Role of Non-invasive Ventilation in Managing Life-threatening Acute Exacerbation of Interstitial Pneumonia

Keisuke Tomii¹, Ryo Tachikawa¹, Kazuo Chin², Kimihiko Murase¹, Tomohiro Handa³, Michiaki Mishima⁴ and Kyosuke Ishihara⁵

Abstract

Introduction  Invasive mechanical ventilation (IMV) is not effective for acute exacerbation of interstitial pneumonia (AE-IP); however, the role of non-invasive ventilation (NIV) for this condition remains unknown.
Methods  Comparisons were made for two periods: before (October 2001 - September 2003) and after (October 2004 - September 2006) the introduction of NIV as the primary method of mechanical ventilation for AE-IP. We retrospectively screened emergent admissions and enrolled consecutively those patients with AE-IP who had acutely worsening hypoxemia with new infiltrates, background chronic interstitial CT changes, and no findings suggestive of other diseases. The two periods were compared primarily for 60-day survival and secondarily for other outcomes associated with mechanical ventilation.
Results  Medical records were retrieved for 11 episodes in 11 patients identified from 485 pre-NIV records and 27 episodes in 22 patients from 859 post-NIV records. Five patients required IMV in the earlier cohort and 9 patients received NIV in the later cohort. Although there was no difference in the PaO2/FiO2 ratio on admission (167 vs. 139), the 60-day survival rate for all episodes in the later cohort was better than in the earlier cohort (27% vs. 65%, p=0.02). Moreover, the NIV-administered group had a better 60-day survival rate (0% vs. 44%, p=0.03), shorter high-care unit stay (17 vs. 6 days, p=0.03) and better-preserved verbal communication (0 vs. 89%) than the IMV-administered group.
Conclusion  Use of NIV in place of IMV for the management of life-threatening AE-IP appears to result in a better 60-day survival rate, lower high-care unit use and better patient tolerability.

Key words: acute exacerbation, idiopathic pulmonary fibrosis, interstitial pneumonia, non-invasive positive pressure ventilation, non-invasive ventilation

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Introduction

Acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) is a fatal event, which can develop without any identifiable cause and is regarded pathologically as diffuse alveolar damage (DAD) with or without organizing pneumonia superimposed on underlying IPF (1-3). Furthermore, it seems to be the most common cause of death in patients with IPF (4). Recently, similar AEs have been reported to occur in other forms of chronic fibrotic interstitial pneumonia (IP) (5), including non-specific interstitial pneumonia (NSIP) (6, 7), collagen vascular disease (CVD) associated-IP (6, 8-10) and chronic hypersensitivity pneumonia (7, 11). How to manage these AEs is a clinically important yet common, unresolved problem for all chronic fibrotic IPs.

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In severe critical hypoxemia, invasive mechanical ventilation (IMV), that is, mechanical ventilation with intubation or tracheostomy, used to be the final procedure for sustaining life, but it is not recommended in the case of AE-IPF because of the extremely high rate of mortality, which cannot be reduced even using this approach (12-15). Recently, it has been reported that non-invasive ventilation (NIV) is effective for early ALI/ARDS (16), which is now regarded pathologically as DAD and should be treated by a lung protective strategy. In the case of AE-IP, DAD is superimposed on underlying IP and the percentage of alveoli effective for gas exchange seems to be more limited than with ARDS. Under such circumstances, we should treat the lungs of those with AE-IP more protectively than those with ARDS. In AE-IP patients, who rarely require ventilatory support, NIV can be applied with low support pressure or with continuous positive airway pressure (CPAP) as long as high FiO2 can be provided by the ventilator. Such NIV may not only further decrease the mean positive pressure but may also be a more favorable option for AE-IP.

To clarify the impact of introducing NIV as the primary method of mechanical ventilation on the prognosis of AE-IP, we conducted a retrospective cohort study comparing outcomes during periods before and after the introduction of NIV at our hospital, where NIV has been applied and continued until recovery or death for the management of AE-IP since 2004.

Methods

Application of NIV for AE-IP

Noninvasive ventilation using BiPAP-Vision (Respironics, Murrysville, PA, USA) was introduced in our emergency department for first-line management of various types of acute respiratory failure in 2004 (17). When patients with AE-IP needed a level of oxygen greater than FiO2 0.5, meaning a PaO2/FiO2 below 120, and had no obvious contraindications such as respiratory arrest, deep coma, cardiovascular instability, airway obstruction or facial problems, NIV was initially applied using a bi-level or CPAP mode. The bi-level mode was selected when patients even on CPAP exhibited breathlessness or respiratory effort as evident by neck muscle tension or if they had CO2 retention (PaCO2>45 torr). The level of CPAP or EPAP was started at 4 cm H2O and gradually increased until the preferred SpO2 level (>92%) was obtained with the FiO2 below 80%. The maximum CPAP or EPAP level, however, was set at 10 cm H2O. Thereafter, it was continued until recovery or death with the consent of the patient or family after discussing how poor the patient’s prognosis would be even if invasive ventilation were used.

Data collection

Data collection and analysis were performed only by coauthors of this paper, and the use of these data was approved by our Institutional Review Board. Data were collected from the medical records of pulmonary emergent admissions during two periods: before and after the introduction of NIV at our hospital. Cases were enrolled as having AE-IP when the admission was not associated with malignancy or failure of organs other than the lungs and when they fulfilled the following criteria: 1) prior diagnosis of chronic IP, 2) the presence of underlying interstitial changes on HRCT, 3) acute worsening of dyspnea and hypoxemia within one month to the level of more than 10 mmHg below previous values, 4) appearance of new infiltrates in both lung fields, and 5) no signs or clinical course suggestive of bacterial infection, heart failure, thromboembolic disease or drug-induced pneumonitis. These criteria were based on the definition of AE-IPF in “Idiopathic Interstitial Pneumonias: Diagnosis and Treatment” from the Japanese Respiratory Society (18).

Bacterial infection was denied when the culture of sputum or BAL obtained at admission was negative or when antibiotics were not prescribed from the time of admission until an obvious secondary infection occurred.

In this study, we intended to reveal the survival benefit obtained after the introduction of NIV for the care of life-threatening AE-IP. Comparison between only those given IMV in the pre-NIV period and those given NIV in the post-NIV period seemed inadequate because indications for IMV were different than for NIV. Therefore, we primarily compared the entire population of patients with AE-IP who were admitted emergently and who might have become candidates for mechanical ventilation. Each patient’s survival was tracked, as far as possible, beyond our hospital records until death occurred.

Data analysis

Primary outcome was 60-day survival of each AE-IP episode experienced by enrolled patients and comparisons of outcome during the pre-NIV and post-NIV period were made by the Kaplan-Meier curves employing a Log-rank test, in which, for each episode, the patient was censored when he or she had survived 60 days after the admission. In order to specify the difference between results of IMV and NIV, we separately compared the 60-day survival of individual patients administered either of the two modes of mechanical ventilation (IMV in pre-NIV period vs. NIV in post-NIV period), their ventilator settings, patient status after mechanical ventilation, such as duration of mechanical ventilation, ICU-stay, preserved verbal communication and oral intake, and associated complications. These parameters and background demographic data of the two cohorts were compared by the unpaired t test for numerical data and chi-square or Fisher’s exact test for categorical data. All of the above were performed by the statistical package JMP 7.0.2 (SAS Institute, Inc., Cary, NC, USA).
Table 1. Characteristics of Patients Enrolled

<table>
<thead>
<tr>
<th></th>
<th>Pre-NIV cohort</th>
<th>Post-NIV cohort</th>
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<tbody>
<tr>
<td>No. patients</td>
<td>11</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>69.2 (9.8)</td>
<td>71.6 (10.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>Male (%)</td>
<td>8 (73)</td>
<td>12 (55)</td>
<td>0.46</td>
</tr>
<tr>
<td>Presence of distinct honeycombing (IPF pattern) (%)</td>
<td>5 (45)</td>
<td>8 (36)</td>
<td>0.71</td>
</tr>
<tr>
<td>Association with CVD (%)</td>
<td>6* (55)</td>
<td>3* (14)</td>
<td>0.03 †</td>
</tr>
<tr>
<td>LTOT before AE (%)</td>
<td>3 (27)</td>
<td>10 (45)</td>
<td>0.46</td>
</tr>
<tr>
<td>Previous AE episodes (%)</td>
<td>2 (18)</td>
<td>3 (14)</td>
<td>1</td>
</tr>
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</table>

*1 systemic sclerosis (SS), 1 mixed connective tissue disease, 1 polymyositis-dermatomyositis (PM-DM) and 3 rheumatoid arthritis in the pre-NIV period, and 1 SS and 2 PM-DM in the post-NIV period.
†Statistically significant difference.

Results

Enrolled cases

Twenty-three cases were retrieved from the 485 screened records of emergent admissions for pulmonary etiologies prior to the introduction of NIV, while 44 cases were retrieved from 859 screened records after the introduction of NIV. Thereafter, the criteria for enrollment as a subject with AE-IP were applied and 11 episodes from 11 patients (pre-NIV cohort) and 27 episodes from 22 patients (post-NIV cohort) were finally entered into the study (Fig. 1).

Background and medical treatments

There were no statistical differences between the two cohorts with respect to mean age, gender ratio, rates of accompanying IPF-consistent honeycombing on HRCT, long-term oxygen therapy performed before AE and previous episodes of AE (Table 1). The rate of association with CVD, however, was significantly higher in the pre-NIV cohort, with 3 more cases having rheumatoid arthritis. At our hospital, surgical lung biopsy was not usually performed for those considered to have usual interstitial pneumonia (UIP) by CT; moreover, about half of the patients were transferred to our institution after the occurrence of AE without any chance of biopsy. Therefore, lung histology of underlying chronic IP was obtained only in 4 cases in the post-NIV cohort (2 non-UIP from surgical lung biopsy, 2 non-UIP and 2 CVD-associated IP by postmortem examination), but the rate of IPF in the study population was predicted to be similar to those having distinct honeycombing on HRCT. All of the episodes analyzed were considered to involve no obvious pulmonary bacterial infection according to negative BAL culture (3 of 11 pre-NIV episodes, 2 of 27 post-NIV episodes), negative sputum culture (8 pre-NIV, 18 post-NIV).
and/or no use of antibiotics (2 pre-NIV, 9 post-NIV). The severity of the AE as assessed by the first blood gas analysis after admission did not differ significantly (PaO2/FiO2: pre-NIV 167±103 vs. post-NIV 139±64) and all patients were treated acutely with high-dose corticosteroids, which were occasionally combined with intravenous cyclophosphamide (pre-NIV: 18% vs. post-NIV: 11%) or other oral immunosuppressants (pre-NIV: 18% vs. post-NIV: 33%). No case in this study was treated with sivelestat sodium hydrate or polymyxin B-immobilized fiber column. Before the introduction of NIV, 5 of the 11 patients had had invasive ventilation; however, after NIV was introduced it was applied in 10 patients, including 2 having CPAP only. Invasive ventilation was applied in only one of the 22 patients in the post-NIV cohort, who was comatose (Table 2).

60-day survival of the entire episodes of AE-IP

Cause of death in all patients who died within 60 days of admission was AE-IP or an associated complication. Five patients in the post-NIV group experienced AE-IP twice, and one episode was excluded from the 60-day survival analysis because AE had recurred 42 days after the admission. Kaplan-Meier analysis of survival at 60 days after all AE-IP episodes was significantly improved in the post-NIV cohort (27.3% vs. 65.4%, Log-rank p=0.02) (Fig. 2).

**IMV vs. NIV**

In order to make a direct comparison of survival, ventilator settings and patient status between those in the pre-NIV period who were administered IMV and those who received NIV in the post-NIV period, we excluded two episodes. For one episode, NIV had been administered for an indication that was not usual, namely, deteriorating multi-organ failure; that patient died within 24 hours. In the other episode, IMV was administered in the post-NIV period due to deep coma. The ratio of PaO2 to FiO2 on admission among this population was significantly lower in the NIV group (220±126 vs. 106±50, p=0.03) (Table 3). Mechanical ventilation was initiated in the emergency department in 1 of 5 episodes (20%) in the IMV group and 6 of 9 (67%) in the NIV group (Table 3). Applied peak inspiratory positive pressure (not above PEEP; 22.4±7.1 vs. 11.0±2.4 cm H2O, p=0.001) and end-expiratory pressure (10.8±4.1 vs. 7.2±1.0 cmH2O, p=0.03) were significantly higher in the IMV group. Survival at 60 days (Fig. 3) was markedly better in the NIV group than in the IMV group (0% vs. 44.4%, Log-rank p=0.03). Additionally, the duration of stay in the ICU or intermediate-care unit was significantly shorter in the NIV group (17.0±12.6 vs. 5.8±4.9 days, p=0.03) and verbal communication was significantly better preserved in the NIV group (0% vs. 89%, p=0.003).

**Discussion**

After the introduction of NIV as the initial method of mechanical ventilation for AE-IP patients in our hospital, 60-
Figure 3. Overall survival curves of patients administered mechanical ventilation (IMV in pre-NIV period vs NIV in post-NIV period). IMV: invasive mechanical ventilation, NIV: non-invasive ventilation.

Table 3. Ventilator Settings and Patient Status during Mechanical Ventilation (IMV in Pre-NIV Vs. NIV* in Post-NIV Period)

<table>
<thead>
<tr>
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<th>IMV in pre-NIV</th>
<th>NIV in post-NIV</th>
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<tbody>
<tr>
<td>No. episodes</td>
<td>5</td>
<td>9*</td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2 on admission; mean (SD)</td>
<td>220 (126)</td>
<td>106 (50)</td>
<td>0.03 §</td>
</tr>
<tr>
<td>Immediate initiation of IMV or NIV† (%)</td>
<td>1 (20)</td>
<td>6 (67)</td>
<td>0.09</td>
</tr>
<tr>
<td>Applied peak inspiratory positive pressure, cm H2O; mean (SD)</td>
<td>22.4 (7.1)</td>
<td>11.0 (2.4)</td>
<td>0.001 §</td>
</tr>
<tr>
<td>PEEP or EPAP; cmH2O; mean (SD)</td>
<td>10.8 (4.1)</td>
<td>7.2 (1.0)</td>
<td>0.03 §</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, days; mean (SD)</td>
<td>17.6 (15.2)</td>
<td>11.7 (6.9)</td>
<td>0.33</td>
</tr>
<tr>
<td>ICU and intermediate-care unit stay, days; mean (SD)</td>
<td>17.0 (12.6)</td>
<td>5.8 (4.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Preserved verbal communications after mechanical ventilation (%)</td>
<td>0 (0)</td>
<td>8 (89)</td>
<td>0.003 §</td>
</tr>
<tr>
<td>Preserved oral intake after mechanical ventilation (%)</td>
<td>0 (0)</td>
<td>4 (44)</td>
<td>0.22</td>
</tr>
<tr>
<td>Fatal complications related to mechanical ventilation (%)</td>
<td>3¶ (38)</td>
<td>0 (0)</td>
<td>0.03 §</td>
</tr>
</tbody>
</table>

* Two episodes in the post-NIV cohort were excluded from this comparison as they had been out of NIV indications. (One given NIV was in multi-organ failure and died within 24 hours and the other given IMV was in deep coma.) †Mechanical ventilation begun immediately in the emergency department. §Statistically significant difference. ¶Ventilator-associated pneumonia and sepsis.

IMV: invasive mechanical ventilation, NIV: non-invasive ventilation, PEEP: positive end-expiratory pressure, EPAP: expiratory positive airway pressure.

Day survival significantly improved in the overall cohort of patients who had been emergently admitted. Moreover, the direct comparison between IMV in the pre-NIV period and NIV in the post-NIV period showed a significant survival benefit at 60 days despite the rather limited number of patients for the comparison. These improvements in survival might not be attributed only to the introduction of NIV, but the use of NIV also appeared to be associated with significantly shorter high-care unit stays and better patient tolerance as shown by preserved communication. Therefore, NIV seems to be preferable not only for its survival benefits but for issues related to patients’ quality of life and usage of medical resources. To date, studies addressing the effectiveness of mechanical ventilation for acute respiratory failure from IPF or AE-IPF have been unable to reveal any benefits (12-15), therefore, this is the first study to demonstrate the effectiveness of NIV in the management of AE-IP or AE-IPF.

Pathologically, AE-IP is regarded as DAD with or without organizing pneumonia superimposed on underlying IP (1-3). Therefore, the rate of alveoli effectively used for gas exchange seems to be more limited than with ARDS, in which DAD can occur without any underlying pulmonary disease. As a low-pressure lung protective strategy is required in ARDS to prevent pressure- or ventilator-induced lung injury and promote a better prognosis (19), we should treat the patient’s lungs more protectively in AE-IP. NIV offers several advantages over IMV in this respect. First, NIV can improve gas exchange and may avoid the need for intubation itself as shown in ARDS (16), which would reduce or avoid complications such as ventilator-associated pneumonia (20, 21). Secondly, NIV can be initiated immediately upon admission so that AE-IP can be treated earlier and with lower pressures. Thirdly, NIV can be terminated when necessary and even used intermittently so that positive pressure can be used for a shorter duration. Fourth, patients do not need to be deeply sedated and they can maintain their autonomy and verbal communication, which, in turn, helps to promote better oral and bronchial hygiene. Due to these factors, we can speculate that survival would be better in those receiving NIV in comparison with IMV regardless of the severity of the hypoxic state on admission.

As the diagnosis of IP was evolving and the number of...
HRCT scans were increasing during the entire time period covered by this study, which stretches from October 2001 to September 2006, these changes may have influenced the detection rate of underlying IPs, particularly in the post-NIV period (October 2004 to September 2006). For example, cases of AE with mild underlying IP seemed to be included to a greater extent in the post-NIV period. Therefore, the trend toward improved survival in the NIV group may simply reflect that the illness had not progressed as far in that group as in the earlier group. Furthermore, the more AE became recognized, the more attention was paid as to how it developed and the more patients may have been transferred to our hospital at an earlier stage in the AE, although in reality, hypoxemia on admission expressed by PaO2/FiO2 had been greater in the NIV group than in the IMV group. In the future, it will be necessary to examine what other factors can contribute to this trend of improved survival.

Exclusion of the possibility of superimposed infection is the most challenging issue in the diagnosis of AE-IP. First, it is difficult to discriminate whether the infection is involved in the process of AE or is a simple comorbidity. Since external stimuli on IP-associated lungs, such as an operation (22) or BAL (23), have been reported to be a cause of AE, infection might also be a cause of AE as pneumonia becomes a cause of ARDS. Although our data contain the uncertainty of excluding superimposed infections, its value in proposing better management of AE-IP is not reduced, considering that most of the previous literature showing a poor prognosis in mechanically ventilated IPF patients included subjects with various comorbidities such as infection, heart failure and pneumothorax (12, 13, 24).

Before the introduction of NIV, CVD associated-IPs were significantly more frequent without a clear reason being evident. Recently, Park et al (5) reported that AE could occur in idiopathic NSIP and CVD-IPs and that the prognoses were similarly as poor as with IPF. Suda et al (10) also indicated that AE occurred in CVD-IPs and had a poor prognosis similar to that in IPF. Olson et al (11) reported a case series of AEs of fibrotic hypersensitivity pneumonitis with a similarly poor prognosis. Although further investigation is necessary regarding the prognostic difference between AEs in patients with idiopathic IPs and CVD-IPs, based on these previous reports, it seems unlikely that a better prognosis for AE-IP in the post-NIV cohort might be attributable to inhomogeneity of the underlying IPs.

Pressure-controlled synchronized intermittent mandatory ventilation and/or the pressure support mode was used for IMV in the pre-NIV period and the peak inspiratory pressure (22± 7 cm H2O) applied might have been a source of harm. However, this was unlikely because those pressures were far lower than the plateau pressures used in the ARDSNnet study (32± 8 cm H2O) (19). Therefore, the ventilator settings in the IMV group were considered not to be harmful, but IMV seemed to be no more effective than NIV in this study. New modes of invasive ventilation presently employed for ARDS, such as high PEEP and low tidal volume, may have the potential to change the degree of effectiveness of IMV somewhat, although this seems less likely in view of one recent report (25).

This was a retrospective historical control study in one facility only and therefore there were some limitations related to its design. The medical staff, equipment for managing respiratory failure other than the use of a ventilator, and other supportive drugs may have changed between the periods and could have generated various confounding factors. However, we could not find any drugs that could have had a significant effect on the results.

In conclusion, administering NIV as the primary method of mechanical ventilation appears to be an acceptable strategy and should be tried in the management of severe acute respiratory failure produced by AE-IP.

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