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Outcome of reintubated patients after scheduled extubation☆

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Abstract

Purpose: The main objective of study was to evaluate the outcome of patients who require reintubation after elective extubation.

Materials and Methods: This is an observational, prospective cohort study including mechanically ventilated patients who passed successfully a spontaneous breathing trial. Patients were observed for 48 hours after extubation. During this time, reintubation or use of noninvasive positive pressure ventilation was considered as a failure. Reintubated patients were followed after the reintubation to register complications and outcome.

Results: A total of 1,152 extubated patients were included in the analysis. Three hundred thirty-six patients (29%) met the criteria for extubation failure. Extubation failure was independently associated with mortality (odds ratio, 3.29; 95% confidence interval, 2.19-4.93). One hundred eighty patients (16% of overall cohort) required reintubation within 48 hours after extubation. Median time from extubation to reintubation was 13 hours (interquartile range, 6-24 hours). Reintubation was independently associated with mortality (odds ratio, 5.18; 95% confidence interval, 3.38-7.94; $P < .001$). Higher mortality of reintubated patients was due to the development of complications after the reintubation.

Conclusions: In a large cohort of scheduled extubated patients, one third of patients developed

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extubation failure, of whom half needed reintubation. Reintubation was associated with increased mortality due to the development of new complications after reintubation.

1. Introduction

Postextubation respiratory failure after elective discontinuation of mechanical ventilation is a common event associated with significant morbidity and mortality [1]. Reintubation, which occurs in 6% to 23% within 48 to 72 hours after planned extubation [1], is a relevant consequence of respiratory failure after extubation. Patients who require reintubation have been noted to have a significantly higher mortality rate than those who are successfully extubated on the first attempt [2,3]. Limited data are available regarding the reasons associated with mortality after extubation failure.

We studied a prospective cohort of mechanically ventilated patients who were electively extubated following current criteria for weaning. The main objective of this study was to evaluate the variables associated to mortality in reintubated patients.

2. Methods

2.1. Patients

Patients older than 18 years, who had undergone mechanical ventilation for more than 48 hours, and who had been scheduled extubated after a successful spontaneous breathing trial were enrolled from 36 intensive care units in 7 countries from September 2005 to December 2006 (see Appendix for the list of investigators). Patients with a tracheostomy were excluded. Because of the observational, noninterventionist design of the study, the research ethics board waived the need for informed consent.

2.2. Follow-up

Patients were assessed daily for the presence of the following readiness to wean criteria: (*a*) improvement in the underlying condition that lead to acute respiratory failure, (*b*) alertness and ability to communicate, (*c*) core temperature less than 38°C, (*d*) no vasoactive drugs (excluding dopamine below 5 μg/kg per minute), and (*e*) ratio Pao_2 to Fio_2 higher than 200 with positive end-expiratory pressure no greater than 5 cm H_2O. When patients met these criteria, a spontaneous breathing trial with T-piece, continuous positive airway pressure, or pressure support 7 cm H_2O or greater was performed. At 5 minutes and at the end of the spontaneous breathing trial, the following variables were recorded: arterial blood gases, tidal volume measured by a spirometer or the ventilator, respiratory rate, heart rate, systolic blood pressure, and the level of sedation-agitation determined by Richmond Agitation-Sedation Scale [4]. The primary physician terminated the trial if the patient had any of the following signs of poor tolerance: a respiratory frequency of more than 35 breaths/min, Sao_2 below 90%, heart rate above 140 beats/min or a sustained increase or decrease in the heart rate of more than 20%, systolic blood pressure above 200 mm Hg or below 80 mm Hg, and agitation, diaphoresis, or anxiety [5]. Patients who did not tolerate the spontaneous breathing trial were placed back on mechanical ventilation. In these patients, a daily spontaneous breathing trial was performed until they were extubated. For the purpose of the study, we included in the analysis the data corresponding to spontaneous breathing trials that were followed by extubation. The decision to extubate was made by the attending physician. Patients were classified, according to the weaning process, into 3 groups: (*a*) simple weaning, which includes patients who successfully pass the initial spontaneous breathing trial and are successfully extubated on the first attempt; (*b*) difficult weaning, which includes patients who require up to 3 spontaneous breathing trial or as long as 7 days from the first spontaneous breathing trial to achieve successful weaning; and (*c*) prolonged weaning, which includes patients who require more than 3 spontaneous breathing trial or more than 7 days of weaning after the first spontaneous breathing trial [6].

Patients who tolerated the spontaneous breathing trial were extubated within next 120 minutes and followed for the next 48 hours or to discharge from intensive care unit, whichever came first. In this period, the following variables were registered: hourly respiratory rate, heart rate, systolic blood pressure, and peripheral oxygen saturation; worst Richmond Agitation-Sedation Scale and fluid balance within an 8-hour nursing shift; and daily leukocyte count and new infiltrates in the chest radiograph. During this time, reintubation or use of noninvasive positive pressure ventilation was considered as a failure. Because of the observational and noninterventionist design of the study, criteria or indication for reintubation and/or application of noninvasive ventilation was not protocolized.

In case of reintubation, we registered the date and time as well as the reason for reintubation, which was selected from the following list: (1) upper airways obstruction (defined as stridor and/or laryngeal edema); (2) increased work of breathing (defined as respiratory rate >35 breaths/min and/or use of accessory respiratory muscles); (3) decreased level of consciousness (defined as a score <0 point on the Richmond Agitation-Sedation Scale); (4) hypoxemia (defined as an Spo_2 lower than 90% despite an Fio_2 >0.5); and (5) respiratory acidosis (defined as an arterial pH <7.30, with a

$Paco_2$ >50 mm Hg). Reintubated patients were followed during the new period of mechanical ventilation for up to 15 days. During this time, we recorded daily the occurrence and time of onset of new postreintubation complications: acute respiratory distress syndrome, severe sepsis, ventilator-associated pneumonia, and organ failure (cardiovascular, renal, hepatic, and hematologic), defined as a score higher than 2 points on the Sequential Organ Failure Assessment Score [7]. For the purpose of this study, we defined early onset as the occurrence of a complication within the first 72 hours after reintubation and late onset as the occurrence after 72 hours. In these patients, the date of the second extubation and if they required a new reintubation within the following 48 hours were registered. In all patients included in the study, we documented the need for tracheostomy and the vital status on discharge from the intensive care unit.

2.3. Statistical analysis

Continuous variables were expressed as mean values and SDs, and as median values and interquartile range, as appropriate. Comparisons were made using the Student *t* test. Categorical variables were expressed as proportions and were compared using the Pearson χ^2 test. A hazard function for the hourly probability of reintubation was estimated.

We performed 2 backward stepwise logistic regressions: (1) to estimate the relationship between extubation failure and mortality (in this analysis, we entered the following variables: age, Simplified Acute Physiology Score II [SAPS II], reason to begin mechanical ventilation, days of mechanical ventilation before extubation, duration of weaning [categorized in simple weaning, difficult weaning, and prolonged weaning] as a dummy variable [taking as reference the category simple weaning], and extubation failure) and (2) to estimate if reintubation was associated with intensive care unit mortality. The following variables were entered in the model: age, SAPS II, reason for mechanical ventilation, days of mechanical ventilation, duration of weaning (categorized in simple weaning, difficult weaning, and prolonged weaning) as a dummy variable (taking as reference the category simple weaning), and reintubation and use of noninvasive positive pressure ventilation after extubation. The threshold for entry of variables into the models was $P < .10$ and, for removal of variables from the model, $P < .05$. All analyses were performed with SPSS 17.0 statistical package (SPSS Inc, Chicago, Ill).

3. Results

During the study period, 1152 scheduled extubated patients were included (Fig. 1). From this cohort, 336 patients (29%) met the criteria for extubation failure. In Table 1, the baseline characteristics of the study cohort are shown. Patients with extubation failure were older, had higher severity of illness, and were more likely to have been admitted with pneumonia, as reason for mechanical ventilation. These patients had a statistically significant—although with little clinical relevance—worse clinical (both

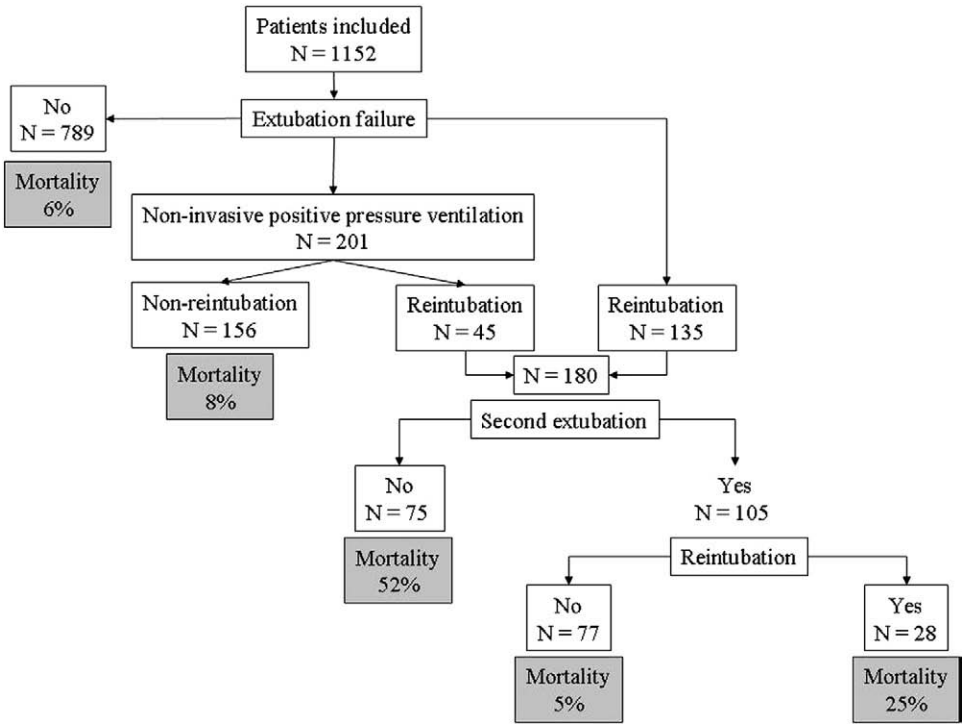

Fig. 1 Flow chart of the study.

Table 1 Baseline characteristics of study cohort

Characteristic	No extubation failure, n = 816	Extubation failure, n = 336	*P*
Age (y), mean (SD)	56 (18)	61 (17)	<.001
Female, n (%)	289 (35)	138 (41)	.07
SAPS II, mean (SD), points	41 (15)	45 (15)	.002
Reason to start mechanical ventilation, n (%)			
Chronic obstructive pulmonary disease	57 (7)	33 (10)	.10
Asthma	22 (3)	3 (1)	.06
Other chronic pulmonary disease	6 (.7)	1 (.3)	.38
Coma	138 (17)	41 (12)	.04
Neuromuscular disease	9 (1)	2 (1)	.52
Acute respiratory failure			
Postoperative	161 (20)	61 (18)	.57
Acute respiratory distress syndrome	22 (3)	11 (3)	.59
Congestive heart failure	44 (5)	17 (5)	.82
Aspiration	26 (3)	10 (3)	.85
Pneumonia	87 (11)	56 (17)	.005
Sepsis	92 (11)	40 (12)	.76
Trauma	54 (7)	17 (5)	.32
Cardiac arrest	27 (3)	11 (3)	.98
Other	71 (9)	33 (10)	.55
Days of mechanical ventilation before extubation, median (interquartile range)	6 (4-9)	6 (4-9)	.82
Method of spontaneous breathing trial, n (%)			
Pressure support ≤7 cm H_2O	452 (55)	175 (52)	.30
T piece	189 (35)	115 (34)	.72
Continuous positive airway pressure	75 (9)	46 (14)	.01
Arterial blood gases before extubation			
pH, mean (SD)	7.43 (0.05)	7.41 (0.06)	<.001
$Paco_2$ (mm Hg), mean (SD)	38 (9)	38 (10)	.86
Ratio Pao_2 to Fio_2, mean (SD)	278 (109)	257 (105)	.006
Rapid shallow breathing index, (breaths/min per liter), median (interquartile range)	48 (35-62)	53 (41-73)	<.001
Systolic blood pressure (mm Hg), mean (SD)	139 (23)	140 (26)	.70
Heart rate (beats/min), mean (SD)	92 (17)	95 (19)	.01
Richmond Agitation-Sedation Scale, n (%)			
−5 to -1 points	139 (17)	63 (19)	.51
0 points	537 (66)	231 (69)	.33
+1 to + 5 points	140 (17)	42 (12.5)	.05
Tracheobronchial colonization before extubation, n (%)	224 (27.5)	93 (28)	.85
Fluid balance after extubation (mL), median (interquartile range)	−550 (−2017 to 1015)	−238 (−1292 to 692)	.18
Positive fluid balance (%)	335 (41)	156 (46)	.09
Duration of weaning, n (%)			
Simple weaning	649 (79.5)	262 (78)	.55
Difficult weaning	150 (18)	59 (18)	.95
Prolonged weaning	17 (2)	15 (4.5)	.02
Outcomes			
Length of stay in the intensive care unit (d), median (interquartile range)	10 (7-16)	14 (9-24)	<.001
Mortality in the intensive care unit, n (%)	52 (6)	63 (19)	<.001

higher rapid shallow breathing index and heart rate) and gasometrical status (lower pH and ratio Pao_2 to Fio_2) at the end of the spontaneous breathing trial.

Patients who failed extubation had a higher mortality and a longer stay in the intensive care unit (Table 1). After adjustment for other variables (age, SAPS II, reason for mechanical ventilation, days of mechanical ventilation, and duration of weaning), extubation failure was independently associated with mortality in the intensive care unit (odds ratio, 3.29; 95% confidence interval, 2.19-4.93; $P < .001$). Noninvasive positive pressure ventilation after extubation was used in 201 patients. Forty-five patients (22%) of those who received noninvasive positive pressure ventilation were reintubated.

One hundred eighty patients (16% of overall cohort) were reintubated within 48 hours after scheduled extubation. The

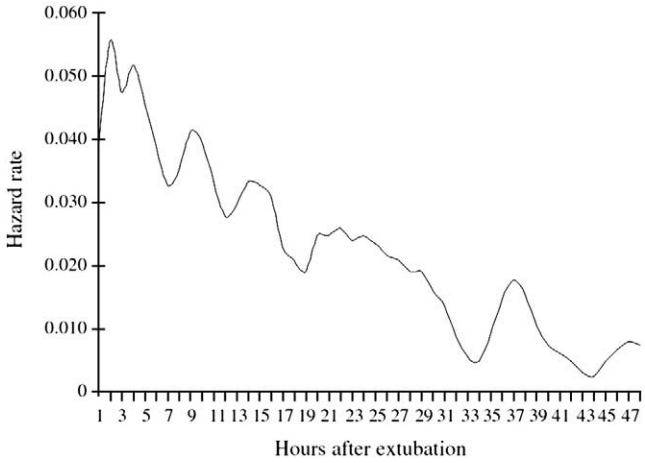

Fig. 2 Hourly hazard rate for reintubation within first 48 hours after extubation. The hazard function presents the probability of reintubation in each hour, given that a patient is event-free. Estimation of the hazard function shows the event rate per hour over the follow-up period.

median time from extubation to reintubation was 13 hours (interquartile range, 6-24 hours). There was a decrease in the hourly hazard for reintubation during the observation period (Fig. 2). Reintubation was attributed to increased work of breathing in 89 patients (49%), to hypoxemia in 32 patients (18%), to decreased level of consciousness in 23 patients (13%), to respiratory acidosis in 20 patients (11%), and to upper airways obstruction in 16 patients (9%).

Mortality of reintubated patients was 28% (50 of 180 patients). Mortality of reintubated patients after noninvasive positive pressure ventilation was similar to mortality of reintubated patients who did not received noninvasive positive pressure ventilation after extubation (29% [13/45 patients] vs 27% [37/135 patients]; $P = .77$). Table 2 shows the results of univariate analysis for mortality in the cohort of reintubated patients. After adjustment for other variables (age, SAPS II, reason for mechanical ventilation, days of mechanical ventilation, duration of weaning, and noninvasive positive pressure ventilation), reintubation was independently associated with mortality in the intensive care unit (odds ratio, 5.18; 95% confidence interval, 3.38-7.94; $P < .001$).

After reintubation, the following organ failures were observed: cardiovascular failure in 49 patients (27%), renal failure in 21 patients (12%), hepatic failure in 15 patients (8%), and hematologic failure in 12 patients (7%). In addition, the following complications developed after reintubation: ventilator-associated pneumonia in 55 patients (31%), sepsis in 38 patients (21%), and acute respiratory distress in 22 patients (12%). The density incidence of ventilator-associated pneumonia was 43.5 cases per 1000 mechanical ventilation days. Reintubated patients with a positive culture from tracheobronchial aspirate before extubation were more likely to develop ventilator-associated pneumonia after reintubation: 44% (26/59 patients) vs 17% (13/76 patients) in patients with negative cultures vs 36% (16/45 patients) in patients in whom cultures were not obtained. Most of the complications were diagnosed in the first 72 hours (early onset) after reintubation.

Higher rates of complications and organ failure were observed among patients who died compared with those who survived (Table 3). The timing of occurrence of the complications was similar among dead and alive patients (Table 3).

4. Discussion

The main finding of our study was that death in reintubated patients was associated with complications and organ failures that developed after reintubation.

As in other studies [2,8-16], we observed that both extubation failure and reintubation were associated with increased mortality. Several reasons have been suggested to explain this relationship [1]. First is the act of intubation itself. The death attributable to intubation, in the studies, which have evaluated the incidence of death at the time of or within 30 minutes after intubation, is around 2% [17-20]. In our study, we did not collect data related to complications associated to intubation technique. Nevertheless, the median time between reintubation and death was 13 days, and only 4 patients (8%) died within the first 24 hours after reintubation.

The second reason to explain the higher mortality in reintubated patients is that reintubation is a marker for increased disease severity. In our study, patients' severity of illness on admission to the intensive care unit was similar between reintubated and nonreintubated patients. In addition, our study patients improved from the condition for which they were ventilated. We believe that their illness severity when weaning was started was similar in both groups because they all met the standard readiness to wean criteria.

The third explanation for the higher mortality is the development of a new medical condition during the interval between extubation and reintubation. This possibility is supported by Epstein and Ciubotaru [3], who have shown that the mortality increased in proportion to the time between extubation and reintubation. However, we did not observe this pattern in our study. In fact, the lag time between extubation and reintubation was similar in survivors and nonsurvivors. Nevertheless, we think that, during this time, patients developed a new problem that required a new period of mechanical ventilation. Accordingly, the observed mortality in reintubated patients in our study was similar to the reported mortality after a first period of mechanical ventilation in epidemiologic studies [21,22] despite significant differences in the prevalence of complications such as acute respiratory distress syndrome, sepsis, and ventilator-associated pneumonia.

Table 2 Univariate analysis of factors associated with mortality in reintubated patients

	Died, n = 50	Alive, n = 130	*P*
Age (y), mean (SD)	68 (15)	59 (18)	.002
Female, n (%)	16 (32)	52 (40)	.32
SAPS II (points), mean (SD)	46 (15)	44 (13)	.33
Reason to start mechanical ventilation			
Chronic obstructive pulmonary disease	6 (12)	16 (12)	.95
Asthma	–	1 (1)	1.00
Coma	6 (12)	20 (15)	.56
Neuromuscular disease	–	2 (1.5)	1.00
Acute respiratory failure			
Postoperative	10 (20)	17 (13)	.24
Acute respiratory distress syndrome	2 (4)	6 (5)	1.00
Congestive heart failure	3 (6)	5 (4)	.53
Aspiration	2 (4)	4 (3)	.67
Pneumonia	8 (16)	19 (15)	.82
Sepsis	6 (9)	12 (12)	.58
Trauma	1 (2)	12 (9)	.12
Cardiac arrest	2 (4)	3 (2)	.54
Other	4 (8)	13 (10)	.68
Days of mechanical ventilation before extubation, median (interquartile range)	7 (5-12)	5 (3-9)	.03
Duration of weaning, n (%)			
Simple weaning	36 (72)	106 (81.5)	.59
Difficult weaning	10 (20)	19 (15)	.46
Prolonged weaning	4 (8)	5 (4)	.28
Time from extubation to reintubation (h), median (interquartile range)			
In the overall cohort	16 (6-24)	12.5 (6-24)	.48
In patients reintubated after noninvasive positive pressure ventilation	21 (5-27.5)		.77
In patients reintubated without previous noninvasive positive pressure ventilation	15 (6-23)	12 (6-22)	.54
Reason for reintubation, n (%)			
Upper airway obstruction	4 (8)	12 (9)	1.00
Increase of work of breathing	28 (56)	61 (47)	.27
Decrease of level of conscience	7 (14)	16 (12)	.76
Hypoxemia	8 (16)	24 (18.5)	.69
Respiratory acidosis	3 (6)	17 (13)	.18
Days of mechanical ventilation after reintubation, median (interquartile range)	5 (3-8)	5 (3-9)	.89
Noninvasive positive pressure ventilation after extubation, n (%)	13 (26)	32 (25)	.85
Tracheostomy, n (%)	18 (36)	55 (42)	.44

Reintubation has been reported as a risk factor for ventilator-associated pneumonia [3,13,23]. Torres et al [13] reported that 47% of reintubated patients develop nosocomial pneumonia after reintubation as compared with 10% of matched control patients. In our study, the rate of ventilator-associated pneumonia (27%) was lower than that reported by Torres et al [13] but higher than that reported in other epidemiologic studies [24]. An interesting finding in our study was that reintubated patients who had, at the time of extubation, tracheobronchial colonization by potential pathogenic microorganisms were more likely to develop ventilator-associated pneumonia after reintubation.

Extubation failure has been defined as the need for reintubation within 24 to 72 hours of planned extubation [8]. With this definition, the range of patients who fail extubation is between 2% to 25% based on the study population and the time frame used for the analysis [8]. In this study, we used a more liberal definition of extubation failure, including patients who received noninvasive ventilation postextubation and reintubated patients. Using these criteria, 1 in 3 patients fulfilled criteria for extubation failure. This prevalence was similar to previously published data [9-12].

Noninvasive positive pressure ventilation has emerged as a promising therapy to avert respiratory failure after weaning [25]. This therapy has been evaluated in 2 different scenarios with different results: (*a*) as a preventive therapy for respiratory failure [10-12,26,27] and (*b*) as a treatment of postextubation respiratory failure [9,28]. Noninvasive positive pressure ventilation reduces the incidence of respiratory failure in selected populations of patients when it is applied early after extubation. In a pooled data analysis [10-12], respiratory failure was present in 14% in patients managed with noninvasive positive pressure ventilation vs 32% in control group (relative risk, 0.43; 95% confidence interval, 0.29-0.64). In addition, although individually only a study

Table 3 Comparison of incidence and onset of complications after reintubation among dead and alive patients

		Died, n = 50	Alive, n = 130	*P*
Cardiovascular failure	n (%)	23 (46)	26 (20)	<.001
	Days from reintubation to event, median (interquartile range)	1 (1-3)	1 (1-3)	.82
	Early onset (%)	18 (78)	21 (81)	.83
Renal failure	n (%)	13 (26)	8 (6)	<.001
	Days from reintubation to event, median (interquartile range)	1 (1-5)	1 (1-5)	.46
	Early onset, n (%)	6 (69)	9 (75)	.78
Hepatic failure	n (%)	8 (16)	7 (5)	.03
	Days from reintubation to event, median (interquartile range)	1 (1-5)	2 (1-3)	.90
	Early onset, n (%)	5 (63)	6 (86)	.57
Hematologic failure	n (%)	10 (20)	2 (1.5)	<.001
	Days from reintubation to event, median (interquartile range)	1 (1-4)	5 (1-9)	.45
	Early onset, n (%)	7 (78)	1 (50)	.49
Ventilator-associated pneumonia	n (%)	26 (52)	29 (22)	<.001
	Days from reintubation to event, median (interquartile range)	1 (1-5)	3 (1-4)	.22
	Early onset, n (%)	19 (73)	20 (69)	.74
Sepsis	n (%)	18 (36)	20 (15)	<.001
	Days from reintubation to event, median (interquartile range)	1 (1-8)	2 (1-8)	.66
	Early onset, n (%)	13 (72)	12 (60)	.43
Acute respiratory distress syndrome	n (%)	15 (30)	7 (5)	<.001
	Days from reintubation to event, median (interquartile range)	1 (1-3)	1 (1-2)	.73
	Early onset, n (%)	12 (80)	6 (86)	.75

[27] reported a statistically significant reduction in the reintubation with the early application of noninvasive positive pressure ventilation after extubation, the pooled data of studies, which evaluated this outcome [10-12,27], showed a reduction of reintubation from 21% to 10% (relative risk, 0.50; 95% confidence interval, 0.32-0.78). On the other hand, in the 2 studies [9,28] that evaluated noninvasive positive pressure ventilation as a treatment of postextubation respiratory failure, this therapy did not show any benefit in the reintubation rate or mortality. In the current study, we considered the use of noninvasive positive pressure ventilation postextubation as a criterion for extubation failure, but its application was not protocolized. Therefore, we do not know in what circumstances it was applied, preventive or therapeutic. Nevertheless, noninvasive positive pressure ventilation was associated with a significant reduction in the need for reintubation. The mortality in patients who received this therapy (13%) was between the mortality reported in preventive studies (6%) and that reported in therapeutic studies of noninvasive positive pressure ventilation (22%). However, patients who were reintubated despite the use of noninvasive positive pressure ventilation had similar mortality to reintubated patients who did not received noninvasive positive pressure ventilation.

Our study has several limitations. The study was observational and noninterventional. We did not provide a specific protocol related to the use of noninvasive ventilation after extubation. We opted for this study design to describe the problem of extubation failure because it occurs in the usual clinical practice and to identify potential protective measures that could prevent this complication.

Appendix A. Investigators in this study

Argentina: *Coordinator*: Carlos Apezteguia (Hospital Profesor A. Posadas, El Palomar, Buenos Aires).

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