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ORIGINAL

Safety of performing fiberoptic bronchoscopy in critically ill hypoxemic patients with acute respiratory failure

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Abstract *Background:* The safety of fiberoptic bronchoscopy (FOB) in nonintubated critically ill patients with acute respiratory failure has not been extensively evaluated. We aimed to measure the incidence of intubation and the need to increase ventilatory support following FOB and to identify predictive factors for this event. *Methods:* A prospective multicenter observational study was carried out in eight French adult intensive care units. The study included 169 FOB performed in patients with a PaO_2/FiO_2 ratio $\leq$300. The main end-point was intubation rate. The secondary end-point was rate of increased ventilatory support defined as an increase in oxygen requirement >50 %, the need to start noninvasive positive pressure ventilation (NI-PPV) or increase NI-PPV support. *Results:* Within 24 h, an increase in ventilatory support was required following 59 bronchoscopies (35 %), of which 25 (15 %) led to endotracheal intubation. The existence of chronic obstructive pulmonary disease (COPD; OR 5.2, 95 % CI 1.6–17.8; $p = 0.007$) or immunosuppression (OR 5.4, 95 % CI 1.7–17.2; $p = 0.004$] were significantly associated with the need for intubation in the multivariable analysis. None of the baseline physiological parameters including the PaO_2/FiO_2 ratio was associated with intubation. *Conclusions:* Bronchoscopy is often followed by an increase in ventilatory support in hypoxemic critically ill patients, but less frequently by the need for intubation. COPD and immunosuppression are associated with the need for invasive ventilation in the 24 h following bronchoscopy.

Keywords Bronchoscopy · Intensive care unit · Respiratory insufficiency · Respiration · Artificial

Introduction

Fiberoptic bronchoscopy (FOB) is widely used in intensive care units (ICUs) [1–3] as a diagnostic or therapeutic procedure [4, 5] and sometimes as an aid to performing intubation [6]. Studies of bronchoscopy performed in mechanically ventilated patients suggest an acceptable safety profile, except for the occurrence of hypoxemia as the main adverse event [7–11]. Data are lacking in hypoxemic critically ill patients breathing spontaneously, except in hematology and oncology patients. In this situation, some authors recommend performing FOB for accurately diagnosing the cause of acute respiratory failure (ARF), despite the supposed high risks associated with bronchoscopy-induced respiratory deterioration leading to the need for endotracheal intubation. The administration of continuous positive airway pressure (CPAP) [12] or noninvasive positive-pressure ventilation (NI-PPV) [13] has been suggested to improve the tolerance of FOB with bronchoalveolar lavage (BAL). However, these were single-center studies with small series of patients, and the degree of hypoxemia during the procedure was the main evaluation criterion. Thus, the safety of FOB in critically ill nonintubated patients with hypoxemic ARF remains unclear, and these patients may probably constitute the largest population of patients managed with bronchoscopy in the ICU. Furthermore, no data are available on the safety of bronchoscopy in ICU patients who are recovering from acute organ insufficiency or who have chronic cardiac or respiratory diseases.

We designed this prospective multicenter observational study to evaluate the safety of FOB in critically ill nonintubated patients with hypoxemic ARF. Our objectives were to determine the subset of patients in whom intubation or an increase ventilatory support were necessary within 24 h of performing FOB, and to identify the factors predicting these events.

Patients and methods

Study design and ethical consideration

This prospective, observational, multicenter study was approved by the Ethics Committee of the Francophone Society for Critical Care. Each participant was informed orally and via a written document. Patients who had undergone several FOB procedures could not be included twice.

Study population

We screened all consecutive patients admitted to eight university hospital ICUs between June 2005 and July 2006, in whom FOB was indicated. Patients were eligible if they met all the following criteria: age $\geq$18 years, oxygen supplementation $\geq$8 L/min or NI-PPV, with a PaO_2/FiO_2 ratio $\leq$300. Exclusion criteria were age <18 years, pregnancy, unstable angina and recent (less than 1 week) myocardial infarction, cranial hypertension, platelet level $<40 \times 10^9$/L, treatment-limiting decisions (including modification of ventilator support). Before FOB, oxygen supplementation was increased to obtain a SpO_2 higher than 94 %. Noninvasive ventilation was allowed during bronchoscopy if oxygenation or respiratory rate (RR) was not considered safe by the physicians in charge (generally SpO_2 <90 % or RR >30/min). These changes in oxygen supplementation or ventilatory support during and in the 30 min following FOB were not considered as a need to increase ventilatory support in the study.

For each patient, the following data were recorded: demographics, comorbid conditions and underlying diseases, treatment with anticoagulants or antiplatelet agents, severity scores (Simplified Acute Physiological Score II, SAPS II. and Organ Dysfunction and INfection score), and baseline physiological variables, including RR, heart rate (HR), and systolic blood pressure. Baseline blood gases, i.e., PaO_2/FiO_2 ratio and $PaCO_2$, prothrombin time, platelets, blood urea and serum creatinine were recorded. In spontaneously breathing patients, the inspired fraction of oxygen is estimated by the oxygen flow into the high FiO_2 mask [$FiO_2 = 0.21 + (0.03 \times$ oxygen flow in liters per minute)] [14].

Radiological patterns were described as unilateral or bilateral, alveolar or interstitial infiltrates, possibly associated with pleural involvement.

Evaluation criteria

The primary evaluation criterion (end-point) was defined as the need for intubation with invasive mechanical ventilation within 24 h of FOB, whether the patient had or did not have NI-PPV at baseline. The secondary evaluation criterion was designed to assess the need for increased ventilatory support within 24 h of bronchoscopy, defined as follows: (1) the need for invasive mechanical ventilation; (2) an increase in oxygen delivery of >50 % in patients breathing spontaneously with no pressure support; (3) an increase in levels of inspiratory or expiratory pressures of >20 % in patients breathing spontaneously with NI-PPV, or an increase in levels of FiO_2 of >20 % in patients breathing spontaneously with NI-PPV, or an increase in daily duration of pressure support in patients breathing spontaneously with NI-PPV; and (4) initiation of NI-PPV in patients breathing spontaneously with no pressure support.

NI-PPV was initiated as recommended by standard guidelines [15], and predefined criteria were used for initiating invasive ventilation [16].

Other possible bronchoscopy-related complications within 24 h of FOB, such as death, cardiac arrest, cardiac arrhythmia, pneumothorax or hemoptysis, were recorded.

Statistical analysis

Results are expressed as medians and minimal and maximal values for continuous variables and percentages for categorical variables.

Groups were compared using the Mann-Whitney and χ^2 tests for continuous and categorical variables, respectively, in the univariable analysis. The alpha error was set at 0.05; p values are two-tailed. An increase of at least 15 % in patients requiring an increase in ventilatory support was expected on the basis of previous studies comparing noninvasive support and oxygen in hypoxemic patients [12, 13]. Multivariable analysis aimed to provide evidence for the variables that predicted intubation. A forward logistic regression, with a Hosmer-Lemeshow goodness of fit test, was performed. Six categorical variables potentially impacting the initiation of invasive ventilation and showing a significant difference between the two groups, with $p < 0.10$, were included in models of logistic regression: COPD, immunosuppression, NI-PPV support before FOB, RR (cut-off <30/min and increase defined as ≥30/min), HR (cut-off was <100/min and increase defined as ≥100/min). These cut-off values were chosen because they were close to the median and clinically significant. Regression coefficients were considered significant with a p value <0.05. Cumulative event curves were assessed by the Kaplan-Meier method.

Statistical analyses were performed using SPSS 13 software (SPSS, Chicago, IL).

Results

Overall, 181 consecutive FOB were performed in 169 patients during the 14-month study period, among them 169 first FOB were included in this study. Demographic data are presented in the Table 1. Reasons (multiple in some cases) for performing FOB were immunodeficiency (in 62 patients, 37 %), atelectasis (in 49, 29 %), hospital-acquired pneumonia (in 46, 27 %), acute diffuse infiltrative pneumonia (in 45, 27 %), community-acquired pneumonia (in 20, 12 %), hemoptysis (in 5, 3 %), suspected malignancy (in 5, 3 %), and chronic diffuse infiltrative pneumonia (in 1, 1 %).

Bronchoscopy provided the diagnosis in 100 procedures (59 %), and the results led to the introduction or discontinuation of a treatment in 86 procedures (51 %). The need for intubation and invasive mechanical ventilation was recorded in 25 procedures (15 %) during the 24 h following FOB (Fig. 1). Overall, the need to increase ventilatory support within 24 h was recorded in 59 FOB (35 %). NI-PPV was started in 17 procedures (10 %). In the 17 remaining procedures, oxygen delivery was increased by more than 50 % (in 5) or NI-PPV support

Table 1 Demographics, and radiological, physiological and biological data at baseline. The data are presented as either number (percent) or median (range)

	Total	Invasive ventilation initiated		
		No	Yes	p value
Number of FOB procedures	169	144	25	
Age (years)	59 (23–91)	59 (23–88)	64.5 (35–91)	0.723
Male gender	115 (68)	98 (68)	17 (68)	0.996
Body mass index (kg/m^2)	23 (14–38)	24 (14–38)	22 (17–35)	0.198
Interstitial opacities	43 (26)	36 (26)	7 (28)	0.749
Bilateral opacities	63 (38)	51 (36)	12 (48)	0.451
Pleural syndrome	28 (17)	24 (17)	4 (16)	0.888
SAPS II score	38 (6–99)	37 (6–81)	43 (19–99)	0.107
ODIN score	2 (0–8)	2 (0–8)	2 (1–6)	0.118
Respiratory rate (breaths/min)	26 (14–52)	26 (14–52)	30 (18–50)	0.043*
Heart rate (beats/min)	98 (47–155)	97 (47–155)	112 (74–132)	0.014*
Systolic blood pressure (mmHg)	127 (69–191)	127 (69–1910	125 (92–172)	0.689
PaO_2/FiO_2 (mmHg)	194 (61–300)	196 (61–300)	184 (92–293)	0.819
PaO_2 (mmHg)	72 (39–167)	70 (39–167)	78 (44–132)	0.492
FiO_2 (%)	53 (25-100)	50 (25–100)	60 (25–100)	0.197
$PaCO_2$ (mmHg)	40 (24–91)	40 (24–91)	37 (24–80)	0.245
Prothrombin time (%)	76 (14–100)	77 (14–100)	71 (37–100)	0.276
Platelets ($\times 10^9$/L)	253 (6–740)	258 (6–740)	236 (41–663)	0.378
Blood urea (mmol/l)	7 (1.5–47)	7 (1.5–47)	10.9 (2.8–39.2)	0.198
Serum creatinine (μmol/l)	79 (30–664)	78 (30–601)	93 (32–664)	0.760

SAPS II simplified acute physiologic II, *ODIN* organ dysfunction and infection
* $p < 0.05$

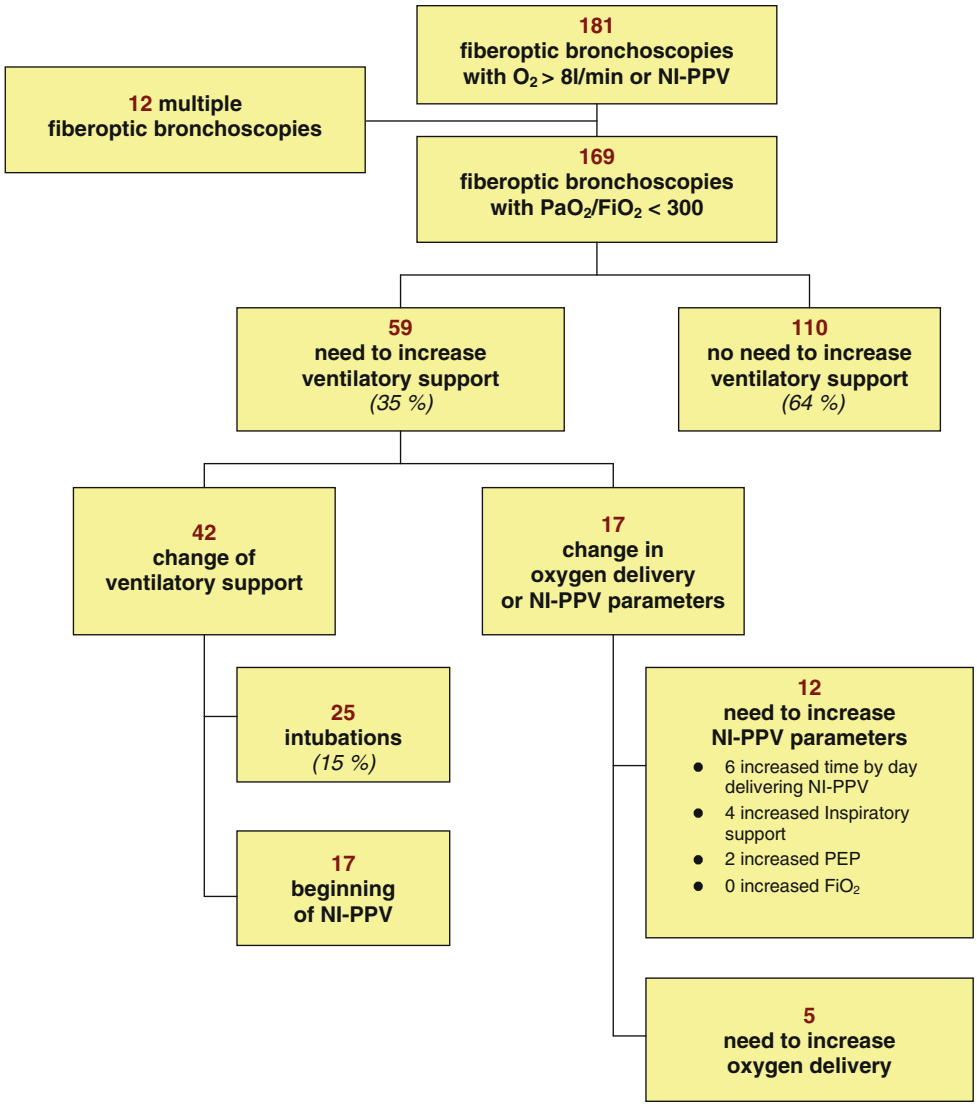

Fig. 1 Changes in modality of oxygenation delivery in acutely ill hypoxemic patients undergoing FOB. The percentages are relative to the whole population. *NI-PPV* noninvasive positive-pressure ventilation, *PEEP* positive end-expiratory pressure, FiO_2 inspired fraction of oxygen

was increased (in 12). The median time to the need to increase ventilatory support was 3.75 h (25–75 h, interquartile range 3.45–8.79 h; Fig. 2). Following 20 bronchoscopies (12 %), ventilatory support was increased (including seven intubations with invasive mechanical ventilation) within 2 h of the procedure.

Altogether, 11 patients had other events within 24 h of FOB. Cardiac arrest occurred in four patients, cardiac arrhythmia in nine, and pneumothorax in two. One cardiac arrest occurred during the procedure which was stopped, and the patient died 5 h later, whereas the other three occurred between 17 and 23 h after the procedure. These cardiac arrests complicated multiorgan failure in two of these patients, and a massive hemoptysis in the last of these patients. This hemoptysis was the original indication for FOB, and it recurred the following day. Two patients developed pneumothorax, one 2 h and the other 11 h after bronchoscopy. Both patients had undergone BAL without bronchial biopsy. In one of the patients the pneumothorax occurred after intubation in one of these patients, and after mechanical ventilation in the other patient who had acute exacerbation of idiopathic pulmonary fibrosis. It has to be noted that, although 18 % of patients were on anticoagulant therapy, no bleeding event was reported during/after FOB.

Altogether, 36 patients (21 %) died in the ICU. The median time from bronchoscopy to death was 12 days (1–92 days). Three patients died within 24 h of bronchoscopy.

Factors predicting initiation of invasive ventilation after bronchoscopy

Initiation of invasive mechanical ventilation (endotracheal intubation) was associated with HR ($p = 0.014$),

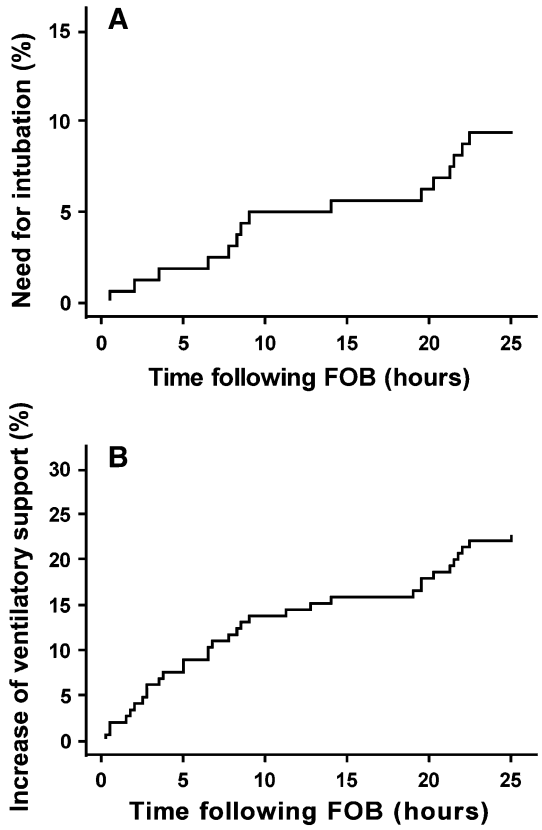

Fig. 2 Cumulative incidence of the need for intubation (**a**) and increased ventilatory support (**b**) within 24 h of bronchoscopy

RR ($p = 0.043$; Tables 1, 2, 3; univariate analysis), immunosuppression ($p = 0.036$) and hematological malignancy ($p = 0.023$), and administration of NI-PPV before FOB ($p = 0.043$). Blood gas and level of hypoxemia were not associated with the need to increase ventilatory support (Table 1). Neither were the characteristics of FOB (Table 3). Finally, factors associated with invasive ventilation in the multivariate analysis were COPD ($p = 0.007$) and immunosuppression ($p = 0.004$) (Table 4).

Discussion

In this study, one-third of the FOB procedures performed in hypoxemic patients breathing spontaneously were complicated by an increase in ventilatory support. Endotracheal intubation was required in 15 % of the procedures overall but this complication occurred 2 h after bronchoscopy in only 4 % of the procedures (Fig. 2). Other complications such cardiac arrhythmias and hemoptysis were infrequently observed. Factors independently associated with the need for invasive ventilatory support were COPD and immunosuppression

Table 2 Underlying diseases and comorbidities. The data are presented as number (percent)

	Total	Invasive ventilation initiated		
		No	Yes	*p* value
Number of FOB procedures	169	144	25	
Cardiovascular disease	65 (38)	54 (38)	11 (44)	0.537
Coronary artery disease	29 (17)	26 (18)	3 (12)	0.459
Chronic obstructive pulmonary disease	26 (15)	19 (13)	7 (28)	0.058
Chronic restrictive pulmonary disease	15 (9)	12 (8)	3 (12)	0.552
Immunosuppression	89 (53)	71 (49)	18 (72)	0.036*
Hematological malignancy	34 (20)	25 (17)	9 (36)	0.023*
HIV-positive	21 (12)	20 (14)	1 (4)	0.166
Solid organ transplantation	4 (2)	3 (2)	1 (4)	0.561
Solid cancer	15 (9)	13 (9)	2 (8)	0.975
Corticosteroid therapy	39 (23)	31 (22)	8 (32)	0.251
Immunosuppressive drugs	25 (15)	20 (14)	5 (20)	0.427
Diabetes	24 (14)	19 (13)	5 (20)	0.322
Chronic renal failure	21 (15)	16 (11)	5 (20)	0.182
Neurological swallowing impairment	20 (12)	18 (13)	2 (8)	0.520
Tobacco use	68 (40)	55 (38)	13 (52)	0.194
Anticoagulant therapy	31 (18)	28 (19)	3 (12)	0.375
Anti-platelet therapy (%)	20 (12)	17 (12)	3 (12)	0.978

* $p < 0.05$

in the multivariable analysis. Despite high RRs and HRs being associated with the need for invasive support in the univariate analysis, none of the physiological parameters before FOB was independently associated with a need for invasive support in the multivariate analysis. These results may be partially explained by a relative small number of events and a lack of statistical power.

To our knowledge, this is the first study of the safety of bronchoscopy in patients with ARF. FOB is well known to be associated with alterations in gas exchange. In hypoxemic intubated patients, FOB has been reported to induce a drop in PaO_2 of up to 30 % with a return to baseline within 2 h [11]. As a result, FOB is traditionally considered hazardous in hypoxemic patients. Although acute hypoxemia is not listed as a contraindication to bronchoscopy in international guidelines [7], there is general agreement that a pulse oximetry value greater than 90 % or a PaO_2 value greater than 8 kPa is necessary to perform bronchoscopy with safety. In our series, 34 % of the bronchoscopies were followed by increased ventilatory support and 15 % by a need for endotracheal intubation. However, whether or not bronchoscopy was a separate causative factor is unclear. The SAPS II score (38 ± 15) indicated severe physiological impairment, and oxygenation was severely altered before bronchoscopy, as underlined by the PaO_2/FiO_2 ratio and mean RR of our patients. Although increased ventilatory support was required in 59 procedures, this was needed within 2 h after bronchoscopy in only 20 procedures. As shown in

Table 3 Characteristics of the 169 bronchoscopy procedures. The data are presented as either number (percent) or median (range)

	Total	Invasive ventilation initiated		
		No	Yes	*p*
Number of FOB procedures	169	144	25	
Number of BAL performed	102 (60)	86 (60)	16 (64)	0.686
Volume of fluid injected (ml)	150 (20–200)	150 (20–200)	150 (80–200)	0.191
Volume injected − volume recovered (ml)	81 (14–195)	85 (14–195)	70 (40–170)	0.366
NI-PPV support				
Before bronchoscopy	64 (38)	50 (35)	14 (56)	0.043*
During bronchoscopy[a]	54 (32)	44 (31)	10 (40)	0.350
Duration of FOB (min)	11 (3–60)	15 (3–40)	11 (3–60)	0.373

* $p < 0.05$

[a] NI-PPV during bronchoscopy represents the number of patients in whom NI-PPV was used to improve FOB tolerance

Table 4 Factors associated with initiation of invasive ventilation within 24 h after bronchoscopy in multivariable analysis

	Odds ratio	95 % confidence interval	*p* value
COPD	5.3	1.6–17.8	0.007
Immunosuppression	5.4	1.7–17.2	0.004

The Hosmer-Lemeshow chi-squared test for the final model yielded a *p* value of 0.787 suggesting a model with good predictive value

Fig. 2, a fixed number of patients worsened each hour after bronchoscopy, suggesting gradual deterioration of the respiratory status. We suggest that respiratory status deterioration is more likely to represent the natural progression of the underlying disease. Support for this hypothesis can be found in studies of acute lung injury outcomes, in which the intubation rate is close to that seen in our study [18–20].

The use of CPAP or NI-PPV during bronchoscopy has been suggested to improve safety in patients with acute hypoxemia. Both methods improved the tolerance of the procedure. However, they were evaluated only in single-center studies, each involving fewer than 40 patients and using physiological evaluation criteria [12, 13, 21]. In our study, the 64 patients who had NI-PPV before and/or during FOB were more severely affected than the 105 patients without NI-PPV with in particular a lower PaO_2/FiO_2 ratio and a higher $PaCO_2$ (data not shown). The lack of standardized procedures among ICU centers for performing FOB with concomitant use of NI-PPV does not permit us to draw a firm conclusion about the beneficial use of NI-PPV in this setting.

The yield of bronchoscopy and BAL in immunocompromised patients, most notably those with hematological malignancies, remains controversial. It was estimated to be about 33 % in studies with large percentages of neutropenic patients, most of whom were receiving empiric antibiotic therapy [22]. This low diagnostic yield and the high mortality rate in patients with hematological malignancies who require endotracheal intubation underline the need for carefully evaluating the risk of intubation related to bronchoscopy. In a multicenter study of 148 cancer patients, of whom 45 were not intubated, respiratory status deteriorated after bronchoscopy in 49 % of the patients, a change in ventilatory support was required in 35 % and endotracheal ventilation in 27 % [23]. BAL has been associated with invasive ventilation but not with higher mortality [22]. Thus, in cancer patients, bronchoscopy with BAL generally has a low yield, but does not seem to increase mortality. In our study of nonintubated patients, 89 patients had immunosuppression, including 34 with hematological malignancy. By multivariate analysis, only immunosuppression was associated with change in ventilatory support after bronchoscopy in our study confirming the risk of respiratory deterioration in these patients. However, a recent study conducted by Azoulay et al. compared the incidence of respiratory failure in oncology patients following noninvasive and invasive testing including FOB did not show any difference between the groups, which argues for a worsening of respiratory failure unrelated to FOB [24].

Among underlying diseases, COPD was independently associated with intubation after FOB. Little is known about FOB tolerance in patients with chronic respiratory failure [25], but one can imagine precipitating hypercapnic ventilatory failure with the increased functional respiratory capacity, as shown during FOB [17]. Currently, no prospective study has focused on FOB tolerance and safety in this group of patients even though this procedure is often considered appropriate in patients with cancer or an infectious diagnosis. The small number of COPD patients ($n = 26$) in our study did not allowed us to determine if NI-PPV in this setting of hypoxemic respiratory failure in COPD increases the safety of FOB, and further study may be warranted.

Our study had several limitations. First, four ICUs were in respiratory departments, and their senior physicians performed large numbers of bronchoscopies, most notably in patients with ARF. Although no center effect

was found in our study (data not shown), tolerance and safety of bronchoscopy may improve with physician experience. Second, most of the bronchoscopies in our study were performed to evaluate infections. The high proportion of infections may have spuriously increased the diagnostic yield of bronchoscopy (59 % of bronchoscopies). Third, the bronchoscopic procedure was not standardized. However, the need to perform intubation was not influenced by bronchoscopy duration, BAL, injected BAL volume, or recovered BAL volume. Surprisingly, the injected BAL volume was about 150 ml, i.e., the amount generally used in stable patients. Finally, The FIO_2 ratio has been only estimated in nonventilated patients in whom there may be a question about the lack of relationship between baseline PaO_2/FiO_2 ratio and intubation after FOB.

In this observational study, we looked for factors that predicted a need for increased ventilatory support after bronchoscopy. By multivariate analysis, the need for invasive ventilatory support was not associated with the extent of radiological opacities, PaO_2/FiO_2 ratio, BAL, or injected BAL volume. COPD and immunosuppression were the only factors associated with the risk of intubation. The time-course between FOB and these events suggest that deterioration in respiratory status might be related to the natural course of the ARF rather than bronchoscopy.

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Conflicts of interest None.

Appendix

FOBREA Study Group

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