

Mechanical Ventilation in Patients with End-Stage Idiopathic Pulmonary Fibrosis

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Key Words

Acute respiratory failure · Idiopathic pulmonary fibrosis · Invasive mechanical ventilation · Non-invasive mechanical ventilation

Abstract

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. **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. **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. **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 ± 6 vs. 19.5 ± 5.9 ; $p = 0.01$). Both ventilatory strategies temporarily increased $\text{PaO}_2/\text{FiO}_2$ as compared with spontaneous breathing (group A: 148.5 ± 52 vs. 99 ± 39 , $p = 0.0004$; group B: 134 ± 36 vs. 89 ± 26 , $p = 0.0004$). NIV reduced the respiratory rate (26 ± 7 vs. 36 ± 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). **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.

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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 [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.

ARF was defined as an acute and rapidly progressive decline in respiratory function and exacerbation of dyspnoea within a few days, associated with a deterioration of hypoxaemia with a partial pressure of arterial oxygen/fraction of inspired oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) <250 [2].

Sepsis and shock diagnoses were based on American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (1992) criteria [11].

To assess the disease severity, we recorded the last pulmonary function tests and high-resolution computed tomography of each patient before ARF onset. An experienced study-blinded radiologist (P.M.) calculated a high-resolution computed tomography score, according to literature [2].

Assessment of IPF Patients with ARF

On the respiratory ward, demographic information, average duration of the disease from diagnosis to hospital admission, arterial blood gas, respiratory rate (RR) and heart rate were analysed. The decision to initiate NIV or to perform endotracheal intubation (ETI), in the presence of the patient’s acute alteration of consciousness [12], depended on the clinical evaluation by the attending physician in the respiratory ward.

In presence of contraindications to NIV [13], individuals underwent ETI and invasive MV (iMV) was performed, unless patients had previously declared a wish not to be resuscitated.

NIV was carried out in a respiratory intermediate intensive care unit (RIICU).

During ICU/RIICU stay and upon discharge, we also recorded the reason for admission, Acute Physiology and Chronic Health Evaluation (APACHE) II score [14], length of stay, duration of MV (MV days and MV h/day), NIV failure, ETI and in-hospital mortality rate (%).

Effectiveness of MV was calculated according to the criteria of Meduri et al. [15] slightly modified by means of the comparison between the best $\text{PaO}_2/\text{FiO}_2$ after a spontaneous breathing trial before starting MV (T0) and the best $\text{PaO}_2/\text{FiO}_2$ during an MV trial (T1). MV was considered to correct PaO_2 with a difference between $\text{PaO}_2/\text{FiO}_2$ (T1) and $\text{PaO}_2/\text{FiO}_2$ (T0) >100 , to improve PaO_2 with a difference ≥ 50 , and to fail PaO_2 correction with a difference <50 .

MV Settings

Patients admitted to the ICU underwent ETI with cuffed tubes (internal diameters 7.5–8.5 mm), after intravenous administration of midazolam (2.5–5 mg) or fentanyl (1 $\mu\text{g}/\text{kg}$) for sedation; all patients received propofol (1.5–2 mg/kg of measured body weight); 7 patients also received vecuronium (0.1 mg/kg) or pancuronium (0.05 mg/kg) to obtain a better adaptation to MV. Both iMV and NIV were performed by Puritan Bennett 7200A[®] ventilator (Nellcor Puritan Bennett Inc. 4280, Pleasanton, Calif., USA). Conventional ventilation (iMV) was applied in a volume-controlled mode with a mean delivered tidal volume (TV) value of 7.5 ml/kg (range 6–9) of measured body weight. Positive end expiratory pressure (PEEP) was set in order to obtain the best oxygenation with the fewest side effects on haemodynamics [16]; arterial oxygen saturation was measured online.

NIV was performed in pressure support mode (NIPSV); a helmet (CaStar[®]; Starmed, Mirandola, Italy) was used as an interface for all patients. Pressure support, PEEP and flow-by trigger [17] values were adjusted in order to obtain the best oxygenation and to reduce RR and were modified on the basis of blood gas data.

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

In both MV settings (ICU/RIICU), 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/RIICU 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 \pm 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

Parameters	Study population (n = 34)
Gender, M/F	26/8
Age, years	60 ± 11
Onset of IPF, months	17.9 ± 17.2
Home oxygen therapy, n	12
TLC, % predicted	59 ± 14
FVC, % predicted	57.6 ± 8.5
FEV ₁ , % predicted	59 ± 12
DLCO, % predicted	45 ± 13
HRCT score	2.4 ± 0.7
Heart rate, beats/min	113 ± 24
RR, breaths/min	38 ± 9.5
Arterial pH	7.41 ± 0.09
PaO ₂ /FiO ₂	101 ± 36
PaCO ₂ , mm Hg	39.3 ± 9
SaO ₂ , %	79.3 ± 11
Glasgow coma scale	14.4 ± 1.8

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 spon-

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

Parameters	Group A (n = 15)	Group B (n = 19)	Significance
Age, years	64.6 ± 10	56 ± 11	p = 0.03
Heart rate, beats/min	112 ± 25	120 ± 20	n.s.
RR, breaths/min	33 ± 14	36 ± 9	n.s.
Arterial pH	7.34 ± 0.14	7.4 ± 0.07	n.s.
PaO ₂ /FiO ₂	99 ± 39	89 ± 26	n.s.
PaCO ₂ , mm Hg	57.5 ± 23	49 ± 15.4	n.s.
Base excess	1.2 ± 7.4	4.2 ± 6.2	n.s.
Glasgow coma scale	12.3 ± 3.4	14.6 ± 0.8	n.s.
APACHE II score	24.2 ± 6	19.5 ± 5.9	p = 0.01
Onset of IPF, months	18.6 ± 16	17.8 ± 18	n.s.
DLCO, % predicted	44 ± 6	48 ± 12	n.s.
HRCT score	2.37 ± 0.8	2.56 ± 0.5	n.s.

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.

taneous 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).

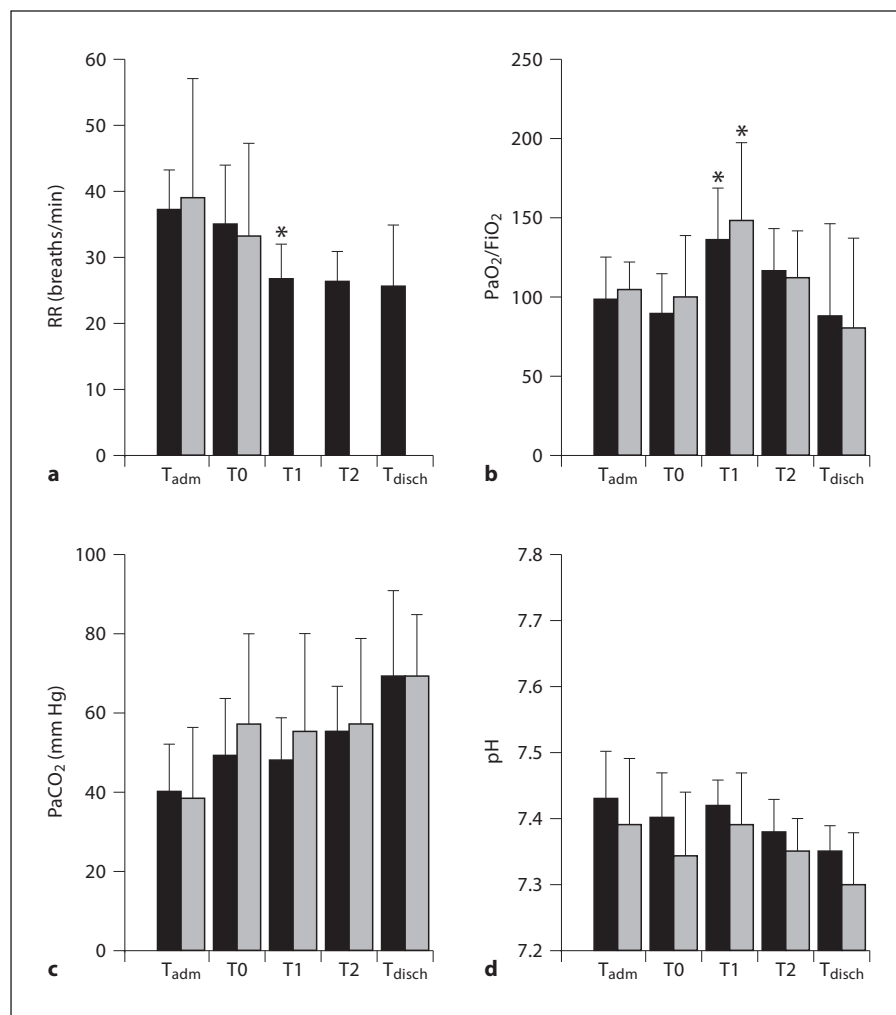
The disease severity was quite different between the 2 groups, with patients undergoing iMV showing a significantly higher APACHE II score as compared with subjects undergoing NIV (24.2 ± 6 vs. 19.5 ± 5.9; p = 0.01) (table 2).

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).

Fig. 1. Evolution of the RR, PaO₂/FiO₂, PaCO₂ and pH during MV settings. T_{adm} = Time of respiratory ward admission; T₀ = time of RIICU (black histograms, NIV) or ICU (grey histograms, iMV) admission; T₁ = best values obtained during MV; T₂ = time when variables began worsening; T_{disch} = time of discharge/death. * Significant differences between T₀ and T₁.



We observed a transitory significant increase in PaO₂/FiO₂ values (148.5 ± 52 vs. 99 ± 39 ; $p = 0.0004$), with no significant effects on PaCO₂ and pH values. Conventional ventilation temporarily corrected PaO₂/FiO₂ in 4 patients, improved PaO₂/FiO₂ 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 *Enterobacterium cloacae*, *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 H₂O (range 15–22), PEEP 7 ± 2 cm H₂O (range 4–10), FiO₂ $67 \pm 24\%$ (range 40–90).

NIV determined a temporary significant improvement in PaO₂/FiO₂ in comparison with spontaneous breathing (134 ± 36 vs. 89 ± 26 ; $p = 0.0004$) with no significant effects on PaCO₂ 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 PaO₂/FiO₂ in 1 patient who was discharged after 7 days, and improved PaO₂/FiO₂ in 9 pa-

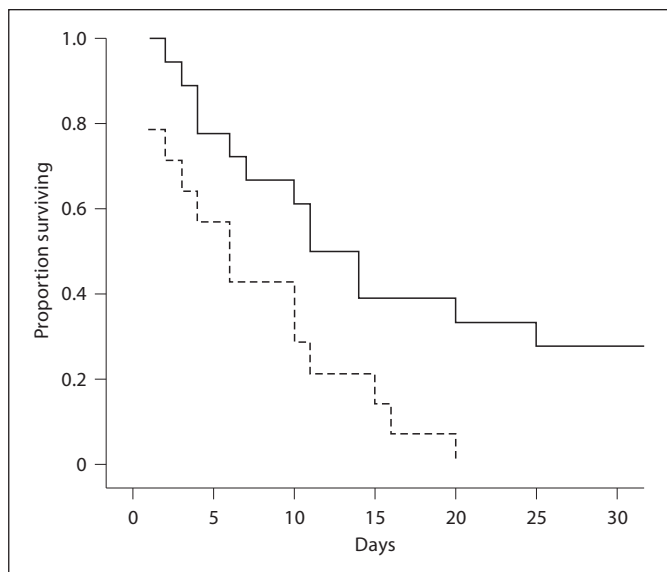


Fig. 2. Survival curve of patients included in the study. Continuous line = Group B patients; dotted line = group A patients. Survivors are not represented in this curve.

tients; 4 of them were discharged after 16 ± 3.5 days. In 5/19 individuals (26.3%), despite the observed improvement in oxygenation, NIV was withdrawn because of poor compliance (3 patients), pneumothorax (1 patient) and blood emesis (1 patient). All of them requested not to be resuscitated and died after 16 ± 5.4 days.

NIV failed to improve $\text{PaO}_2/\text{FiO}_2$ in 9 individuals: 5 underwent iMV and died after 8.8 ± 5.8 days and 4 died before undergoing ETI. The duration of NIV varied greatly among the 19 patients (median 9 days, with a range of 1–28 days) for 15 ± 2.2 h/day.

In the 14 patients who died during NIV (mortality rate 74%), the causes of death were cardiac arrest in 5 patients, cardiogenic shock in 8, and septic shock in 1 patient.

In all the 5 survivors, the causes of ARF were identified (2 pneumonias, 1 heart failure, 1 pneumonia associated with pleuritis, 1 ARF after BAL).

Four of them died within 6 months from hospital discharge (range 2–6 months), 1 is still alive, and none of them were on the waiting list for lung transplantation.

Figure 1 shows the trend of RR, $\text{PaO}_2/\text{FiO}_2$, PaCO_2 and pH during MV.

Duration of MV (iMV plus NIV) positively correlated with the time of evolution of IPF ($R = 0.45$; $p = 0.018$).

The survival curve of patients included in the study is shown in figure 2 (in-hospital mortality rate 85%: 100% for iMV, 74% for NIV).

Discussion

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 hypoxaemia 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 CO_2 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 hypoxaemia, CO_2 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 $\text{PaO}_2/\text{FiO}_2$ in 25% of subjects, but similarly to the observations of Nava and Rubini [18], it did not modify CO_2 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 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 RIICU.

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.

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