Acute effects of NPPV in interstitial lung disease with chronic hypercapnic respiratory failure

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Summary
Objective: A case series evaluating the acute effects of noninvasive positive pressure ventilation (NPPV) in patients with chronic hypercapnic respiratory failure (HRF) secondary to interstitial lung diseases (ILD).

Patients and methods: Ten patients with ILD were retrospectively evaluated. All had restrictive lung function (mean TLC, 47.6 ± 12.6% predicted) and chronic hypercapnic respiratory failure (mean pH = 7.39 ± 0.02). Arterial blood gas analysis and lung function were compared before and after the application of controlled pressure-limited NPPV.

Results: Daytime PaCO₂ during spontaneous breathing decreased by 5.4 ± 1.3 mmHg (95% confidence interval, 4.5–6.3), from 57.7 ± 5.1 mmHg to 52.3 ± 5.9 (p < 0.001); while daytime PaO₂ increased by 3.4 ± 3.3 mmHg (95% confidence interval, 1.0–5.8), from 63.7 ± 3.5 mmHg to 67.1 ± 3.4 (p = 0.01); and TLC increased by 3.9 ± 4.5% (95% confidence interval, 0.7–7.1), from 47.6 ± 12.6% mmHg to 51.5 ± 10.0% (p = 0.023).

Conclusions: In patients with ILD and chronic HRF controlled NPPV is tolerated and can acutely improve blood gas levels. Further studies examining the long-term benefits need to be explored.

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Introduction
Interstitial lung diseases (ILD), or diffuse parenchymal lung disease, may have known or unknown causes. The term refers to a heterogeneous group of non-neoplastic disorders resulting from damage to lung parenchyma which affect not only the interstitium, but also the airspaces, peripheral airways and vessels. These chronic diseases are characterised by breathlessness, increasing hypoxia and
hyperventilation. Hypercapnia can occur even in cases of acute exacerbations (e.g., due to infections, heart failure or thromboembolism) or in late stages of the diseases because the lungs become so stiff and the resistance increases to such a point that the respiratory muscles can no longer sustain the loads. A consensus conference for long-term use of NPPV in patients with chronic hypercapnic respiratory failure recommended NPPV in chronic neuromuscular diseases, thoracic cage disorders, severe stable COPD and nocturnal hypoventilation from additional disorders such as obesity hypoventilation syndrome. In ILD there are only few data about NPPV in respiratory failure due to acute exacerbations of idiopathic pulmonary fibrosis but there are no reports about the use of NPPV in stable ILD with chronic hypercapnic respiratory failure. To the best of the authors’ knowledge, this is the first case series about NPPV in patients with ILD and chronic hypercapnic respiratory failure.

Materials and methods

Patients

The case records of ten patients with ILD who had been treated with NPPV between April 2005 and April 2008 (3 years) were retrospectively reviewed. All patients were referred to our hospital for clinical management. Chronic hypersensitivity pneumonitis (bird fancier’s lung) was diagnosed in six patients according to published diagnostic criteria. In two patients chronic sarcoidosis was diagnosed by clinical and radiological signs and the histological evidence of non-caseating granulomas obtained by biopsy through bronchoscopy in lung parenchym and/or mediastinal lymph nodes. In a further two patients there was interstitial lung disease without conclusive entity.

All patients had chronic hypercapnic respiratory failure (pH > 7.35) when given NPPV and no patients had signs of acute exacerbation and/or infection.

NPPV

All patients were treated with pressure-limited NPPV in the assist/control mode. Two types of pressure-cycled ventilators were used (VS Integra; Saime; Savigny le Temple, France and Legendair; Airox; Pau, France). Interfaces included customized or commercial nasal masks (Comfort Gel; Respironics; Murrysville, PA, USA) with a chinstrap to minimize oral leaks, or full-face masks (Ultra Mirage or Mirage Full Face; ResMed; San Diego, CA, USA). A one-way circuit with an expiratory valve was used in all patients. Passive humidification using a heat and moisture exchanger (Hygrovent S; Medisize bv; Hillegom, the Netherlands) was provided for all patients. NPPV was introduced as described in patients with stable COPD, and inspiratory pressure was increased until further increases were not tolerated by the patient. All patients had been receiving long-term oxygen therapy prior to NPPV treatment and this was not changed during the NPPV period.

Improvements in blood gas levels during nocturnal NPPV were verified by blood gas measurements and/or transcutaneous capnography at night while patients were receiving NPPV.

Data collections and measurements

Pulmonary function test measurements were obtained with the patients in a sitting position. The forced spirometry readings were obtained using a pneumotachographic spirometer and lung volumes were determined using body plethysmography (Masterlab-Compact Labor; Viasys Healthcare; Hoechberg, Germany). Pulmonary function measurements were performed before initiating NPPV and either during the first visit after the establishment of NPPV or at the next control visit in the clinic after six to eight weeks. Blood gas measurements were obtained at rest from arterialized earlobe during spontaneous breathing (ABL 700; Radiometer; Willich, Germany) before initiation of NPPV and after stable establishment of NPPV but at least 2 h after cessation of nocturnal NPPV. Inspiratory mouth occlusion pressures (ZAN; ZAN Gerätetechnik; Oberthulba, Germany) were measured during both quiet breathing (P0.1) and during maximal inspiratory mouth pressure (Pimax).

Statistical analysis

Statistical analysis was performed using statistical software SPSS (Version 14.01, SPSS Inc., Chicago, IL, USA). Data are presented as mean ± SD or as mean differences with 95% confidence intervals. After testing for normal distribution (Kolmogorov–Smirnov test), a comparison of measurements before and after treatment with NPPV was performed using the paired t test. Statistical significance was assumed with a p value below 0.05.

Results

Ten patients with ILD were evaluated (Table 1). The mean age of the ten patients (nine female, one male) was 60 ± 6 years (range, 52–70 years). Chronic hypersensitivity pneumonitis (bird fancier’s lung) was diagnosed in six patients, chronic sarcoidosis of the lung in two patients, and lung fibrosis without conclusive entity in a further two patients. All patients had moderate to severe restrictive lung function pattern (mean TLC = 47.6 ± 12.6% predicted) and no coexisting airflow limitation (FEV1/FVC = 91.4 ± 3.3). Inspiratory mouth occlusion pressure was measured in seven patients before NPPV was started. The inspiratory mouth occlusion pressure 100 ms after the onset of inspiration during quiet breathing (P0.1) was 3.15 ± 0.8 mmHg, and during maximal inspiration (Pimax), 28.8 ± 6.7 mmHg.

In eight patients a transthoracic echocardiography was performed. In only one patient could a left heart dysfunction be detected (ejection fraction 35%), but with normal pulmonary capillary wedge pressure. The estimated right ventricular systolic pressure in transthoracic echocardiography was elevated (RVSP 63.1 ± 21.7 mmHg). Six patients also underwent right heart catheterization for invasive measurement of resting hemodynamics. Pulmonary hypertension, defined as a mean pulmonary artery pressure
mPAP > 25 mmHg, was present in five patients (mean mPAP 31.7 ± 10.2 mmHg).

In all patients a pressure-limited controlled mode of NPPV was initiated. A mean inspiratory pressure of 28.1 ± 2.5 cm H2O (range, 24–30 cm H2O) was achieved. The mean respiratory rate was 23.5 ± 3.4 breaths/min (range, 20–32 breaths/min). Supplemental oxygen was administered with a mean flow of 2.5 ± 1.4 L/min (range, 1–5 L/min).

The mean body mass index (BMI) was 27.8 ± 5.9 kg/m² (range, 18–37 kg/m²). Four patients were obese (BMI ≥ 30 kg/m²).

The mean PaO2 during the established long-term oxygen therapy was 63.7 ± 3.5 mmHg and the mean PaCO2 was 57.7 ± 5.1 mmHg. All patients had chronic hypercapnic respiratory failure with pH = 7.39 ± 0.02. After stable establishment of controlled pressure-limited NPPV, blood gas levels during spontaneous breathing and lung function improved significantly (Table 2). There was a significant reduction of PaCO2 from 57.7 ± 5.1 mmHg to 52.3 ± 5.9 mmHg (p < 0.001) and a significant increase of PaO2 from 63.7 ± 3.5 mmHg to 67.1 ± 3.4 mmHg (p = 0.011). The TLC improved from 47.6 ± 12.6% pred. to 51.5 ± 10.0% pred. (p = 0.023).

Discussion

The present case series shows for the first time the acute effects of noninvasive positive pressure ventilation on blood gas analysis and lung function in ten patients with chronic hypercapnic respiratory failure in ILD. All patients had moderate to severe restrictive lung function pattern (mean TLC = 47.6 ± 12.6% predicted) and no coexisting airflow limitation (FEV1/FVC = 91.4 ± 3.3). All of our patients were on controlled pressure-limited NPPV with a mean inspiratory pressure of 28 cm H2O. With this modus we achieved a significant improvement in blood gas levels and partially in lung function during spontaneous breathing. PaCO2 was decreased by a mean of 5.4 mmHg, PaO2 increased by a mean of 3.4 mmHg, and the TLC increased by a mean of nearly 4% of the predicted value.

Generally, in ILD, despite some acute reasons for respiratory failure such as infections, heart failure, thromboembolism or pneumothorax, respiratory failure occurs commonly, often as a terminal event after a prolonged course of illness. In hypersensitivity pneumonitis, a granulomatous form of ILD mostly with an identifiable cause, a chronic course can progress to pulmonary fibrosis with respiratory failure and is associated with a poor long-term prognosis. Sarcoidosis is another chronic granulomatous interstitial lung disease with two possible outcomes: in the majority of cases it is a self-limiting disease, but there is also a possibility of progression to extensive fibrotic lung disease with terminal respiratory failure.

More information exists about respiratory failure in idiopathic pulmonary fibrosis, particularly about the management of acute respiratory failure (ARF). It was shown that in mechanically ventilated patients with end-stage fibrosis due to acute respiratory failure, the elastances and resistances of the respiratory system were...
significantly altered. These abnormalities in lung mechanics may be responsible for the onset of hypercapnia.2

In 2001, three studies were published about the outcome of patients with idiopathic pulmonary fibrosis and acute respiratory failure admitted to an intensive care unit. Saydain et al demonstrated that there was a high failure rate in 38 patients with ARF even if they needed invasive or noninvasive mechanical ventilation support.4 In a report from Blivet et al, 15 patients with idiopathic pulmonary fibrosis and ARF all needed invasive mechanical ventilation. In two patients a prior trial of noninvasive ventilation was done without success. Thirteen patients died in the intensive care unit or shortly thereafter.14 In another case series all but one of 23 patients with ARF in idiopathic pulmonary fibrosis died while receiving mechanical ventilation. The survivor successfully received a lung transplant six hours after initiating mechanical ventilation.15 In a review about patients with IPF ventilated in intensive care it was summarized that the outcome in the intensive care unit is very poor and mechanical ventilation is mostly futile. Postsurgical patients with respiratory failure have a better survival as the precipitating condition is likely reversible.16 This very poor prognosis was not only in patients with idiopathic pulmonary fibrosis. Of 20 patients with severe ARF, 6 had pulmonary fibrosis associated with collagen vascular diseases. All but 3 required mechanical ventilation with a 100% mortality because of refractory hypoxemic respiratory failure.17

In severe cases of chronic pigeon breeder’s lung, a hypercapnic respiratory failure is associated with pulmonary hypertension.18 Six of our ten patients had chronic bird fancier’s lung. Five of these six patients had pulmonary hypertension either detected by transthoracic echocardiography or right heart catheterization.

Mechanical ventilation can be a bridge to lung transplantation in end-stage lung disease. There are some case reports about NPPV as a bridge to lung transplantation in patients with CF, COPD or sarcoidosis.19 In a retrospective study by Madden et al about NPPV in 113 patients with CF, noninvasive ventilation failed to correct hypercapnia but it was still useful for “bridging the gap” between respiratory failure and lung transplant.20 Two of our patients (no. 2 and 8) were listed for lung transplants. Patient no. 2 died while awaiting a lung transplant due to pulmonary infection with sepsis, patient no. 8 is still awaiting their transplant.

Table 2 Blood gas levels and lung function parameters prior to NPPV and after acute establishment of NPPV in patients with chronic HRF due to interstitial lung diseases.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Prior NPPV</th>
<th>After NPPV</th>
<th>Treatment effect</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.39 ± 0.02</td>
<td>7.42 ± 0.02</td>
<td>0.03 ± 0.01</td>
<td>0.02–0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>57.7 ± 5.1</td>
<td>52.3 ± 5.9</td>
<td>−5.4 ± 1.3</td>
<td>−6.3 to −4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>63.7 ± 3.5</td>
<td>67.1 ± 3.4</td>
<td>3.4 ± 3.3</td>
<td>1.0–5.8</td>
<td>0.011</td>
</tr>
<tr>
<td>HCO₃⁻, mmol/L</td>
<td>31.9 ± 1.5</td>
<td>31.7 ± 1.8</td>
<td>0.2 ± 1.4</td>
<td>−0.8–1.2</td>
<td>0.662</td>
</tr>
<tr>
<td>TLC, % pred.</td>
<td>47.6 ± 12.6</td>
<td>51.5 ± 10.0</td>
<td>3.9 ± 4.5</td>
<td>0.7–7.1</td>
<td>0.023</td>
</tr>
<tr>
<td>FVC, % pred.</td>
<td>40.8 ± 15.6</td>
<td>44.3 ± 14.7</td>
<td>3.5 ± 5.2</td>
<td>−0.2–7.2</td>
<td>0.064</td>
</tr>
<tr>
<td>FEV₁, % pred.</td>
<td>44.1 ± 16.1</td>
<td>48.0 ± 15.9</td>
<td>3.9 ± 6.1</td>
<td>−0.5–8.3</td>
<td>0.073</td>
</tr>
<tr>
<td>FEV₁/FVC %</td>
<td>91.4 ± 3.3</td>
<td>92.5 ± 5.8</td>
<td>1.1 ± 3.8</td>
<td>−1.7–3.8</td>
<td>0.389</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.

Some important limitations of our investigation should be noted. The small subject numbers and the single-center, retrospective nature of the design limit our results, particularly the statistical analysis. Since there was no long-term follow-up, it is unknown how long the patients will continue to use NPPV. However, the aim of this study was to test the principle of NPPV in patients with interstitial lung diseases and chronic HRF and further prospective, randomized controlled trials will be needed to confirm our results.

In summary, there are no reports about noninvasive ventilation in interstitial lung diseases such as idiopathic lung fibrosis, chronic hypersensitivity pneumonitis or chronic pulmonary sarcoidosis with chronic hypercapnic respiratory failure in the recent literature. We have demonstrated that noninvasive positive pressure ventilation can acutely improve chronic hypercapnic respiratory failure in patients with interstitial lung diseases. Using controlled pressure-limited NPPV with a mean inspiration pressure of 28 cm H₂O and a mean respiratory rate of 23.5 breaths/min a significant decrease of PaCO₂ and increase of PaO₂ could be achieved.

Conflict of interest statement

None for all authors.

References