Treatment of Acute Exacerbations of Chronic Respiratory Failure*

Integrated Use of Negative Pressure Ventilation and Noninvasive Positive Pressure Ventilation

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Study objectives: Acute respiratory failure (ARF) can be treated with either invasive mechanical ventilation (IMV) or noninvasive mechanical ventilation (NIMV), which can spare the complications of artificial airways. To evaluate the efficacy of an integrated approach using negative pressure ventilation (NPV) with iron lung and noninvasive positive pressure ventilation (NPPV), we performed a prospective study in a group of patients admitted to our respiratory ICU (RICU) for ARF due to exacerbation of chronic respiratory failure (CRF).

Setting: RICU at “R. Silvestrini” Hospital in Perugia, Italy.

Patients and methods: One hundred fifty-two consecutive patients were included in the study and treated with iron lung as first choice or, when contraindicated or not tolerated, with NPPV using a nasal or facial mask. After 2 h of noninvasive mechanical ventilation (NIMV), the patients were reevaluated; in case of clinical deterioration, patients receiving NPV were switched to NPPV. When NPPV as a first or second line of treatment failed the patients were intubated.

Measurements and results: One hundred fifty-two patients received NIMV, 97 with iron lung as the first choice of treatment, and 55 with NPPV. Six patients treated with NPV were switched to NPPV during the first 2 h of treatment. Twenty-five patients required IMV. The success rate of the integrated use of NIMV (NPV plus NPPV) was 81.6%, compared to that of NPV (83.5%) and NPPV (70.5%). Twenty-one patients (13.8%) required tracheostomy; the duration of hospital stay was significantly lower in patients treated with NIMV only. Thirty patients required mechanical ventilation at home. Few severe complications were observed in patients receiving IMV.

Conclusions: The integrated use of two NIMV techniques is effective in patients with acute exacerbation of CRF. In most cases intubation and tracheostomy were avoided, thus reducing the complication rate of mechanical ventilation.

Key words: acute respiratory failure; chronic respiratory failure; negative pressure ventilation; noninvasive positive-pressure ventilation; respiratory ICU

Abbreviations: ABG = arterial blood gas; ARF = acute respiratory failure; CRF = chronic respiratory failure; ETCO₂ = end-tidal CO₂; FiO₂ = fraction of inspired oxygen; HR = heart rate; IMV = invasive mechanical ventilation; NIMV = noninvasive mechanical ventilation; NPPV = noninvasive positive pressure ventilation; NPV = negative pressure ventilation; RICU = respiratory ICU; RR = respiratory rate; SaO₂ = arterial oxygen saturation; VAP = ventilator-associated pneumonia

Positive pressure ventilation via endotracheal tubes is the standard treatment for patients with acute respiratory failure (ARF). However, this very effective method may lead to complications associated with intubation, ventilator-associated infections, difficult weaning, and potential negative effects on diaphragmatic contractile activity. In the late 1980s and 1990s, the use of noninvasive ventilation increased, thus reducing the complications of invasive ventilation. Uncontrolled and randomized studies have shown that noninvasive positive pres-
sure ventilation (NPPV) can reduce the intubation rate in patients with COPD, whereas only a few studies had negative results. The global success rate in avoiding intubation in studies with favorable findings was 83%, but there was a wide range of different results. Only a few nonrandomized studies have been published evaluating noninvasive mechanical ventilation (NIMV) in the treatment of ARF caused by other clinical conditions such as restrictive disease and neuromuscular diseases.

After a long period of disuse, except in a single center with an uncontrolled study population, the benefit of negative pressure ventilation (NPV) with iron lung and poncho wrap in hypercapnic respiratory failure has been recently described. In a case-control study, the authors suggested that NPV may be comparable to invasive mechanical ventilation (IMV) for efficacy in the treatment of ARF due to COPD exacerbations. In a multicenter study, NPV was found to be comparable for efficacy to NPPV in COPD exacerbations. We began using the iron lung 15 years ago as first-choice treatment and NPPV with nasal or full face mask as an alternative in patients with acute-on-chronic respiratory failure. As no study has taken into consideration the integrated use of NPV and NPPV in the treatment of ARF, we evaluated whether the use of an integrated protocol of NPV and NPPV could prevent IMV, and reduce tracheostomy and related complications in patients admitted to our respiratory ICU (RICU) for exacerbation of chronic respiratory failure (CRF). The length of hospital stay and need for home mechanical ventilation were recorded.

Materials and Methods

Patient Population

In the last 2 years, 290 patients were admitted to our RICU for ARF due to exacerbation of CRF. One hundred fifty-two consecutive patients who satisfied the inclusion/exclusion criteria were admitted to the study. Inclusion criteria were ARF due to exacerbation of CRF with uncompensated respiratory acidosis, PaCO₂ > 70 mm Hg and pH ≤ 7.30, and need of mechanical ventilation. Exclusion criteria were invasive ventilation in emergency department before RICU admission, previous tracheotomy, CNS disease unrelated to respiratory failure, and end-stage cancer. Lung function test was performed using a Morgan body plethysmograph (P.K. Morgan; Kent, UK) before discharge in 120 collaborative patients. All patients received standard medical treatment for underlying disease and the condition precipitating acute exacerbation of CRF. Informed consent was obtained prior to study inclusion from patients or next of kin.

Study Design

At RICU admission, the patients were assessed and treated with NIMV using the iron lung as first choice, or NPPV with nasal or full face mask when NPV was contraindicated or not tolerated. Exclusion criteria for iron lung treatment are reported in Table 1. After 2 h, patients were reevaluated (physical examination, arterial blood gas [ABG] analysis). In the case of significant clinical deterioration (see criteria for intubation below) or absolute intolerance of the noninvasive ventilation modality, NPV patients were switched to NPPV and NPPV patients to IMV. The study protocol is shown in Figure 1.

Treatment With NIMV

The iron lung (MOD c 900; Coppa Biella; Biella, Italy) was set at pressure ranging from −35 to −45 cm H₂O; respiratory rate (RR), 15 to 18 breaths/min; positive pressure, 5 to 15 cm H₂O in control mode. Inspiratory time, inspiratory time, end-expiratory pauses, and end-inspiratory pauses were regulated according to the diagnosis at inclusion (expiratory time range, 0.9 to 1.3 s; inspiratory time range, 0.6 to 0.9 s; end-expiratory pause, 0.4 to 0.6 s; end-inspiratory pause, 0.3 to 0.5 s). Initially, ventilatory support was administered in three treatment periods with three 1-h breaks for meals and personal hygiene. ABG analysis was analyzed after 2 h of treatment and during interruptions of mechanical ventilation. During mechanical ventilation, the patient was clinically evaluated continuously and monitored noninvasively for the following: arterial oxygen saturation (SaO₂), RR, heart rate (HR); ECG, noninvasive arterial BP, and end-tidal CO₂ (ETCO₂) [Passport 2; Datascope; Montvale, NJ]. When necessary, further ABG analyses were performed.

A capnograph used during iron lung ventilation by nasal cannula proved useful in this condition to observe the shape of the capnographic curve and to follow the trend of ETCO₂ during mechanical ventilation, as the absolute value of ETCO₂ correlates poorly with arterial PaCO₂. When there was an improvement in two consecutive analyses (pH > 7.30 and PaCO₂ < 70 mm Hg), the hours of ventilation were progressively reduced until it was possible to discontinue ventilation. Forty-eight hours prior to discharge, ventilatory support was discontinued. Oxygen was supplied by nasal prongs or Venturi mask with high fraction of inspired oxygen (FiO₂) in the case of severe hypoxemia; SaO₂ was maintained at ≥ 90%. When the patient could not be completely weaned from NIMV, he was sent home with a ventilator.

NPPV was provided with a volume-cycled ventilator (Monnal DCC; Taema; Antony, France; or EOLE 3XO; Saime; Savigny Le Temple, France) in assist/control mode, low trigger (−2 cm

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**Table 1—Reasons for Using NPPV Instead of NPV at Admission**

<table>
<thead>
<tr>
<th>Variables</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron lung contraindication</td>
<td>13</td>
</tr>
<tr>
<td>Severe left ventricular failure*</td>
<td>13</td>
</tr>
<tr>
<td>Obstructive sleep apnea syndrome</td>
<td>9</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>4</td>
</tr>
<tr>
<td>Obesity</td>
<td>8</td>
</tr>
<tr>
<td>Upper airway pathology†</td>
<td>4</td>
</tr>
<tr>
<td>Arrhythmias‡</td>
<td>9</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
</tr>
</tbody>
</table>

*Systolic BP < 80 mm Hg.
†Vocal cord dysfunction (n = 2), intrathoracic gout (n = 1), partial tracheal stenosis (n = 1).
‡Arrhythmias causing hemodynamic instability (systolic BP < 80 mm Hg).
H₂O) with a tidal volume of 10 to 15 mL/kg (ideal body weight) adjusted to obtain sufficient expiratory volume and comfort for the patient. A positive end-expiratory pressure (4 to 5 cm H₂O) was used when indicated. Oxygen supplementation was administered through the ventilator circuit to maintain SaO₂ ≥ 90%.

The treatment schedule was progressively reduced using the same criteria as for NPV ventilation until mechanical ventilation could be withdrawn.

Criteria for Intubation

The following criteria described by Brochard and coworkers modified according to our experience were used: respiratory arrest, respiratory pauses with loss of consciousness or gasping for air, HR < 50 beats/min with loss of alertness, and hemodynamic instability with systolic arterial BP < 70 mm Hg, and Pao₂ < 45 mm Hg despite ventilation and oxygen therapy. The presence of any one of these criteria was an indication for intubation.

Treatment With IMV

After endotracheal intubation (sedation was achieved using IV midazolam), the patient was connected to the same type of ventilator used for NPPV delivering a tidal volume of 8 to 10 mL/kg, controlled modality in the first hours of ventilation, followed by alternating current modality. The patients were weaned using the method of single day T-tube trial lasting 2 h, as previously described. The weaning attempt was considered a failure when patients had PaO₂/Fio₂ < 150 and/or a RR > 40 breaths/min, and/or a HR > 150 beats/min or new onset of arrhythmia, agitation, anxiety, or diaphoresis.

Monitoring

Noninvasive monitoring was used in all patients. Spirometric data and physical examination (respiratory muscle activity) were also recorded.

Tracheostomy Criteria

After 8 to 12 days of IMV (except in diseases that excluded possibility of weaning) and after three failed weaning attempts, patients underwent surgical tracheostomy. We used a tracheostomy/failed attempts time schedule according to guidelines that are being drawn up by an interdisciplinary committee (RICU, ICU, thoracic surgery, and ear, nose, and throat specialists) in our hospital.

Six patients in the NPV group and one patient in the NPPV group who could not be weaned from noninvasive ventilation, after a trial with noninvasive PPV, underwent surgical tracheostomy. Despite good ABG analysis findings during NIMV, these patients did not tolerate mechanical ventilation suspension for more than a few hours. They were allowed to choose between intubation and IMV or immediate tracheostomy, and they decided for the second choice of treatment. The reasons for weaning failure in these patients were malnutrition and severe emphysema with limited autonomy of spontaneous ventilation.

Home Ventilation

Patients in the NIMV group who could not discontinue mechanical ventilation continued NIMV plus long-term oxygen therapy at home, following the scheme used in the last days of hospitalization.

Statistical Analysis

The primary end point was improvement in ABG analysis value during NIMV. Secondary end points were evaluation of mortality rate during hospital stay, the need for IMV and tracheotomy, length of hospitalization, and complication rate. Results are expressed as mean and SD. Groups were compared using the unpaired or paired t test as appropriate; χ² was used to compare frequency distributions. Failure rate was death or need of endotracheal ventilation for NIMV and death from IMV.

Figure 1. Study protocol and outcome of patients (PTS).
Results

One hundred fifty-two consecutive patients were included in the study. The underlying diseases causing CRF in our patients were COPD (110 patients, 72.4%), neuromuscular disease (12 patients, 7.9%), chest wall disease (22 patients, 14.5%), and lung fibrosis (8 patients, 5.3%). Patient characteristics (n = 152) at RICU admission were as follows: age, 71.5 ± 10.6 years; 105 male patients; PaO₂, 52.05 ± 14.9 mm Hg; PaO₂/FiO₂, 200.3 ± 48.4 (in 26 patients); PaCO₂, 82.9 ± 16.5 mm Hg; pH 7.26 ± 0.07; and APACHE (acute physiology and chronic health evaluation) II score, 19.1 ± 4.8. Spirometry, performed before discharge in 120 patients, showed FEV₁ of 0.86 ± 0.2 L and FEV₁/FVC of 51.2 ± 17.5. The causes of ARF were COPD exacerbation (n = 101), pneumonia (n = 26), pleural effusion (n = 5), pneumothorax (n = 4), thoracic trauma (n = 3), and right ventricular failure (n = 13).

Of the 152 patients admitted, 97 patients were treated with NPV by iron lung as first choice, and 55 patients were treated with NPPV by nasal or full face mask when iron lung treatment was contraindicated. Six patients (6.1%) treated with NPV were changed to NPPV when iron lung treatment was contraindicated. APACHE II score was 20.6 ± 5.2 in the NPV group, 23.3 ± 6.8 in the NPPV group, and 19 in the NPV group and 19 in the NPPV group (p < 0.001).

The characteristics of patients treated with NPV or NPPV were quite similar; only PaCO₂ at RICU admission was significantly higher in the NPV group (Table 2). ABG analysis and RR improved significantly in most patients after 2 h of noninvasive treatment (Table 3). Success rate of the integrated use of NIMV (NPV plus NPPV) was 81.6%, while that of NPV and NPPV was 83.5% and 70.5%, respectively.

Sixteen patients were assigned to IMV after the 2-h initial trial of noninvasive ventilation (early failure) and 9 patients in the following days of noninvasive treatment (late failure); 3 patients died during NIMV. The failure rate of NIMV (NPV plus NPPV) was 18.4% (Fig 1). There was a higher number of early failures in the NPPV group (p < 0.05), whereas there was no significant difference in the rate of late failures between the NPV and NPPV groups (Table 2).

One hundred thirty-nine patients survived and were discharged (91.4%). Thirteen patients admitted with hypercapnic-induced coma were treated with iron lung; 11 patients (85%) responded well and were discharged; 2 patients required IMV. The length of hospital stay was 12.4 ± 4.5 days in the NPV group, 14.2 ± 10.8 days in the NPPV group, (NS) 19.2 ± 16 days for IMV group (p < 0.01 vs NPV and NPPV); 30 patients needed home mechanical ventilation (27 patients with NPPV and 3 patients with NPV, poncho wrap), 11 in the NPV group and 19 in the NPPV group (p < 0.001).

Twenty-one patients (13.8%) underwent tracheotomy because of the impossibility to wean: 14 patients after a period of IMV and 7 patients (6 patients with iron lung, and 1 patient with NPPV) after NIMV. The patients treated only with NIMV had fewer major complications: three pneumothorax (2.2%; two with NPPV and one with NPV); two ventilator-associated pneumonia (VAP, 1.6%) both from the NPPV group; one multiorgan failure (0.08%) from the NPV group; and seven aspirations (four with NPV, and three with NPPV) [5.1%]. However, the patients treated with IMV had a higher rate of major complications: one pneumothorax (4%), three VAPs (12%), three multiorgan failures (12%), five cardiac complications (20%), and one tracheal stenosis (4%). The total rate of major complications was 56% for IMV and 9.5% for NIMV (p < 0.01). Minor undesirable effects of the two noninvasive techniques are shown in Table 4. We also evaluated the frequency

### Table 2—Baseline Parameters, Success and Failure Rate of Two Groups of Patients Treated With NIMVs

<table>
<thead>
<tr>
<th>Variables</th>
<th>NPV (Iron Lung)</th>
<th>NPPV</th>
<th>p Value (t Test or χ²-square Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>97</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>72.3 ± 8.1</td>
<td>70 ± 10.8</td>
<td>0.119 (NS)</td>
</tr>
<tr>
<td>COPD, No. (%)</td>
<td>72 (74.2)</td>
<td>42 (76.3)</td>
<td>&gt; 0.75 (NS) 1</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>54.8 ± 14</td>
<td>53.6 ± 16.2</td>
<td>0.28 (NS)</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>198.1 ± 43</td>
<td>201.9 ± 52</td>
<td>0.34 (NS)</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>89.1 ± 16.4</td>
<td>79.3 ± 15.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>pH</td>
<td>7.26 ± 0.04</td>
<td>7.26 ± 0.07</td>
<td>0.296 (NS)</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>28 ± 5.4</td>
<td>28 ± 5.1</td>
<td>0.287 (NS)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>20.6 ± 3.9</td>
<td>20.3 ± 6.3</td>
<td>0.26 (NS)</td>
</tr>
<tr>
<td>Early failure</td>
<td>91</td>
<td>13</td>
<td>&lt; 0.05 2</td>
</tr>
<tr>
<td>Late failure</td>
<td>7</td>
<td>5</td>
<td>&gt; 0.5 3</td>
</tr>
<tr>
<td>Success rate, %</td>
<td>83.5</td>
<td>70.5</td>
<td>&lt; 0.04</td>
</tr>
</tbody>
</table>

* Data are presented as No. or mean ± SD unless otherwise indicated. APACHE = acute physiology and chronic health evaluation; NS = not significant.
1 Six patients failed in NPV group switched to NPPV.
2 χ² test.

### Table 3—Study Results

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>After 2 h of NIMV</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂</td>
<td>52.05 ± 14.9</td>
<td>67.1 ± 11.2</td>
<td>72.6 ± 19.2</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>200.3 ± 48.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO₂</td>
<td>82.9 ± 16.5</td>
<td>72.1 ± 12.6</td>
<td>56.5 ± 9.1</td>
</tr>
<tr>
<td>pH</td>
<td>7.26 ± 0.07</td>
<td>7.4 ± 0.09</td>
<td>7.4 ± 0.05</td>
</tr>
<tr>
<td>RR</td>
<td>28.3 ± 5.2</td>
<td>25.3 ± 6.8</td>
<td>20.6 ± 3.45</td>
</tr>
</tbody>
</table>

* Data are presented as mean ± SD; n = 152. p < 0.001.
of failure of NIMV in our group of patients, according to the disease leading to CRF (COPD, chest wall disease, neuromuscular disease, and lung fibrosis), and found no significant difference (Fig 2).

**DISCUSSION**

The results of our study show that the integrated use of two modalities of NIMV, NPV and NPPV, was effective in correcting ARF, avoiding the need for endotracheal ventilation and tracheotomy in most patients and reducing the duration of ventilation and the hospital stay accompanied by a low incidence of ventilation-related complications.

IMV is very effective treatment for respiratory failure but can be associated with many complications, especially in patients requiring prolonged intubation. Complications included laryngeal and tracheal trauma with potential long-term effects, such as stenosis. In addition, sinusitis and VAP can occur during IMV. The incidence of complications is closely related to the duration of invasive ventilation, particularly the acquisition of VAP.21

Difficult weaning is often a problem in patients with COPD who undergo invasive ventilation. To avoid these problems and reduce hospital stay, many ICUs perform tracheostomy precociously, leading to high human and social costs due to this artificial airway. In the last 10 years, many studies have reported positive results regarding NIMV treatment for exacerbation of CRF primarily in patients with COPD.

The iron lung is our first choice of treatment for several reasons. Patients with acute exacerbation of CRF often present inspiratory muscle weakness, rapid shallow breathing, and excessive CO₂ reten-

**Table 4—Minor Unwanted Effects During NIMV**

<table>
<thead>
<tr>
<th>Variables</th>
<th>NPV (n = 82)</th>
<th>NPPV (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air leaking</td>
<td>0</td>
<td>28 (51.8)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>0</td>
<td>6 (11.1)</td>
</tr>
<tr>
<td>Nasal ulceration</td>
<td>0</td>
<td>34 (62.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (7.3)</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>Meteorism</td>
<td>22 (26.8)</td>
<td>6 (11.1)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%).

**Figure 2.** Failure rate (early and late): COPD (20 of 110 patients), neuromuscular diseases (2 of 12 patients), chest wall diseases (4 of 22 patients), lung fibrosis (1 of 8 patients). No significant difference was found.
tion. The iron lung improves the performance of respiratory muscles and restores sufficient respiratory compensation.16 Furthermore, many patients in the early phase of ARF are restless and do not tolerate NPPV with nasal or full face mask, whereas with the iron lung these patients receive ventilation effectively. Tracheobronchial secretions are often a problem in patients treated with NIMV and require efficient cleaning of the airways (with catheter or fiberoptic bronchoscope). This is achieved more easily when the iron lung is used.22 Noncontrolled studies23–25 indicate a better survival rate when patients with COPD and ARF are treated with the iron lung vs IMV. Using controlled ventilation via iron lung, patients with COPD in hypercapnic-induced coma can be safely treated.26

The recent introduction of NPV with a microprocessor-based thermistor trigger affords assisted NPV, improves the synchrony between patient and ventilator, and reduces the incidence of upper airway collapse.27 When the iron lung is contraindicated, impracticable due to the subject’s characteristics or ineffective after 2 h of treatment, the use of intermittent positive pressure ventilation with an oral or full face mask may avoid endotracheal intubation. In our series, the number of complications was similar between the two modalities of noninvasive ventilation. In the NPPV group, a significant percentage of patients acquired nasal skin pressure necrosis; in the iron lung group, meteorism and vomiting were the most frequent complications. Use of nasal gastric drainage and prokinetic drugs can avoid these complications in the majority of patients. Long-term home ventilation was required in a significant number of patients, especially in the NPPV group. There was a higher number of early failures in the NPPV group, while the success rate was higher in the NPPV group. Although many centers prefer pressure support ventilator for this type of patient, in this study we used volume-cycled ventilators in the NPPV group because this is the standard nurse-operated equipment in our RICU, which has resulted in highly satisfactory results since its introduction.

One study limitation could be patient selection on inclusion. In particular, those in need of immediate intubation were not included in the study. Another could be that the use of NMV, particularly iron lung ventilation, requires an expert medical and paramedic team able to switch immediately to IMV when necessary.

In our opinion, despite the aforementioned limitations, the possibility of using negative and positive noninvasive pressure ventilators in a RICU as part of the first line-treatment of ARF due to exacerbations of CRF can increase the possibility of resolving exacerbations without invasive procedures. In our series, 81.6% of the patients who had severe respiratory acidosis due to COPD exacerbations or other chronic lung diseases were treated successfully without invasive ventilation and with a very low complication rate. Our patients had a relatively short hospital stay, considering the severity of the clinical conditions on RICU admission, also by organizing, when indicated, long-term mechanical ventilation at home in patients with difficult weaning. The use of the iron lung as first choice of treatment in 64% of patients admitted to the study with a success rate of 83% confirms the efficacy of this device in the treatment of exacerbation of CRF.

REFERENCES


