes in electromyographic activity of parasternal muscles (measured in three patients) had a trend similar to that observed for PTPdi indicate that NPV is able to unload both diaaphragm and rib-cage inspiratory muscles.

In patients with acute exacerbation of COPD, PEEPi and dynamic hyperinflation due to expiratory flow limitation are frequently observed (36–38). During spontaneous breathing PEEPi acts as an inspiratory threshold load which must be fully counterbalanced by the inspiratory muscles before starting to produce inspiratory flow and volume. Furthermore, during assisted modes of mechanical ventilation PEEPi increases the magnitude of the inspiratory effort required to trigger the ventilator (39), contributing to patient discomfort and patient–ventilator asynchrony (40, 41). In patients with acute exacerbations of COPD the application of low levels of continuous positive airway pressure (CPAP), during spontaneous breathing, and external PEEP, during positive pressure ventilation, can substantially unload the inspiratory muscles by offsetting most of PEEPi, without creating further hyperinflation (30, 31). Although from theoretical predictions similar physiologic effects on respiratory mechanics should be obtained with the application of CNEP during spontaneous breathing and NEEP during NPV, to our knowledge, no previous studies have investigated this issue. The present study provides evidence that in patients with acute respiratory failure due to COPD, −5 cm H2O of CNEP counterbalanced dynamic PEEPi and reduced inspiratory muscle effort without causing significant pulmonary hyperinflation, as previously shown with low levels of CPAP (30, 31). Furthermore, we found that CNEP was able to improve slightly but significantly PaCO2 and pH. This effect on arterial blood gases was probably explained by the improvement in ventilatory pattern during the application of CNEP that could result in increased alveolar ventilation.

An important finding of the present study was that NPV, provided in assisted mode by a microprocessor-based iron lung, was able to improve Ve and arterial blood gases, and to unload markedly the inspiratory muscles in patients with acute exacerbation of COPD. The present data extend the results of previous studies showing that NPV improved Ve and arterial blood gases (13, 15), and decreased electromyographic activity of diafragm (12, 14–16) and PTPdi (15, 17) in patients with stable COPD. Belman and coworkers have compared the effects of noninvasive positive pressure ventilation, provided in control mode by a volume-cycled ventilator, and NPV, provided in control mode by a poncho-wrap ventilator, in normal subjects and patients with stable COPD (17). They found that several indexes of diafragm effort, electromyographic activity, transdiaphragmatic pressure swing, and PTPdi were consistently lower during positive pressure ventilation than NPV (17). Although we did not perform a direct comparison between NPV and noninvasive positive pressure ventilation in our patients, it is important to note that the reduction in diafragm effort and the improvement in arterial blood gases we found were within the range of those obtained in patients with acute exacerbations of COPD with noninvasive positive pressure ventilation (31–33). The discrepancies between the findings of the present study and those of Belman and coworkers (17) could be explained, at least in part, by the different types of negative pressure ventilators used. It has been previously shown in patients with stable COPD that the decrease in electromyographic activity of diafragm was greater during NPV with an iron lung as compared with a cuirass (12). Furthermore, whereas we used a new model of microprocessor-based iron lung which offers wide flexibility in setting pressure and timing, the negative pressure pump used in the study of Belman and coworkers (Thompson Maxivent) provides control NPV with fixed inspiratory/expiratory ratio of 1:1.2 that may be inappropriate for patients with airflow limitation and prolonged expiratory time (42).

Five of the seven patients we studied exhibited nontriggering inspiratory efforts during NPV. This type of patient–ventilator asynchrony has been previously reported with assisted modes of positive pressure ventilation (33, 40, 43, 44), and it may be explained by several factors, such as ventilator trigger apparatus performance and sensitivity, weakness or fatigue of

| TABLE 2. ARTERIAL BLOOD GASES DURING SPONTANEOUS BREATHING AND DIFFERENT TYPES OF NPV* |
|-----------------------------------------------|-----------------|-----------------|-----------------|
|                                | PaO2 (mm Hg)    | PaCO2 (mm Hg)   | pH              |
|                                |                |                |                 |
| SB                             | 65 ± 1.3        | 73 ± 2.0       | 7.31 ± 0.01     | 2.6 ± 0.3       |
| CNEP                           | 67 ± 1.3        | 69 ± 1.91      | 7.33 ± 0.01     | 2.6 ± 0.3       |
| NPV                            | 72 ± 1.53       | 63 ± 2.43      | 7.38 ± 0.01     | 2.6 ± 0.3       |
| NPV-NEEP                       | 73 ± 1.53       | 62 ± 2.33      | 7.39 ± 0.01     | 2.6 ± 0.3       |

* Values are expressed as mean ± SE.
† Oxygen flow administered to patients.
§ p < 0.05, treatment versus SB.
‡ p < 0.001, treatment versus SB.

Figure 2. Recordings of volume, Pill, Pga, Pdi, and Ptank in a patient with acute exacerbation of COPD during NPV. Nontriggering inspiratory efforts are identified by negative swings in Ppl and positive swings in Pdi (arrows) that are not matched with a ventilator-assisted breath.
inspiratory muscles, blunted respiratory drive, increased inspiratory airway resistance, and presence of PEEPi (41). The present study was not specifically designed to assess the performance of the thermistor triggering system used to deliver assisted NPV. However, this technology is probably slower and less sensitive to the inspiratory efforts than that of the most recent flow and pressure triggering systems of positive pressure ventilators, and this factor could contribute to patient–ventilator asynchrony. The observation that the application of NEEP during NPV caused a significant reduction in both dynamic PEEPi and nontriggering inspiratory efforts suggests that PEEPi was another factor that contributed, at least in part, to patient–ventilator asynchrony.

In conclusion, we have shown that CNEP and assist NPV provided by microprocessor-based iron lung are able to improve ventilatory pattern and arterial blood gases, and to unload inspiratory muscles in patients with acute exacerbation of COPD. It also appears that NEEP added to NPV reduces dynamic PEEPi and nontriggering inspiratory efforts, improving patient–ventilator interaction. The availability of a new generation of negative pressure ventilators capable of providing different types of NPV could widen the field of application of noninvasive mechanical ventilation to patients in whom mask positive pressure ventilation failed or in whom it is not indicated, further reducing the need of endotracheal intubation. Controlled clinical trials are needed to provide this necessary piece of information.

References


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