Mechanical Ventilation in Patients with End-Stage Idiopathic Pulmonary Fibrosis

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Abstract

\textbf{Background:} Acute respiratory failure (ARF) occurring during idiopathic pulmonary fibrosis (IPF) is associated with a poor prognosis. In this subset of individuals, mechanical ventilation (MV) may be required. \textbf{Objectives:} We analysed the characteristics of a group of IPF patients undergoing MV for ARF in order to give some indications on the supposed prognosis. \textbf{Methods:} Hospital records of 34 consecutive patients with IPF, who underwent MV for ARF, were retrospectively examined. Demographic data, time from diagnosis, gas exchange, Acute Physiology and Chronic Health Evaluation (APACHE) II score, ARF causes and MV failure were recorded. \textbf{Results:} Fifteen subjects (group A) underwent invasive MV and 19 patients (group B) non-invasive ventilation (NIV). The 2 groups were different for disease severity (APACHE II score 24.2 $\pm$ 6 vs. 19.5 $\pm$ 5.9; p = 0.01). Both ventilatory strategies temporarily increased PaO\textsubscript{2}/FiO\textsubscript{2} as compared with spontaneous breathing (group A: 148.5 $\pm$ 52 vs. 99 $\pm$ 39, p = 0.0004; group B: 134 $\pm$ 36 vs. 89 $\pm$ 26, p = 0.0004). NIV reduced the respiratory rate (26 $\pm$ 7 vs. 36 $\pm$ 9 with spontaneous breathing; p = 0.002). Duration of MV correlated with the time of evolution of IPF (r = 0.45; p = 0.018). The in-hospital mortality rate was 85% (100% for invasive MV, 74% for NIV). Four of the 5 survivors died within 6 months from hospital discharge (range 2–6 months). \textbf{Conclusions:} MV does not appear to have a significant impact on the survival of patients with end-stage IPF. NIV may be useful for compassionate use, providing relief from dyspnoea and avoiding aggressive approaches.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive inflammatory interstitial lung disease characterized by relative unresponsiveness to therapy and a poor prognosis with a median survival after diagnosis ranging from 3 to 5 years \cite{1}. Although the clinical course is usually slowly progressive, some patients experience a rapid decline, and acute respiratory failure (ARF) can develop during the course of the disease. In this subset of subjects, mechanical ventilation (MV) may be required, although

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its effectiveness lacks consensus [2–7]. Recently, Suh and coworkers [8] reported that an early diagnostic and therapeutic approach including a ‘lung protective’ MV led to a favourable outcome in patients with ARF during acute interstitial pneumonia, renewing the discussion on MV effectiveness in IPF patients with ARF.

Poor prognosis associated with a higher risk of infections occurring during conventional MV may suggest the use of non-invasive MV (NIV).

The aim of our retrospective study was to describe the characteristics of a group of IPF patients admitted for ARF in our centre, and to give some indications on putative prognosis.

**Materials and Methods**

**Patients**

From January 2000 to January 2007, 34 consecutive patients with IPF underwent MV for ARF for at least 12 h [9] at S. Camillo-Forlanini Hospital, Rome. In 16 subjects, the diagnosis was obtained by lung biopsy, and in the remaining 18 by the presence of all major and at least 3 minor European Respiratory Society/American Thoracic Society criteria for IPF diagnosis [10].

Internal review board approval for the review of medical records was obtained.

Subjects with known causes of interstitial lung disease (e.g., collagen vascular diseases, radiation/drug toxicity, neoplasm, environmental exposure, infections and post-operative observation after non-thoracic procedures) were excluded from evaluation.

**MV Settings**

During MV, transcutaneous oxygen saturation was measured by a finger probe.

In both MV settings (ICU/RICU), the blood gas balance was measured on admission, after modifying the ventilator setting, and at discharge.

The criteria for NIPSV discontinuation and shift to IMV were: onset of coma, cardiovascular instability or poor compliance to NIV device.

All along the ICU/RICU stay, corticosteroids (methylprednisolone 0.5–1 g/day) and broad-spectrum antibiotic regimens were administered to all the patients.

**Statistical Analysis**

All statistical analyses were performed using STATISTICA 6 software (Stat Soft, Inc., Tulsa, Okla., USA).

Continuous variables were expressed as the mean ± standard deviation. Comparisons between groups of patients were performed by the Mann-Whitney U test; the Wilcoxon test was used for intra-group analysis. Correlations between variables were calculated using the Spearman rank correlation test. The survival curve was estimated using the Kaplan-Meier method.

All p < 0.05 values were considered statistically significant.
Table 1. Baseline characteristics of patients included in the study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study population (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>26/8</td>
</tr>
<tr>
<td>Age, years</td>
<td>60 ± 11</td>
</tr>
<tr>
<td>Onset of IPF, months</td>
<td>17.9 ± 17.2</td>
</tr>
<tr>
<td>Home oxygen therapy, n</td>
<td>12</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>59 ± 14</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>57.6 ± 8.5</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>59 ± 12</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>45 ± 13</td>
</tr>
<tr>
<td>HRCT score</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>113 ± 24</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>38 ± 9.5</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.41 ± 0.09</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>101 ± 36</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>39.3 ± 9</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>79.3 ± 9</td>
</tr>
<tr>
<td>Glasgow coma scale</td>
<td>14.4 ± 1.8</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± standard deviation from the mean. TLC = Total lung capacity; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 s; DLCO = carbon monoxide diffusing capacity; HRCT = high-resolution computed tomography; SaO₂ = arterial oxygen saturation.

Results

Baseline characteristics of patients included in the study are summarized in table 1.

On admission, all patients were on oral corticosteroids (prednisone 20–40 mg/day); 6 of them were on corticosteroids and azathioprine and 4 on corticosteroids and cyclophosphamide. Twelve patients were receiving long-term home oxygen therapy; none of them was on home MV. Six patients were on a waiting list for lung transplantation, 14 were potential candidates, and the remaining subjects did not fulfill the criteria for the lung transplantation program mainly due to their age.

All patients had severe functional and radiological impairment. On hospital admission, microbiological investigations for a suspected pulmonary infection (sputum culture and/or endotracheal aspiration and/or bronchoalveolar lavage, BAL) were performed upon all patients, before the introduction of an empirical antibiotic treatment.

During respiratory ward stay, although oxygen therapy in spontaneous breathing was administered at a high flow rate, no improvement in oxygenation was observed (PaO₂/FiO₂ at admission 101 ± 36 vs. PaO₂/FiO₂ in spontaneous breathing 93.3 ± 33; p = n.s.). An increase in PaCO₂ levels (39.3 ± 9 vs. 53 ± 19 mm Hg; p = 0.0005) and a pH shifting towards acidosis (7.41 ± 0.09 vs. 7.37 ± 0.11; p = 0.007), associated with a light deterioration of mental status (Glasgow coma scale at respiratory ward admission 14.4 ± 1.8 vs. Glasgow coma scale at ICU/RIICU admission 13.4 ± 3.3; p = N.S.) were also observed. The average respiratory ward length of stay before initiating MV was 8.5 ± 6.7 days (range 1–20).

With the worsening of clinical conditions, 15 individuals met the criteria to undergo ETI and iMV (group A) and 19 subjects were admitted to the RIICU and received NIV (group B).

The disease severity was quite different between the 2 groups, with patients undergoing iMV showing a significantly higher APACHE II score as compared with subjects undergoing NIV (24.2 ± 6 vs. 19.5 ± 5.9; p = 0.01) (table 2).

Patients in the ICU

Precipitating causes of respiratory failure were known in 4 subjects (27%) undergoing iMV (2 pneumonias, 1 heart failure and 1 cardiogenic shock). The remaining patients had no immediate precipitating factors, and the worsening of respiratory function was attributed to the progression of IPF.

The mean values of the iMV setup were collected: TV 590 ± 128 ml (range 350–750), PEEP 6 ± 2 cm H₂O (range 2–7), FiO₂ 84 ± 18% (range 70–90).

Table 2. Patient characteristics at RIICU/ICU admission (T0)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (n = 15)</th>
<th>Group B (n = 19)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64.6 ± 10</td>
<td>56.1 ± 11</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>112 ± 25</td>
<td>120 ± 20</td>
<td>n.s.</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>33 ± 14</td>
<td>36 ± 9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.34 ± 0.14</td>
<td>7.4 ± 0.07</td>
<td>n.s.</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>99 ± 39</td>
<td>89 ± 26</td>
<td>n.s.</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>57.5 ± 23</td>
<td>49 ± 15.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Base excess</td>
<td>1.2 ± 7.4</td>
<td>4.2 ± 6.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Glasgow coma scale</td>
<td>12.3 ± 3.4</td>
<td>14.6 ± 0.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>24.2 ± 6</td>
<td>19.5 ± 5.9</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Onset of IPF, months</td>
<td>18.6 ± 16</td>
<td>17.8 ± 18</td>
<td>n.s.</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>44 ± 6</td>
<td>48 ± 12</td>
<td>n.s.</td>
</tr>
<tr>
<td>HRCT score</td>
<td>2.37 ± 0.8</td>
<td>2.56 ± 0.5</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± standard deviation from the mean. n.s. = Not significant; DLCO = carbon monoxide diffusing capacity; HRCT = high-resolution computed tomography.
We observed a transitory significant increase in PaO$_2$/FiO$_2$ values (148.5 ± 52 vs. 99 ± 39; p = 0.0004), with no significant effects on PaCO$_2$ and pH values. Conventional ventilation temporarily corrected PaO$_2$/FiO$_2$ in 4 patients, improved PaO$_2$/FiO$_2$ in 4 and failed to improve gas exchange in 7 patients.

The RR was not analysed because patients underwent iMV in a volume-controlled mode (RR = 12 breaths/min).

The median iMV duration was 7 days (range 1–16), with 20 ± 3.5 h/day.

All patients died after 7.3 ± 6.7 days; the causes of death were septic shock in 4 patients (nosocomial pneumonia due to *Enterobacter cloaca*, *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Acinetobacter baumannii*), cardiac arrest in 4 and heart failure with cardiogenic shock in 7 patients.

**Patients in the RIICU**

The causes of ARF were known in 8 patients (42%; 3 pneumonias, 2 pneumonias with pleuritis, 1 pulmonary embolism, 1 congestive heart failure and 1 ARF after BAL).

The following initial NIPSV setting was used: pressure support 18 ± 4 cm H$_2$O (range 15–22), PEEP 7 ± 2 cm H$_2$O (range 4–10), FiO$_2$ 67 ± 24% (range 40–90).

NIV determined a temporary significant improvement in PaO$_2$/FiO$_2$ in comparison with spontaneous breathing (134 ± 36 vs. 89 ± 26; p = 0.0004) with no significant effects on PaCO$_2$ and pH values.

Importantly, NIV determined a significant decrease in RR (26 ± 7 vs. 36 ± 9 breaths/min; p = 0.002) in all individuals.

NIV corrected PaO$_2$/FiO$_2$ in 1 patient who was discharged after 7 days, and improved PaO$_2$/FiO$_2$ in 9 pa-
Mechanical Ventilation in IPF

Dis­cu­sion

This observa­tional re­tros­pec­tive study de­scribes the clin­i­cal course, MV set­ting and out­come of 34 end-stage IPF pa­tients who re­ceived MV for ARF.

IPF is a pro­gres­sive and usu­ally lethal dis­ease. The pre­sen­ce of refractory hy­pox­ea and a marked tachy­pnoea char­ac­ter­izes the end stages of the dis­ease and causes ARF in about 40% of pa­tients [4]. In the first stage of ARF, al­ve­olar hy­po­ventilation and hy­per­cap­nia is not a com­mon find­ing, prob­a­bly due to res­pi­ra­tory mus­cle ad­apt­a­tion to the in­creased res­pi­ra­tory work­load as­so­ci­ated with lung stiff­ness. In the late stage, the onset of res­pi­ra­tory fatigue leads to CO₂ re­tention [18]. Con­sistent with this ob­ser­va­tion and ac­cord­ing to the lit­er­a­ture [2–7], in our study, ARF was char­ac­ter­ized by a rap­id wors­en­ing of gas ex­change with se­vere hy­pox­ea, CO₂ re­tention and pH shift towards aci­dosis, as­soci­ated with a de­terio­ra­tion of the men­tal sta­tus. Be­cause of the se­vere al­ter­a­tions in lung me­cha­nics, in or­der to max­i­mize al­ve­olar re­cruit­ment, high TV val­ues are usu­ally ap­plied when per­form­ing con­ven­tion­al MV (iMV) in IPF pa­tients [2–7, 18].

This ven­tila­tory pat­tern may lead to se­rious side ef­fects al­ready de­scribed for acute res­pi­ra­tory distress syn­drome (pneu­mothorax and ven­tila­tor-in­duced lung in­jury) [19].

In our study, we found that iMV was able to tem­porar­ily cor­rect PaO₂/FiO₂ in 25% of sub­jects, but sim­i­lar­ly to the ob­serva­tions of Nava and Rubini [18], it did not mod­i­fy CO₂ re­tention (fig. 1).

In or­der to re­duce the risk of baro­trau­ma, pro­tective ven­tila­tory strat­egies [20] have been per­formed in acute res­pi­ra­tory distress syn­drome, and, re­cent­ly, in IPF pa­tients, ob­tain­ing en­cour­aging re­sults [8].

In a re­cent re­tros­pec­tive study on pa­tients with chron­ic in­ter­stitial lung dis­ease (ILD) in­clud­ing 30 in­di­viduals with IPF, Fernan­dez-Perez and cowor­kers [21] sug­gest that both se­ver­ity of ill­ness and high PEEP val­ues are as­so­ci­ated with a de­creased sur­vival rate.

In our study, the use of PEEP val­ues sim­i­lar to those em­ployed by Fernan­dez-Perez et al. [21] in the sur­vivors’ group was as­so­ci­ated with a worst prog­no­sis (in-hos­pi­tal mor­tal­ity rate 85%), sug­gest­ing that the se­ver­ity of dis­ease should be con­sid­ered cru­cial for the out­come.

Al­tho­ugh NIV is con­sid­ered as a first-line in­ter­ven­tion ther­apy in pa­tients with chron­ic ob­struc­tive pul­mo­nary dis­ease (COPD), and it has been suc­cess­ful­ly per­formed in acute car­di­o­gen­ic pul­mo­nary oedema and in child­hood acute neuromus­cu­lar res­pi­ra­tory fail­ure, its
use in acute hypoxaemic respiratory failure is still under debate [22–25]. Nevertheless, NIV, compared with iMV, has fewer side effects (ventilator-acquired pneumonia and sepsis) [26].

In our study, NIV allowed the temporary correction of PaO₂/FiO₂ in 1 patient, its improvement in 9, but, as observed for iMV, failed to prevent CO₂ retention. We cannot rule out that due to its large volume, the helmet may have contributed to this phenomenon. It has been assumed that breathing with a helmet is similar to breathing in a semiclosed environment, and therefore the PCO₂ inside the helmet is primarily a function of the subject’s CO₂ production and the flow of fresh gas through the helmet. Clinical and physiological studies comparing helmet and face mask effectiveness in delivering NIV showed that the face mask was more effective than the helmet in reducing CO₂ rebreathing [27, 28]. On the other hand, it has been demonstrated that the use of the helmet to provide NIV, allowing the patients to freely communicate, drink and expectorate, improving collaboration with caregivers and clearance of the airways and decreasing the rate of complications directly related to the administration of NIV, may improve patient compliance. According to these observations, it may be possible that the use of a helmet, in the attempt to improve compliance and tolerability of NIV and avoiding the early discontinuation from MV itself, may have contributed to the outcomes observed in our study.

Importantly, a significant reduction in RR was obtained in all NIV patients.

Both ventilatory strategies failed to have a significant impact on survival rate (no survivors in the iMV group and 5 survivors in the NIV group, 4 of whom subsequently died shortly after hospital discharge).

According to the literature, in our study, cardiovascular diseases were the main cause of patients’ death, possibly because of right ventricular failure due to pulmonary hypertension (all patients had electrocardiographic signs of right ventricular overload, and the 7 patients who underwent echocardiography showed severe increase in pulmonary arterial pressure) [1, 29]. Interestingly, we observed that 5 patients had cardiac arrest as cause of death, possibly due to the severe chronic hypoxaemia that characterizes IPF and its worsening during ARF. On the other hand, in our experience, we did not observe a high cardiac arrest rate using NIV in other respiratory diseases (e.g., COPD).

Although the study was not performed to compare the effectiveness of the 2 modalities of ventilation, we believe that the observation that all survivors were treated with NIV (fig. 2) may be mainly due to the different disease severity between the 2 groups, as established by the significantly higher APACHE II score measured in patients undergoing iMV.

Despite that our study was retrospective and limited to 1 medical centre, to the best of our knowledge, no prospective multi-centre studies have been performed in this field and, importantly, to date, our report is the study which analyses the largest sample size of patients undergoing MV because of ARF during IPF.

In IPF patients, NIV has been analysed in only a few retrospective studies evaluating a small number of patients; 5 in the study by Blivet et al. [2], 11 in the study by Fumeaux et al. [4], 7 in the study by Saydain et al. [5], and 1 in the report by Nava and Rubini [18]. Unfortunately, no data on IPF patients treated with NIV are available in the study of Fernandez-Perez et al. [21].

These authors found that NIV avoided ETI in 1/5 (20%), 0/11 (0%), 1/7 (14%) and 0/1 (0%) patients, respectively. In our study, NIV prevented ETI in 5/19 individuals (26%).

Furthermore, since in the only survivor still alive, ARF had arisen as a complication during diagnostic procedures (BAL) and since the patient was discharged after 1 week, we cannot exclude that the clinical conditions may have improved despite therapies.

Still, we cannot rule out that an early intervention with NIV, in patients with a clinical condition not yet as severe as in the iMV group, may have been crucial in the outcome observed.

Conclusion

The institution of MV in patients with ILD may raise philosophical questions based on the expected prognosis [30]. A difference in outcome of ILD patients undergoing MV may be due to clinical and radiologic features and a pathologic ‘pattern’ [31], timing and type of therapeutic intervention, patients’ severity illness score, and MV approach (high vs. low TV and iMV vs. NIV).

Despite its substantial inability to modify the estimated life expectancy of IPF patients, our data, although lacking a validated measurement scale, suggest that NIV, significantly decreasing the RR, may be considered a capital palliative option that, together with other medical supports, may help to reduce patient discomfort, avoiding more aggressive approaches. Furthermore, in addition to this, to the best of our knowledge, this is the first study on IPF patients with ARF performed in a RlICU.
This setting has recently been demonstrated to be a cost-effective alternative to ICUs in the treatment of COPD patients [32]. We cannot rule out that a subset of IPF patients could be less costly treated in RIICUs.

Prospective multi-centre studies should be performed to investigate the role of MV, especially NIV, as a compassionate approach and/or as early intervention in IPF patients with ARF.

References