Prognosis of Patients With Advanced Idiopathic Pulmonary Fibrosis Requiring Mechanical Ventilation for Acute Respiratory Failure*

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Study objective: To evaluate the beneficial effect of mechanical ventilation (MV) in patients with idiopathic pulmonary fibrosis (IPF) who develop acute respiratory failure (ARF), with special emphasis on prognosis.

Design: Retrospective study.

Setting: Ten-bed respiratory ICU that is a part of a respiratory department actively involved in lung transplantation (LTx).

Patients: From 1991 to 1999, 23 patients (mean age, 52.9 years; range, 21 to 82 years) with IPF required MV for ARF. At admission to the ICU, 16 patients were potential candidates for LTx, with 5 patients already on the waiting list.

Measurements and results: Survival and gas exchange under MV were assessed. The precipitating cause of ARF was also analyzed. With the exception of 1 patient who successfully received a single-lung transplant 6 h after initiation of MV, all the remaining 22 patients died while receiving MV (median survival, 3 days; range, 1 h to 60 days). The duration of MV correlated positively with baseline vital capacity (percent predicted) ($R = 0.54; p = 0.01$) and baseline total lung capacity (percent predicted) ($R = 0.71; p < 0.001$), and correlated negatively with baseline $P_{a}CO_{2}$ ($R = -0.47; p = 0.03$) and the duration of evolution of IPF ($R = -0.50; p = 0.01$). Duration of MV did not correlate with the duration of immunosuppressive therapy ($R = -0.24; p = 0.27$) or duration of oxygen therapy ($R = -0.32; p = 0.14$) prior to admission. The precipitating cause of ARF was most often not identified.

Conclusions: Our data support the general belief that MV does not benefit IPF patients presenting with ARF. Initiation of MV in IPF patients is thus questionable and should, in our opinion, be restricted to patients in whom LTx can be performed within a few days after initiation of MV.

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Key words: idiopathic pulmonary fibrosis; lung transplantation; mechanical ventilation

Abbreviations: adODIN = organ dysfunction and/or infection assessed at ICU admission; ARF = acute respiratory failure; endODIN = organ dysfunction and/or infection assessed at discontinuation of mechanical ventilation; $F_{i}O_{2}$ = fraction of inspired oxygen; iniODIN = organ dysfunction and/or infection assessed at initiation of mechanical ventilation; IPF = idiopathic pulmonary fibrosis; LTx = lung transplantation; MV = mechanical ventilation; ODIN = organ dysfunction and/or infection; TLC = total lung capacity; VC = vital capacity

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing inflammatory lung disease of unknown etiology. The prognosis of the disease is particularly severe, with a mean length of survival after diagnosis ranging from 3 to 5 years.1 This poor prognosis is explained by the poor responsiveness to currently employed treatments, including steroids and cytotoxic agents. Studies2,3 evaluating new antifibrotic agents have yielded encouraging results, but the data are still preliminary. Additionally, patients with IPF may also now be considered for lung transplantation (LTx). Guidelines have been published,4 but the timing of referral for transplantation in such patients is not easy to define. Despite progress in the classi-
fication of IPF with the definition of several histologic patterns that are more responsive to therapy,\textsuperscript{5,6} the prognosis in an individual patient remains variable. In some patients, the disease remains stable, whereas in others, life-threatening episodes of acute respiratory failure (ARF) are observed. In the latter patients, mechanical ventilation (MV) may be considered a therapeutic option, but the benefit offered using this strategy is not well documented. In our center, MV has been initiated on several occasions in patients with IPF developing ARF.

The aim of our study was to evaluate the beneficial effect of MV in this setting. To this purpose, we reviewed retrospectively all cases of patients with IPF who received MV for ARF in our center, with special emphasis on overall prognosis. The precipitating cause of ARF was also analyzed.

**Materials and Methods**

**Patients**

Hospital records of 27 consecutive patients with pulmonary fibrosis requiring MV for ARF admitted to our center between September 1990 and October 1999 were retrospectively examined. Our center is a 10-bed respiratory ICU that is a part of a respiratory department actively involved in LTx. The clinical diagnosis of IPF was based on the association of the three following criteria: (1) history of dyspnea and examination findings compatible with the diagnosis of IPF (bilateral crackles and/or clubbing); (2) chest radiograph and/or high-resolution CT scan showing typical pattern of IPF, such as ground-glass areas, irregular linear opacities, and honeycombing;\textsuperscript{2} and (3) no known cause of pulmonary fibrosis, such as hypersensitivity pneumonitis, connective tissue disease, drug or radiation-induced pneumonitis, or less frequent causes. Thus, four patients with pulmonary fibrosis secondary to radiation (n = 2), environmental exposure (n = 1), and sarcoidosis (n = 1) were excluded from analysis and the remaining 23 patients form the basis of the study.

The baseline characteristics of these 23 patients are given in Table 1. We recorded the most recent results of pulmonary function tests performed before the current hospitalization when the patient was considered to be in a stable condition. At admission to the ICU, 16 patients were potential candidates for LTx: 5 patients were already on the waiting list for LTx (mean ± SD waiting time, 18.6 ± 12 days); 3 patients who had completed the preoperative evaluation and who were not yet on the waiting list were enrolled 2.3 ± 3 days after ICU admission; and 8 patients were in the preoperative evaluation phase. The remaining seven patients did not fulfill the selection criteria for LTx program.\textsuperscript{4} Patients considered for LTx had a longer history of IPF, received more immunosuppressive therapy (corticosteroids and/or cytotoxic agents), required more oxygen, and had a longer duration of oxygen therapy than patients who were not suitable for LTx. Additionally, patient candidates for a LTx had worse baseline respiratory function (as assessed by vital capacity [VC] and total lung capacity [TLC]) than those who were not. In 15 of the 23 patients (65%), the diagnosis of IPF was confirmed by histologic examination (by open lung biopsy specimen before admission to the ICU [n = 9], by autopsy [n = 5], or by examination of the explanted lung in the case of LTx [n = 5]). In 14 of these 15 patients, an attempt at classification was made according to the published criteria\textsuperscript{5,6}: usual interstitial pneumonia (n = 8), nonspecific interstitial pneumonia (n = 1), or classification considered impossible (n = 5). In 1 of the 15 patients, open lung biopsy was performed in another country and histologic data were not available.

The decision of initiating MV depended on the attending physician. This decision was based on the presence of at least one of the two following criteria of respiratory failure: severe dyspnea with marked deterioration of oxygen saturation, or oxygen saturation < 80% despite a high oxygen flow rate using a high-
concentration facial mask (Rusch Medical; Le Paget, France), or acute alteration of consciousness with or without marked hypercapnia.

The patients were receiving mechanical ventilation using Cesar (Taema; Paris, France), Erica (Engström; Bromma, Sweden), or Evita 2 (Dräger Medical; Lübeck, Germany) ventilators. The initial settings of the ventilator were adjusted in order to minimize peak airway pressure and to maintain adequate ventilation. To accomplish the goal of limiting peak airway pressure, PaO₂ was permitted to rise. The fraction of inspired oxygen (FIO₂) was 100% at the time of intubation and was then progressively decreased to the lowest level compatible with arterial oxygen hemoglobin saturation > 90%. Thereafter, these settings were adjusted by the attending physician. After intubation, there were no decisions of withdrawal of support or of "do not resuscitate."

Assessment of the Cause of ARF

The precipitating cause of ARF leading to MV was investigated retrospectively by analyzing the medical records of patients. The final diagnosis of the cause of ARF was made after reviewing the clinical, radiologic, ultrasound, microbiologic, hemodynamic, and pathologic records of each patient when available. The diagnosis of pneumonia was considered if the patient met the following criteria: appearance of a new pulmonary infiltrate on chest radiograph and documented pulmonary pathogen, ie, culture of BAL yielding ≥ 10⁴ cfu/mL or culture of Wimberley brush catheter with ≥ 10³ cfu/mL.

Assessment of Patients During ARF

Several parameters were retrieved from the medical records: outcome (death or survival), duration of MV up to extubation or death, and percentage of patients who underwent LTx. Arterial blood gas measurements (Radiometer; Copenhagen, Denmark) obtained before initiation of MV and at different time points after MV (within 6 h after initiating the MV [day 0], daily during the first 5 days, and at day 7 and day 10) were also documented. Concerning the oxygenation parameters, the PaO₂ value measured before MV regardless of oxygen flow rate was taken. After MV, the PaO₂/FIO₂ ratio was calculated. The incidence of nosocomial pneumonia in patients receiving MV was also assessed. The diagnosis of nosocomial pneumonia was based on the following criteria: new pulmonary infiltrate on frontal chest radiograph and documented pulmonary pathogen, ie, culture of BAL yielding ≥ 10⁴ cfu/mL or culture of Wimberley brush catheter demonstrating ≥ 10³ cfu/mL and at least one of the following criteria: fever > 38°C, leucocytosis > 10,000/µL, or purulent respiratory secretions.

The presence of organ dysfunction and/or infection in ICU was evaluated using the organ dysfunction and/or infection (ODIN) model described by Fagon and colleagues. This model includes the assessment of respiratory, cardiovascular, renal, hepatic, hematologic, and neurologic dysfunctions, and the presence of documented infection. Each organ failure and/or infection accounts for one point of the score. The highest score over the 24-h period was recorded. ODIN was assessed at ICU admission (adODIN), at the initiation of MV (iniODIN), and at discontinuation of MV (endODIN). In the patients who died, endODIN corresponded to the highest score within the 24 h before death. In the patients who were already receiving MV at ICU admission (n = 4), the adODIN was taken as iniODIN.

Statistical Analysis

All comparisons were unpaired. Statistical analysis was performed using a computer (Sigma Stat; Jandel Scientific; San Jose, CA). Continuous variables were expressed as mean and SDs for normally distributed variables and then compared using a Student’s t test. Nonnormally distributed variables were expressed as median and 25th to 75th percentile values, and then compared using the Mann-Whitney test. For correlation between nonnormally distributed variables, the Spearman correlation coefficient was used.

The survival curve was estimated using the Kaplan-Meier method. Multiple comparisons between continuous variables were made using analysis of variance for repeated measures. All p values ≤ 0.05 were considered statistically significant.

RESULTS

At the time of intubation (day 0), volume-control ventilation was used with tidal volume ranging from 8 to 13 mL/kg and respiratory rate from 16 to 20 breaths/min. The corresponding mean peak airway pressure that resulted at day 0 was 50 ± 7 cm H₂O (range, 25 to 85 cm H₂O).

A precipitating cause of ARF was identified in nine patients (39%). Investigations performed after intubation in order to assess the cause of ARF were as follows: transthoracic echocardiography (n = 8), right heart catheterization (n = 7), bronchial microbiological sampling (n = 17 including 10 perfibroscopic sampling), and pathologic analysis (n = 9). Seven patients who died very early after intubation were not investigated. Bacterial pneumonia was documented in five patients; in four of them, pneumonia was hospital acquired. The causative agents were Staphylococcus aureus in four patients (the strain was resistant to methicillin in two cases), and Pseudomonas aeruginosa in one patient. Pneumonia was diagnosed 24 h after an open lung biopsy in one patient, and 24 h after a BAL in one patient, whereas no precipitating factor of pneumonia was identified in the remaining patients. The other causes of ARF were left ventricular failure (n = 2), pneumothorax (n = 1), and BAL (n = 1). In the remaining 14 patients, no evident cause was identified. Among these 14 patients, 4 patients presented at ICU admission with an influenza-like syndrome associated with bleeding leucocytosis > 15,000/µL and new pulmonary infiltrate on the chest radiograph. No documented infection was found in these four patients, but they were all already receiving antibiotic therapy at the time of ARF.

With the exception of one patient who successfully received a single-lung transplant 6 h after initiation of MV, the remaining 22 patients died while receiving MV. The survival curve of these 22 patients is shown in Figure 1. The duration of MV varied greatly among these 22 patients (median 3 days; range, 1 h to 60 days). Two patients died within the first 2 h after initiation of MV, and 10 patients (45%) died by the end of day 2. The duration of MV

CHEST / 120 / 1 / JULY, 2001 215
correlated positively with baseline VC (percent predicted) ($R = 0.54; p = 0.01$; Fig 2) and baseline TLC (percent predicted) ($R = 0.71; p < 0.001$; Fig 3). The duration of MV correlated negatively with baseline PaCO$_2$ ($R = -0.47; p = 0.03$) and the duration of evolution of IPF ($R = -0.50; p = 0.01$), and did not correlate with the duration of immunosuppressive therapy ($R = -0.24; p = 0.27$) or duration of oxygen therapy prior to ICU admission ($R = -0.32; p = 0.14$).

Results of arterial blood gas analysis performed just before initiation of MV were available for all 23 patients. Patients had severe hypoxemia (mean PaO$_2$, 59 ± 5 mm Hg) despite high oxygen flow rate (mean oxygen flow rate, 16 ± 9 L/min). Because some patients died (or received LTx in one case) at various time points after initiation of MV, blood gas analysis was not available for every patient at each time point. Blood gas analysis performed within 6 h after the initiation of MV (Fig 4) showed profound hypoxemia (PaO$_2$/FiO$_2$ ratio at 82 ± 38 mm Hg). Only four patients had a PaO$_2$/FiO$_2$ ratio > 100 mm Hg. PaCO$_2$ value recorded just before intubation (47.7 ± 14 mm Hg) was higher ($p = 0.03$) than baseline PaCO$_2$ value, ie, the value obtained when patients were in a stable condition (41 ± 4 mm Hg; Fig 5). In addition, the use of MV failed to rapidly correct PaCO$_2$ since the PaCO$_2$ value measured at day 0 (73 ± 31 mm Hg) was significantly higher ($p < 0.001$) than that measured before intubation (Fig 5). Similarly, PaCO$_2$ values at day 1 and day 2 were still higher than the PaCO$_2$ value measured before MV ($p < 0.001$ and $p = 0.015$, respectively). After day 2, the PaCO$_2$ value did not differ significantly from the PaCO$_2$ value obtained before MV.

At admission to ICU, the adODIN score was 1.40 ± 0.6. Seven patients had an adODIN score > 1. In addition to respiratory failure that was present in all patients, cardiovascular dysfunction was observed in two patients and documented infection was found in five patients (two of whom had also cardiovascular dysfunction). Eleven patients (48%)
developed at least one organ dysfunction and/or infection after the initiation of MV. The endODIN (2.45 ± 0.9) was significantly higher than the iniODIN (1.86 ± 1.0; p = 0.005). Cardiovascular failure (five patients), renal failure (three patients), and a combination of cardiovascular and renal failure (two patients) were the most common organ dysfunctions developing after initiation of MV. Nosocomial pneumonia occurred in four other patients. No significant difference was found between the number of organ dysfunctions in the 10 patients who died within 2 days (2.4 ± 0.96) and that of patients who died after day 2 (2.4 ± 0.95; p = 0.94). Moreover, no correlation was found between the number of organ failures and the duration of MV (R = −0.11, p = 0.6).

In the 10 patients who died within the first 2 days after intubation, the cause of death was oxygenation failure and severe alveolar hypoventilation associated with hemodynamic failure in 8 patients. The other causes of death were brain death related to severe hypoxemia (n = 1) and septic shock associated with left ventricular failure (n = 1). In these 10 patients, the mean PaO2/Fio2 ratio, the mean Paco2, and the mean peak airway pressure within the 24 h before death were 81 ± 56 mm Hg, 90 ± 46 mm Hg, and 60.5 ± 20 cm H2O, respectively. In the 12 patients who died after day 2, causes of death were as follows: oxygenation failure and severe alveolar hypoventilation (n = 3); oxygenation failure and severe alveolar hypoventilation associated with hemodynamic failure (n = 5), with acute renal failure (n = 1) or with bacterial pneumonia (n = 1); hemodynamic failure (n = 1); and acute intestinal obstruction (n = 1).

Blood gas and right-sided hemodynamic measurements were obtained in four patients who received inhaled nitric oxide. Despite this treatment, no significant change in hemodynamic or oxygenation parameters was observed. Nine patients received high-dose corticosteroids (15 mg/kg) after initiation of MV without visible effect on arterial oxygenation.

**Discussion**

Our results indicate that in patients with end-stage IPF presenting with ARF, MV does not lead to improvement in gas exchange and is associated with a poor prognosis. We also found that the precipitating cause of ARF was not identified in the majority of our patients.

Thus, this current study suggests that natural progression of IPF was the most frequent cause of clinical deterioration. This fact has already been reported in the meta-analysis conducted by Panos and colleagues.1 In this study, which included 543 patients, respiratory failure secondary to IPF progression and pulmonary infection were the cause of death in 38% and 2.8% of patients, respectively. The differential diagnosis between progression of IPF and pulmonary infection is quite difficult in such patients. In the present series, among 14 patients without identified cause of ARF, 4 patients presented at hospital admission with an influenza-like syndrome associated with blood leukocytosis > 15,000/µL and new pulmonary infiltrate on chest radiograph. This presentation mimicked pulmonary infection but the microbiological culture results of blood and tracheobronchial aspirates remained negative. Kondoh and coworkers10 described an influenza-like syndrome in three patients corresponding to an exacerbation of IPF. The histology findings in the lungs showed an association of acute lung injury and usual interstitial pneumonia pattern.10 Such changes were also noted in three of our patients on autopsy study (data not shown). According to Kondoh et al,10 the influenza-like syndrome may correspond to either an acute exacerbation of the inflammatory process of the IPF or to a viral infection. In a study11 including 156 cases of IPF, lung cancer represented 12.8% of causes of death, and a recent study12 also reported that the incidence of lung cancer was markedly increased in IPF patients. Nevertheless, lung cancer was not identified in any of our patients, even in those who underwent autopsy. Obviously, since all investigations have not been performed on a systematic basis in each patient, we cannot exclude that, in some patients, the cause of ARF has been missed.

**Figure 5.** Evolution of PaCO2. Vertical bar charts represent means and SDs. Baseline PaCO2 was measured before the current hospitalization with the patient in stable condition; beMV PaCO2 represents the value of PaCO2 measured just before intubation; day 0 corresponds to measurement of PaCO2 within 6 h after intubation. * = p < 0.001 in comparison with baseline PaCO2; † = p < 0.01 in comparison with PaCO2 before MV; ‡ = p = 0.015 in comparison with PaCO2 before MV.
The effectiveness of MV in IPF patients presenting with ARF has not been fully evaluated. The general belief is that this management strategy is not beneficial to patients with IPF, but to our knowledge, no published data are available to support this theory. The fact that all patients in our series (except one who underwent LTx) died after various durations of MV strongly suggests that MV is not an appropriate strategy in these patients. Based on our experience, we recommend that patients with end-stage IPF presenting with ARF should not undergo intensive cardiopulmonary resuscitation unless LTx can be performed urgently.

The initial tidal volumes delivered by the ventilator were relatively high. By analogy with what is already known in patients presenting with ARDS, it is therefore not excluded that the initial ventilator settings may have contributed to lung injury and death. Ventilator strategy based on the use of lower tidal volume might have resulted in a lower mortality rate. If MV is considered in patients with end-stage IPF presenting with ARF, we recommend the use of very low tidal volumes and high ventilator rates (if necessary for adequate ventilation).

LTx has now gained widespread acceptance as a therapeutic option in patients with IPF. Moreover, it has been recently shown that LTx confers a survival benefit in patients with IPF compared with spontaneous survival on waiting lists. Performing LTx in IPF ventilator-dependent patients raises difficult issues. It has been demonstrated that performing LTx in a ventilator-dependent patient carries a significantly increased risk of death during the first year after transplantation. Nevertheless, it has been shown that ventilator-dependent patients with various diseases including COPD or IPF can undergo successful LTx provided they are carefully selected. In particular, short periods of ventilation and absence of organ dysfunction other than their respiratory failure are required. It is thus conceivable to initiate MV in IPF patients who are already on waiting lists and who develop ARF. In those who are not already on a waiting list, the probability of transplantation is very low in France given the current scarcity of donor lungs as well as the absence of effective processes to expedite LTx in urgent situations. This point is illustrated by our series where among the 16 patients evaluated for the feasibility of LTx, only 5 patients were already enrolled on the waiting list and only 1 of these 5 patients underwent LTx. The unpredictable course of IPF should encourage chest physicians to refer IPF patients to transplantation centers early in the course of their disease according to the recently published guidelines for selection of lung transplant candidates. Despite the increased risk of perioperative death in ventilator-dependent patients who undergo LTx, we believe that IPF patients who are already on waiting lists should have priority for the allocation of a graft when they develop ARF and require MV.

Alteration of static compliance is well documented in IPF, and a study by Nava and Rubini indicates that end-stage IPF patients have major alteration of lung mechanics during MV. In particular, markedly elevated levels of pulmonary elastance and total lung resistance were found. The authors also described that dynamic and static elastance of the respiratory system as well as total respiratory resistance correlated positively with the degree of PaCO₂ recorded just before intubation. These alterations are thought to be mostly due to the inflammatory and fibrosing process that progressively involve the lungs. Because the design of our study was retrospective, the data on lung and chest mechanics in patients receiving MV were not available. In our study, the correlations between baseline TLC (percent predicted), VC (percent predicted), baseline PaCO₂, and the duration of MV are in accordance with the data of Nava and Rubini.

In conclusion, in patients with end-stage pulmonary fibrosis presenting with ARF, the precipitating cause is most often not identified. Moreover, our data support the general belief that MV does not benefit these patients. Initiation of MV in IPF patients is thus questionable. We believe that it should be restricted to patients in whom LTx can be performed within a few days after initiation of MV.

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