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Outcome of mechanical ventilation for acute respiratory failure in patients with pulmonary fibrosis

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Abstract *Objective*: During the course of idiopathic pulmonary fibrosis patients may need invasive mechanical ventilation because of acute respiratory failure. We reviewed the charts of all patients with idiopathic pulmonary fibrosis admitted to our ICU for mechanical ventilation to describe their ICU course and prognosis.
Design and setting: Retrospective, observational case series, from December 1996 to March 2001, in an 18-bed medical ICU in a tertiary university hospital.
Patients: Fourteen consecutive patients with idiopathic ($n = 11$) or secondary ($n = 3$) pulmonary fibrosis admitted to the medical ICU for mechanical ventilation.
Measurements and results: Relevant factors of history and hospital course such as diagnostic and therapeutic interventions were retrieved as well as laboratory and radiological results. All patients were admitted for severe acute hypoxemic respiratory failure (PaO_2/FIO_2 111 ± 64 mmHg), with a high clinical suspicion of lower respiratory tract infection. Despite ventilatory support and adjunctive therapies (antibiotics, steroids, or immunosuppressive drugs), all patients gradually worsened and eventually died in the ICU after a mean stay of 7.6 ± 4.6 days.
Conclusions: In this study mechanical ventilation for acute respiratory failure in pulmonary fibrosis patients was associated with a 100 % mortality, despite aggressive therapeutic and diagnostic procedures.

Keywords Pulmonary fibrosis · Mechanical ventilation · Survival · Acute respiratory failure

Introduction

Chronic pulmonary fibrosis (PF) is a progressive interstitial lung disease characterized by fibroblast proliferation and extracellular matrix remodeling [1]. This process may be secondary to systemic diseases [2] such as rheumatoid arthritis [3], systemic sclerosis [4], and sarcoidosis [5], but it may also be a primary process limited to the lung, and known as idiopathic pulmonary fibrosis (IPF) [6]. The prevalence of IPF is low, and patients are usually 50 to 70 years old at presentation [7]; secondary PF patients are more heterogeneous in age [2]. Diagnosis is based on clinical history, high-resolution computed tomography (HRCT), and histology, which shows usual interstitial pneumonia (UIP) [1, 8].

IPF is a progressive disease, and no single therapy has been shown to alter the course of the disease [9]. Survival length from diagnosis varies between 3 and 5 years [10, 11], with a 5-year survival rate of 30–50 % [1]. Pulmonary transplantation has been proposed for IPF patients [12, 13], but its major limitations are the relatively advanced age of IPF patients in the terminal stages and organ availability. Secondary PF patients are a more heterogeneous population and may have a slightly better prognosis [14].

Progressive deterioration is the rule, as a consequence of disease progression, and terminal respiratory failure is the first cause of death in IPF [10]. PF is nevertheless sometimes complicated by transient exacerbations, and acute respiratory failure (ARF) is a possible cause of hospital admission. Very few data can be found in the literature about management of severe ARF in PF. Mechanical ventilation (MV) is sometimes instituted, for instance in patients awaiting lung transplantation [15], but case reports are scarce [16, 17], and only a few case series had been published before this year, concentrating more on lung mechanics [18] or diagnostic procedures [19] than on clinical characteristics [20]. Until recently the prognosis of MV for ARF in IPF of other PF patients has not been described [21, 22]

The purpose of the present retrospective study was to address this question in all such patients admitted to our ICU for MV.

Material and methods

From a computerized database available since December 1996 we retrieved the data on all patients admitted to our institution with a diagnosis of pulmonary fibrosis (ICD-10 code J84.1 and J84.8) from December 1996 to March 2001. We selected patients who required MV for ARF during their ICU stay.

IPF was defined according to American Thoracic Society (ATS) criteria [1] and secondary PF was defined by evidence of fibrosis (dyspnea, pulmonary crackles on auscultation, pulmonary function tests, with fibrosis on HRCT and/or pulmonary biopsy) associated with a pathology known to induce secondary fibrosis. ARF was defined as acute or rapidly progressive decline in respiratory function with exacerbation of dyspnea and hypoxemia.

All the important elements of patients' history (diagnosis criteria, radiological and pathological records, quality of life, course of symptoms) were retrieved from previous hospital charts or from the physician in charge of the patient before the admission. The definite diagnosis of IPF was based on a pulmonary biopsy, showing histological changes compatible with UIP, associated with a restrictive syndrome and impaired gas exchange on pulmonary function testing, and basal reticular peripheral and subpleural abnormalities on HRCT. In the absence of lung biopsy the diagnosis based on major ATS criteria (exclusion of secondary IPF, restrictive syndrome and impaired gas exchange, characteristic HRCT, and no alternative diagnosis on bronchoalveolar lavage (BAL)] and minor ATS criteria (age over 50 years, insidious onset dyspnea, duration longer than 3 months, and inspiratory crackles on auscultation) [1].

For the hospital and ICU stay all medical and radiological reports and all laboratory records, including microbiological and pathological results, issued during the hospital and ICU stay were retrieved and analyzed. Diagnostic and therapeutic procedures were also reviewed. All data were analyzed to describe the demographic and specific disease characteristics of patients.

Results

From December 1996 to March 2001, 14 patients with either IPF or secondary PF were admitted for ARF needing ventilatory support. There were seven men and seven women, with a mean age of 72 ± 8.2 years. Before admission IPF had been diagnosed in 11 patients. One patient had a pulmonary biopsy showing UIP, associated with ATS criteria [1] (exclusion of a known cause of secondary pulmonary fibrosis, abnormal pulmonary function studies, reticular abnormalities on HRCT). Ten other patients had characteristic pattern on HRCT and a normal BAL, excluding other causes of PF. Pulmonary function testing revealed a restrictive syndrome in all these patients (mean total lung capacity 60 ± 8%, mean forced vital capacity 72 ± 19%, mean forced expiratory volume in 1 s 69 ± 19%, mean carbon dioxide transfer factor 49 ± 10%, relative to predicted values), who also fulfilled at least three minor ATS criteria. The remaining three patients had secondary PF, associated with sarcoidosis and rheumatoid arthritis in two cases, and secondary to bleomycin therapy for Hodgkin's disease in the other.

The mean interval between diagnosis and the acute episode was 5.7 years (range 6 months to more than 15 years). Two patients had a long disease course (over 8 years), one of them having sarcoidosis with more than 30 years' course and late secondary lung involvement. The mean time for the other patients was 2.0 years (range 6 months to 7 years). Six patients had never had any prior pharmacological therapy for pulmonary fibrosis. Eight patients received oral prednisone, at various doses, in three cases in association with azathioprine. The last administered dose range of prednisone before admission was 10–80 mg per day (35 ± 28).

The severity of the disease was assessed retrospectively by combining clinical, radiological, and physiological data [1, 23, 24]. All patients described mild to moderate dyspnea (ATS scale [25]) before the acute exacerbation of symptoms, and two of them received intermittent oxygen therapy; HRCT and chest radiography showed bilateral lung involvement in all patients. Resting PaO_2 and exercise PaO_2 could not be retrieved for all patients but were severely impaired in six cases (mean PaO_2 63 ± 18 mmHg). Pulmonary hypertension, assessed by echocardiography, was evaluated in nine patients; it was severe in three cases, moderate in four, and light in one. Finally, all the patients lived independently at home, apparently without significant impairment of daily activities and without any specific respiratory therapy, except for the two patients who received intermittent home oxygen. None of these patients was on a waiting list for lung transplantation, mainly because of their age.

All patients reported progression of dyspnea as the first symptom of their ARF. Unusual cough was de-

Table 1 Patients' characteristics at hospital and ICU admission

Parameter	Hospital admission	ICU admission
Respiratory rate (breaths/min)	34 ± 8	36 ± 10
Heart rate (beat/min)	101 ± 16	103 ± 12
APACHE score (admission)	–	19 ± 6
PaO_2/FIO_2 (mmHg)	175 ± 77	111 ± 65
Leukocytes (10^9/l)	9.3 ± 3.5	9.9 ± 6.0
Band forms (%)	12 ± 11	17 ± 15
C-reactive protein (mg/l)	118 ± 84	195 ± 97
Arterial pH	7.45 ± 0.05	7.43 ± 0.04

scribed by four patients and fever by three. The mean interval between first symptoms and hospital admission was 8.5 ± 7.5 days. On hospital admission, all patients complained of moderate or severe dyspnea. One patient was intubated at home for acute respiratory failure. On physical examination, high respiratory, and heart rate were noted (Table 1), with fever in three patients. Chest auscultation was very similar in all patients, with diffuse velcro-type crackles, and no other specific findings.

On hospital admission (Table 1) only one patient had a significantly high leukocyte count, but C-reactive protein was high in all patients. Blood gas analysis showed moderate to severe hypoxemia, without respiratory acidosis. Chest radiography showed diffuse interstitial infiltrates in all patients, without any focal lesion. Lower respiratory tract infection was suspected in 12 patients, and cardiogenic pulmonary edema and rapidly progressive fibrosis were diagnosed in the other two. Three patients were immediately admitted to the ICU. The remaining patients were treated in the ward (range 1–19 days, mean 4) before ICU admission, prompted by progressive worsening of hypoxemia despite maximal oxygen therapy, all patients developing severe dyspnea [25].

On admission (hospital or ICU), standard microbiological investigations for a suspected pulmonary infection were performed, before any antibiotic therapy was introduced. All blood cultures were negative, and neither sputum Gram staining nor culture were contributory. Empirical antibiotic therapy was started after these investigations in all patients. Thirteen patients had a BAL in the early phase of ICU stay (after tracheal intubation for 11). No germs were detected by Gram staining, and cultures remained sterile. BAL cellularity varied, six patients presenting polymorphonuclear cells predominance, two patients a macrophage predominance, and five mixed results. Two patients had more than 20 % lymphocytes. Table 2 presents the results of BAL.

Seven patients had a chest HRCT during their ICU stay, which confirmed the presence of reticular abnormalities in all patients. No other specific lesions were described, particularly no alveolar infiltrates. Bedside open-lung biopsy was performed in the ICU for three patients, and this confirmed the diagnosis of pulmonary fibrosis, showing usual interstitial pneumonia, with superimposed acute respiratory distress syndrome (ARDS) type lesions in one case, and findings suggestive of viral infection in another.

After ICU admission antibiotic therapy included intravenous clarythromycin plus either ceftriaxone ($n = 6$), cefepime ($n = 3$), or imipenem ($n = 5$), in one case with vancomycin. Eight patients received steroids from day 1 [intravenous methylprednisolone, 500-mg bolus four times daily ($n = 4$); oral prednisone, 1 mg/kg daily; ($n = 3$); oral prednisone, 20 mg daily ($n = 1$)]. High-dose bolus therapy was introduced on day 6 in another patient. Immunosuppressive therapy was started in three patients, after a mean delay of 5 days; two patients received azathioprine and one cyclosporine. These therapeutic options were decided by pneumologist and immunologist because of the worsening of gas exchange and the results of BAL and pulmonary biopsies.

Mechanical ventilatory support was necessary for all patients. Three were intubated before or at ICU arrival

Table 2 Results of initial BAL (*IPF* idiopathic pulmonary fibrosis, *SS* systemic sclerosis, *RA* rheumatoid arthritis, *Bleo* bleomycin-induced fibrosis, *PMN* polymorphonuclear leukocytes)

Patient no.	Diagnosis	Age (years)	Leukocytes (10^4/ml)	PMN (%)	Macrophages (%)	Lymphocytes (%)
1	SS	67	102	89	6	5
2	IPF	89	26	21	57	22
3	IPF	74	25	88	6	6
4	IPF	61	27	47	46	7
5	RA	76	74	54	41	5
6	IPF	66	24	58	39	3
7	IPF	70	36	39	46	15
8	IPF	77	195	58	22	20
9	IPF	76	55	86	12	2
10	IPF	75	52	88	8	4
11	IPF	67	23	1	99	0
12	Bleo	66	3	58	33	7
13	IPF	59	9	47	49	4
Mean		73	50	56	36	8

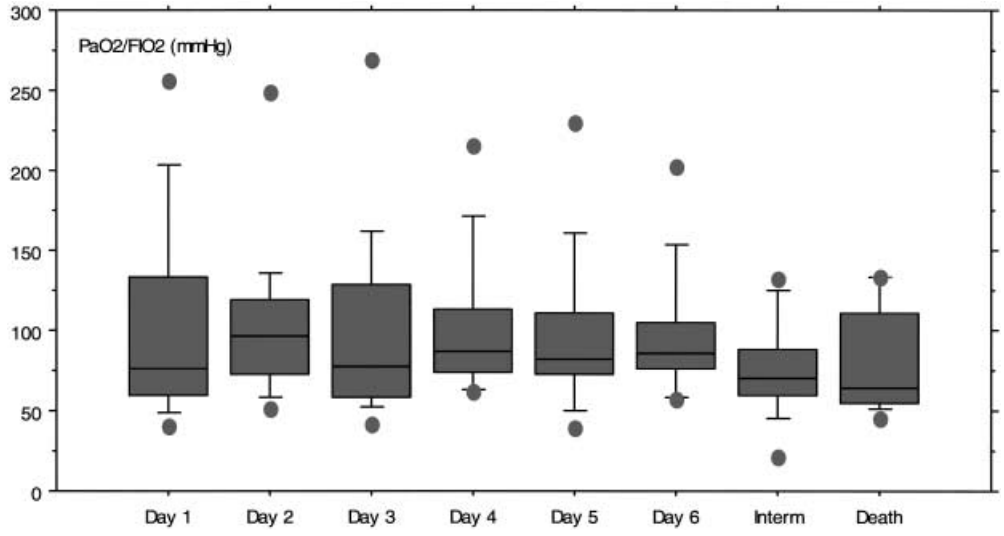

Fig. 1 PaO_2/FIO_2 values from ICU admission to death

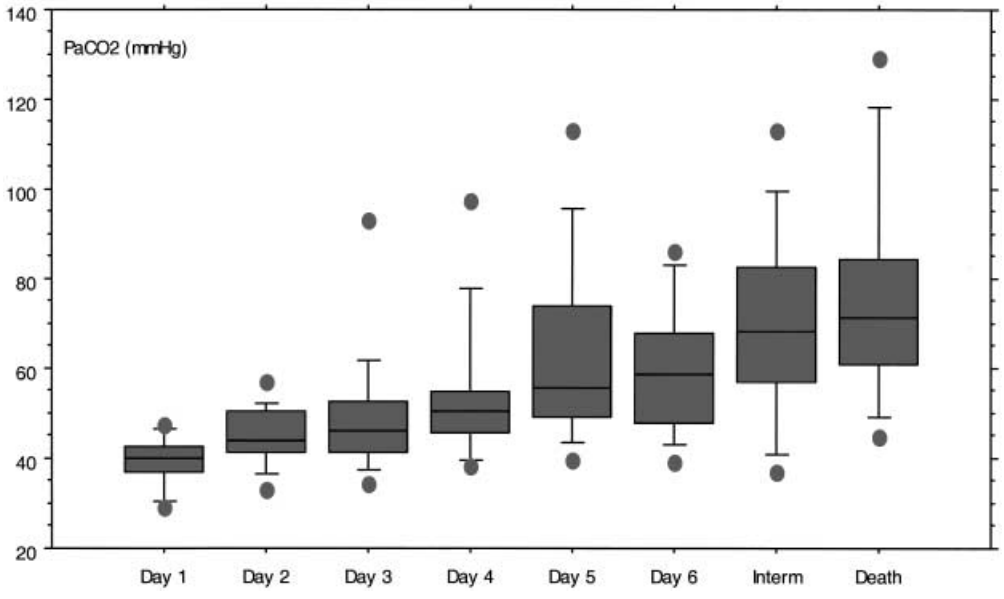

Fig. 2 $PaCO_2$ values from ICU admission to death

because of impending respiratory arrest, and 11 had noninvasive positive pressure ventilation for a mean 37 ± 30 h (range 3–120). This was applied by a face mask, in spontaneous pressure support mode, with high oxygen concentration and positive end-expiratory pressure. Nonetheless, all patients were eventually intubated and mechanically ventilated because of uncorrectable hypoxemia and exhaustion leading to bad compliance. All patients received midazolam and morphine or fentanyl for sedation; seven patients also received vecuronium or pancuronium, at least during certain periods. Paralysis was indicated mainly by difficult ventilation due to high airway pressure or acute episodes of desaturation. After tracheal intubation patients were ventilated in volume assist-control mode, with a tidal volume of 7–9 ml/kg, a pressure limit of 40 mmHg, and a positive end-expiratory pressure set after a trial to achieve the best oxygenation (5–15 cmH_2O). Ventilator parameters were modified according to oxygenation, alveolar ventilation, and respiratory mechanics. During the ICU stay no significant improvement in oxygenation parameters was observed in any patient, and progressive CO_2 retention as well as worsening of respiratory mechanics developed in all patients (Figs. 1, 2).

Lung transplantation was performed in one patient; however, weaning from ventilatory support proved impossible, and the patient died of multiple organ failure. Thirteen patients developed at least one significant

complication during the ICU stay. Nosocomial pneumonia was suspected in seven patients, and four of them had a second BAL, with a positive bacteriological result in two cases (*Pseudomonas aeruginosa* and *Enterobacter cloacae*). Nine patients developed septic shock with multiple organ failure, in six cases with acute renal failure. Two patients died suddenly, one of massive acute hemoptysis and the other of cardiac arrest. For all other patients, intensive care withdrawal or withholding (particularly of extrarenal epuration) was decided, because of refractory respiratory insufficiency and vital organ complications, with an expected bad prognosis in such PF patients. Eventually all patients died despite aggressive diagnostic and therapeutic management. The mean ICU stay was 7.6 ± 4.8 days (range 4–23).

Three patients had an autopsy, which confirmed IPF in two of them and secondary PF associated with bleomycin therapy in the third.

Discussion

IPF is a progressive and lethal disease which leads to terminal respiratory insufficiency in about 40 % of patients [10], secondary to disease progression in most instances, but which can also be the consequence of an acute complication, such as respiratory tract infection and pulmonary embolism. These acute episodes lead to significant worsening of symptoms and respiratory parameters. ARF requiring MV in IPF patients is rarely described in the literature. In our 14-case series this procedure was associated with a grim prognosis (100 % mortality).

The 11 IPF patients whom we describe in this series are comparable to those in literature descriptions regarding their personal characteristics (age and sex) and the duration of their disease before ICU admission [10, 26, 27]. Three patients had secondary PF, but as their clinical course is very similar to the other patients, they were included in the analysis. One of these patients, with PF secondary to sarcoidosis, had a longer period from first symptoms to the acute episode.

All patients presented with nonspecific complaints and clinical examination at admission was not contributive. The suspicion of superinfection of PF was based on symptoms (fever, cough, expectorations) and laboratory findings (leukocytosis or band forms, high C-reactive protein), but no bacteria were isolated in sputum, blood, or BAL. Gas exchange and respiratory mechanics progressively worsened, leading to terminal failure. The majority of patients developed a major complication, either septic shock of ventilator-associated pneumonia, with subsequent multiple-organ failure. Withdrawal of therapy was decided for 12 patients.

Several points need to be discussed, the first being the inclusion of IPF and secondary PF patients. The pathological pattern of the lung disease, although it obviously has distinct causes, was the same in all of these patients. Advanced lung fibrosis is a final common pathway, with a high susceptibility for any secondary lung injury. Although the inclusion of heterogeneous populations in retrospective studies can be a limitation, we chose to overlook it because the clinical characteristics and course of all our patients were very homogeneous.

The validity of the diagnosis of idiopathic or secondary PF also can be considered. Histological confirmation of UIP was eventually obtained in six patients (five IPF, one bleomycin-induced PF) before or during the hospital stay (one preadmission, three open-lung biopsy, two autopsy finding). The IPF patients all had the other ATS criteria for a definite diagnosis. Preadmission work-up was giving a high probability of IPF (four major and at least three minor ATS criteria [1]) in the other IPF patients. Two patients had a systemic disease with lung HRCT showing characteristic pattern of fibrosis, leading to a high probability of secondary PF. Recent papers show that a confident diagnosis can be given by experienced physicians without the need for pulmonary biopsy [8, 28, 29]. Thus we consider that all our patients were correctly included from a diagnostic standpoint.

Several hypotheses could adduced to explain the high mortality rate associated with mechanical ventilation in this population of PF patients. First, as the majority of IPF patients die of terminal respiratory insufficiency, these "acute" episodes of exacerbation could simply represent the natural course of the disease, ventilatory support being useless in this situation. The clinical, radiological, and pulmonary function testing data cannot exclude a very severe lung disease for all of our patients, but based on these results and on the apparent preservation of quality of life we believe that they were not in a terminal state. The fact that only two of them had oxygen intermittent therapy at home, and that none of them was institutionalized despite their age supports the same conclusion and suggests that an acute complication (e.g., infection) occurred during the course of the disease. This was also suggested by the recent history given by the patient.

The second possible explanation for the high mortality is a bacterial or viral respiratory infection which causes the ARF. History and clinical examination were not conclusive, but acute inflammation was present in all patients, with fever and leukocytosis. BAL showed a predominantly polymorphonuclear population, but all BAL bacteriological isolates performed during antibiotic therapy were negative. Finally, inflammatory parameters partially improved, but respiratory parameters worsened despite wide spectrum antibiotics. The role of an acute infection as the initial mechanism triggering ARF thus seems likely but cannot be definitely ascertained; it also seems insufficient by itself to explain the dire clinical course.

This leads to another hypothesis, such as another pathological process taking place after intubation and institution of mechanical ventilation, and acting as a "second-hit" mechanism. Indeed, in severely decompensated IPF patients, hypercapnia is correlated with degrading mechanical properties of the lung [18]. In our series hypercapnia was not present before intubation but appeared progressively. Both the refractory hypoxemia and progressive hypercapnia suggest a secondary acute lung injury. Three possibilities can be discussed: nosocomial pneumonia, worsening after BAL, and ventilator-associated lesions.

Ventilator- or intubation-associated pneumonia could also explain the progressive deterioration in gas exchange, as nine of our patients presented such a complication. However, the worsening of gas exchange was present in the other patients and appeared before the infection in the VAP patients. The third hypothesis is a negative effect of BAL [19], but as all our patients, except one, had a BAL in the early phase of mechanical ventilation, we cannot analyze the role of this procedure in our series.

Mechanical ventilation applied to an injured lung can induce histological and clinical lesions, referred to, respectively, as ventilator-induced lung injury [30] and ventilator-associated lung injury [31]. These lesions are the consequence of pressure (barotrauma) and volume (volotrauma) applied to the preinjured lung [30, 32, 33, 34]. The mechanism of these lesions is uncertain, but stretch-induced inflammation could play an important role an occurrence termed "biotrauma" [30, 35, 36, 37]. In the case of pulmonary fibrosis, and in our series, acute infection or inflammation could act synergistically with MV to induce and maintain lung injury, leading to severe deterioration in gas exchange and respiratory mechanics, with terminal respiratory failure.

These three processes could have played a role in the progressive refractory respiratory failure of our patients, but the latter mechanism, although impossible to ascertain in a retrospective study, could have played a key role. Indeed, in ARDS patients a protective ventilatory strategy has been shown to lower mortality [38], probably by reducing ventilator-induced injury.

The study being performed in a single-center, the results may have been influenced by variations in the management of the patients. For this reason the impact of various diagnostic and therapeutic procedures on outcomes could not be analyzed. Despite these limitations such a series outlines the difficulties in decision-making facing physicians in charge of such patients.

Two other retrospective series have been recently published [21, 22], describing the ICU prognosis of 38 IPF patients with ARF, associated or not with mechanical ventilation. The populations described in these papers are somewhat different from our series: patients were younger in both studies (64 years [37] and 53 years [38]), and presented a more severe lung disease in one series [22]; some patients did not receive invasive MV in one study [21]. A group of seven patients of the second series who were not candidates for lung transplantation were very similar to our patients [22]. Nonetheless, the clinical presentation of ARF (mean PaO_2/FIO_2 113 mmHg [21]) and ICU course after tracheal intubation were very similar to our description, and 35 of the 38 patients died in the ICU or shortly after in the hospital, with a total mortality rate of 92%. In conclusion, the results of these two retrospective studies are in accordance with ours.

In conclusion, IPF is a progressive lethal disease, which often leads to refractory respiratory insufficiency stemming from terminal progression of their disease or acute complications. During the course of their disease, some patients may need ventilatory support. In some cases MV can be a bridge to lung transplantation, but this is a rare occurrence. If MV is necessary and transplantation is not possible, the procedure seems to be associated with a very high mortality, raising questions about the wisdom of its prolonged use. Therefore more studies are needed to explore this critical phase of IPF, with the goal of identifying patients who are more likely to benefit from endotracheal intubation and MV.

Meanwhile a lung- protective approach with MV, such as recommended for ARDS patients, could be an attractive approach, since ventilator-associated lung injury could be an important factor determining the grim prognosis of such patients undergoing prolonged MV.

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