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High Flow Conditioned Oxygen Therapy for Prevention of Reintubation in Critically Ill Patients: A Preliminary Cohort Study

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Abstract

Objective: To determine the impact of delivering high flow conditioned oxygen therapy (HFO) through nasal cannula on prevention of reintubation in mechanically ventilated (MV) critically ill patients. Design: Prospective cohort sturdy. Setting: General ICU of a university hospital. Patients: all patients under MV > 12-h and after scheduled extubation. Exclusion criteria: hypercapnia at extubation, non-scheduled extubation or with do-not-resuscitate orders. Patients were also divided between low and high reintubation risk. Interventions: From September 2011 to September 2012, all patients received HFO after extubation for a fixed 24-h period and were compared with a historical cohort (2008-2011) treated with conventional oxygen therapy and matched for risk of reintubation. Measurements and Main Results: The primary endpoint was reintubation rate within the 72-h following extubation. Statistical analyses included logistic multivariate model. Main Results: Each cohort included 111 patients with similar clinical characteristics. The HFO group showed a non-significant lower reintubation rate (8.1% vs. 15.3%, p = 0.09). Variables independently related to reintubation rate in the multivariate analysis were HFO (OR 0.31 [0.10-0.95] p = 0.04), hypercapnia after extubation (OR 51.20 [11.55-226.63] p < 0.01), APACHE II > 12 at extubation (OR 1.06 [1.01-1.12] p = 0.04) and length of MV (OR 1.16 [1.03-1.30] p = 0.01). The area under the ROC curve for the model was 0.89 (0.77-0.94). Conclusions: Routine HFO after planned extubation appears to be associated with lower reintubation rate.

Keywords

Mechanical ventilation, Weaning, Post-extubation respiratory failure, High flow conditioned oxygen therapy, Outcome.

Key Messages

High flow conditioned oxygen therapy applied immediately after scheduled extubation reduces reintubation rate in a non-selected population of mechanically ventilated patients.

Introduction

Oxygen delivery after extubation is the cornerstone treatment to maintain adequate oxygenation and avoid reintubation. Oxygen is usually delivered through low-flow nasal prongs; when necessary, flow is increased or patients are switched to a high-flow face mask.

Some other interventions after extubation focus on specific causes of reintubation; for example, high risk patients are administered prophylactic corticosteroids before planned extubation to prevent laryngeal edema [1,2] and patients with hypercapnia at extubation are administered noninvasive mechanical ventilation [3]. However, to our knowledge, no other intervention has been proven to reduce reintubation rate in a general population of critically ill patients.

High flow conditioned oxygen therapy (HFO) is a novel therapy that delivers optimal oxygen through a nasal cannula. First, it generates low level positive pressure, ranging from 2.7 to 7.1 cm H_2O, depending on the gas flow and with higher values when patients are breathing with their mouths closed [4-7]. This can attenuate the inspiratory resistance associated with the nasopharynx, thereby reducing the related work of breathing. Second, conditioning the gas mixture can improve conductance and pulmonary compliance with an increase in end-expiratory lung volume [8], probably decreasing irritation of the tracheal mucosa and increasing patient comfort. Technological improvements have increased the absolute humidity of the gas delivered up to 35 mg/l at 40 l/min and 30˚C [9]. Finally, high flow ensures a constant FiO_2 during inspiratory effort and washout of the nasopharyngeal dead space during expiration, theoretically improving oxygenation and carbon dioxide clearance. Nevertheless, clinical studies failed to demonstrate improvements in $PaCO_2$ [10], and have even found mild to moderate increases in $PaCO_2$ [11]. Studies of HFO after extubation in general and postsugical population [10,12,13], found HFO was more comfortable than conventional oxygen in terms of mouth and throat dryness [10,14]. Patients with HFO had fewer desaturation episodes and interface displacements

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[10]; however, the results for other outcomes like improvements in respiratory rate and oxygenation were inconsistent [10,12,14].

Extubation failure remains a clinical challenge, appearing in as much as 20% of critically ill patients. The main reasons for extubation failure are increased work of breathing, secretion retention, heart failure and loss of lung aeration, most of which might be alleviated by HFO´s low-level airway pressurization and gas conditioning.

We hypothesized that delivering HFO through nasal prongs immediately after planned extubation would reduce the rate of reintubation.

Materials and Methods

Patients and Study design

In September 2011, we incorporated HFO after planned extubation into the routine clinical protocol routine for mechanically ventilated (MV) patients in our 8-bed closed medical-surgical ICU in a 300-bed university hospital. Then, we prospectively collected clinical data during the 12-month period from September 2011 through September 2012.

In this study, we included all patients in this period who underwent planned extubation after at least 12 hours MV except those with do-not-resuscitate orders, hypercapnia before extubation, or accidental or self extubation. We compared these patients treated with HFO after extubation with a historical cohort of consecutive patients treated with conventional oxygen therapy selected by matching criteria from medical records dating from February 2008 through July 2011. The institutional review board approved the study.

Endpoints

The primary outcome was extubation failure, defined as the need for reintubation within 72 hours after extubation. Patients with any of the following were immediately reintubated: respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor agitation inadequately controlled by sedation, massive aspiration, persistent inability to remove respiratory secretions, heart rate below 50 min-1 with loss of alertness, or severe hemodynamic instability without response to fluids and vasoactive drugs. We also reintubated patients with postextubation respiratory failure defined as the presence and persistence of any of the following within 72 h of extubation: respiratory acidosis with arterial pH < 7.35 with $PaCO_2$ > 45 mmHg; SpO_2 < 90% or PaO_2 < 60 mmHg at FiO2 ≥ 0.5; respiratory frequency > 35 min-1; agitation, diaphoresis, or decreased consciousness; or clinical signs suggestive of respiratory muscle fatigue and/or increased work of breathing, such as the use of accessory respiratory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces [15].

In addition to analyzing reintubations due to all causes, we separately analyzed reintubations due to respiratory causes. We also analyzed predictors of extubation failure.

Study cohort

Patients from the two groups were matched according to stratification for high risk of reintubation based on the following criteria: > 65 years; MV for congestive heart failure; moderate-to-severe COPD; APACHE II > 12 at extubation; body mass index > 30; difficult or prolonged weaning; ≥ 2 comorbidities; airway patency problems, including inability to deal with respiratory secretions (inadequate cough reflex or > 2 suctioning during the 8 hours previous to extubation); and MV > 7 days.

Protocol

Our weaning protocol included a daily screening of weaning readiness according to the following criteria [16]: recovery from the precipitating illness; respiratory criteria: PaO_2/FiO_2 > 150 mmHg with positive end-expiratory pressure (PEEP) < 8 cmH_2O and arterial pH > 7.32; and clinical criteria: absence of electrocardiographic signs of myocardial ischemia, no need for vasoactive drugs or dopamine (≤ 5 μg/kg/min), heart rate < 140 beats/min, hemoglobin > 8 g/dL, temperature < 38˚C, no need for sedatives, presence of respiratory stimulus, and appropriate spontaneous cough. When patients fulfilled these criteria a spontaneous breathing trial (SBT) either with T-tube or 7 cm H_2O pressure support for 30 minutes was performed. SBT failure criteria were: agitation, anxiety, depressed mental status, diaphoresis, cyanosis, evidence of increasing respiratory effort, increased accessory muscle activity, facial signs of distress, dyspnoea, PaO_2 ≤ 60 mmHg or SaO_2 < 90% on FiO_2 ≥ 0.5, $PaCO_2$ > 50 mmHg or > 8 mmHg increase, arterial pH < 7.32 or ≥ 0.07 decrease, respiratory rate > 35 breaths/min or ≥ 50% increase, heart rate > 140 beats/min or ≥ 20% increase, systolic arterial pressure >180 mmHg or ≥ 20% increase, systolic arterial pressure < 90 mmHg or cardiac arrhythmias.

Patients who tolerated the SBT were reconnected without changes to ventilator settings for rest and evaluation of airway patency. These patients were then extubated; those in the historic cohort received conventional supplementary oxygen and those in the contemporary group received HFO.

The three weaning categories (simple, difficult and prolonged weaning) were defined with standard criteria [16].

High flow oxygen therapy (Optiflow®, Fisher&Paykel Healthcare, Auckland, New Zealand) was applied immediately before extubation through a specific nasal cannula. Flow was initially set at 10 L/min and titrated upwards in 5 L/min steps until patients felt uncomfortable. The temperature of the administered gas was initially set to 37˚C and maintained unless patients reported it was too hot, and FiO_2 was regularly adjusted to target SpO_2 > 92%. After 24 hours, HFO was stopped and switched to conventional oxygen therapy.

Data sources

The historical cohort population was defined with the use of Care Suite Critical Care Manager 8.0© Picis Inc™, and included all patients admitted to our ICU from February 2008 to July 2011. Historical cohort patients were selected adding the matching criteria simultaneously to the admission date to assure the exact combination of the high risk criteria and the consecutive selection. When an exact matching patient did not existed, we tolerated a mismatch in one criterion. When we found two patients fulfilling the same matching criteria we selected the one with similar primary diagnosis (medical vs surgical).

We recorded gender, APACHE II at ICU admission, primary diagnosis, gasometric variables, corticosteroids at extubation, risk factors for reintubation (including suctioning frequency), and lengths of ICU and hospital stays. We also recorded extubation-related complications and adverse events (mainly laryngeal edema and criteria for reintubation).

Statistical analysis

Comparison between the two groups: The univariate analysis to compare homogeneity of two cohorts was performed with Fisher's exact test, Student's t-test, the Mann-Whitney U test, or the chi-square test, as appropriate. The level of significance was set at 0.05.

Risks factors associated to reintubation: Raw relationships between reintubation and its risk factors were analyzed with contingency tables and X2 after tercile categorization. A logistic regression model was designed to assess the probability of reintubation, and the results were expressed as odds ratios (OR) with 95% confidence interval. The independent variables included in the model were HFO and variables that were statistically significant in the univariate analysis at p < 0.1.

Kaplan-Meier curves were plotted to assess the time from extubation to reintubation in the whole population and after classifying patients according to the tolerated flow and compared by means of the log-rank test.

Power estimation: because our historical reintubation rate was 13% in low risk patients and 17% in high risk patients, our 111 patient

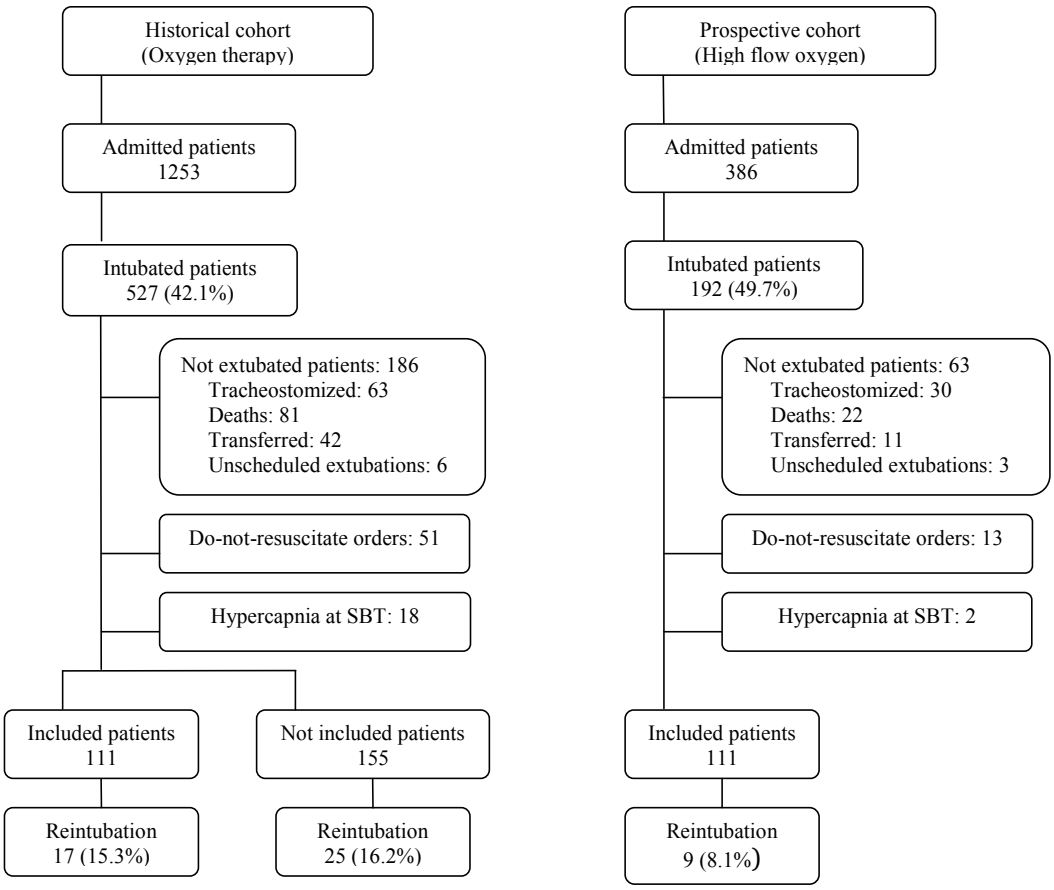

Figure 1: Flow chart of the study

sample size may be able to detect a reduction in reintubation rate of 9%, for a power of 80% and an α-error of 0.05.

Analyses were performed using SPSS statistical software version 13.0 (SPSS Inc.; Chicago, IL).

Results

Both the prospective cohort of HFO patients and the historical cohort of conventional oxygen therapy included 111 patients. A flowchart of the study is presented in Figure 1. Perfect matching was not possible in 12 patients.

The mean values of high risk criteria per patient in the HFO and control group were 4.2 vs 4.1, respectively (p = 0.8).

The univariable analysis comparing the baseline and outcome variables of the two cohorts are presented in table 1 and table 2 respectively. Baseline characteristics of both groups were similar.

Reintubation rate showed a non-significant reduction in the HFO cohort (8.1% vs. 15.3%, p = 0.09). Interestingly, 2 out 9 (22%) reintubated patients in the HFO cohort and 6 out 17 (35%) in the conventional oxygen cohort did not have any risk factors for reintubation.

Unexpectedly, the low risk group showed a greater reduction in the reintubation rate (4% vs. 13%, absolute reduction 9%, relative reduction 67%) as compared to high risk group (11% vs. 17%, absolute reduction 6%, relative reduction 35%), with an even greater difference after excluding patients reintubated for a non-respiratory cause, mainly unscheduled surgery and neurologic complications (2.2% vs. 11.1%, absolute reduction 8.9%, relative reduction 80% in low risk and 7.5% vs. 12.1%, absolute reduction 4.6%, relative reduction 37.5% in high risk).

In the conventional oxygen group, 4 patients developed laryngeal edema after extubation and 3 (75%) needed reintubation, whereas no patient in the HFO group showed laryngeal edema.

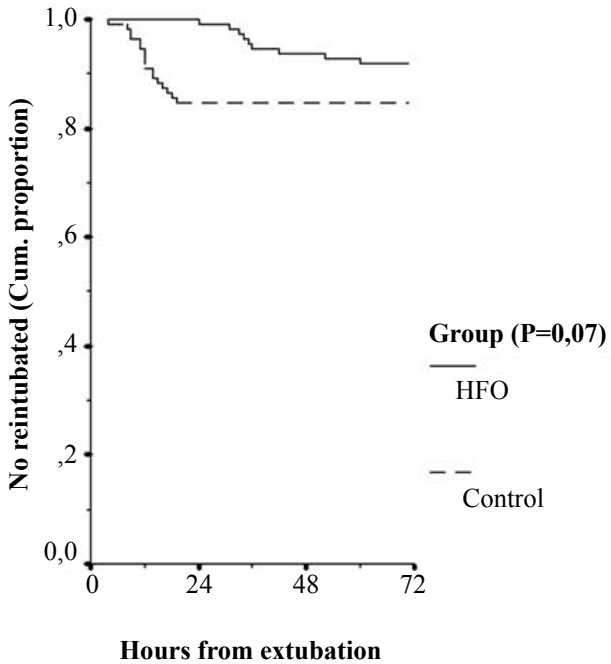

Figure 2: Kaplan-Meier curve for reintubation

Time for reintubation requirement (Figure 2) was significantly longer in the HFO cohort (38 ± 9 vs. 11 ± 4 hours, p = 0.04), with a non-significant difference in ICU mortality rate (3.6% vs. 6.3%, p = 0.08). The ICU length of stay was shorter in the HFO group (11 vs. 14 days, p = .05), with similar hospital length of stay (17 vs. 18 days, p = 0.09).

In the HFO group, FiO_2 > 0.35 at 12-h after extubation was highly associated with reintubation (24 (21%) vs. 2 (2%), p < 0.01). Also gas-

Table 1: Baseline patients' characteristics. Data are expressed as mean ± SD, median (interquartile range), or number and percentage (%).

	HFO Group N = 111	Control Group N = 111	P
Age, years	62.9 ± 16.1	64.5 ± 13.7	0.4
Male sex	70 (63%)	73 (66%)	0.7
Comorbidities:			
COPD	37 (33%)	34 (31%)	0.7
Heart disease	22 (20%)	23 (21%)	0.9
Diagnosis at admission:			
Medical	66 (59%)	66 (59%)	1
Respiratory primary failure*	46 (41.4%)	41 (36.9%)	
Cardiologic primary failure	2 (1.8%)	3 (2.7%)	
Abdominal	6 (5.4%)	10 (9.1%)	
Sepsis (other focus)	5 (4.5%)	8 (7.2%)	
Other	7 (6.3%)	4 (3.6%)	
Surgical	51 (45.9%)	47 (42.3%)	0.8
Scheduled surgery	31 (27.9%)	38 (34.2%)	
Urgent surgery	20 (18.1%)	9 (8.1%)	
Body mass index	27 ± 6.9	27 ± 7.1	0.8
APACHE II at ICU admission	15.1 ± 6.6	15.8 ± 7.5	0.6
APACHE II at extubation	9.6 ± 6.2	9.9 ± 7.1	0.8
PaO2/FiO2 at end of SBT	175 ± 21	180 ± 32	0.8
Length of mechanical ventilation before extubation, days	9.7 ± 4.8	10.1 ± 4.6	0.5
ICU-acquired paresis (MRC score < 48 points)	10 (9%)	7 (6%)	0.6
Corticosteroids (> 12 h before extubation)	16 (14%)	18 (16%)	0.8
High risk variables for reintubation:	66 (59%)	66 (59%)	1
Age > 65 years	54 (49%)	53 (48%)	
Intubation due to heart failure	2 (2%)	1 (1%)	
Moderate-to-severe COPD	29 (26%)	30 (27%)	
APACHE II > 12 at extubation	52 (47%)	51 (46%)	
Body mass index > 30	22 (20%)	24 (22%)	
Inability to deal with respiratory secretions	1 (1%)	0 (0%)	
Difficult or prolonged weaning	29 (26%)	27 (24%)	
≥ 2 comorbidities	34 (31%)	33 (30%)	
Mechanical ventilation > 7 days	56 (50%)	58 (52%)	
Laryngeal edema after extubation	0 (0%)	4 (4%)	0.1

APACHE = acute physiology and chronic health evaluation; ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; MRC = Medical Research Council score; SBT = spontaneous breathing trial.

* Primary respiratory failure included severe pneumonia (23/21), aspiration (3/3), asthma exacerbation (2/1), pulmonary embolism (4/2), and COPD exacerbation (11/12), ARDS (3/2), respectively.

Table 2: Outcome variables. Data are expressed as mean±SD, median (interquartile range), or number and percentage (%).

	HFO Group N = 111	Control Group N = 111	P
FiO_2 at 12-h after extubation	34.6 ± 7.4	35.2 ± 7.6	0.50
Hypercapnia after extubation	8 (7.2%)	7 (6.3%)	0.80
Gas-flow (HFO) at 12-h after extubation, L/min	34.2 ± 4.2	NA	
All-cause reintubation	9 (8.1%)	17 (15.3%)	0.09
Low risk group	2/45 (4.4%)	6/45 (13.3%)	0.26
Non-respiratory related causes	1/2 (50%)	1/6 (16.5%)	0.46
High risk group	7/66 (10.6%)	11/66 (16.6%)	0.31
Non-respiratory related causes	2/7 (28.5%)	3/11 (27.3%)	0.99
Time to reintubation requirement, median hours	35 (24-60)	12 (4-19)	< 0.01
ICU length of stay, days	11 (6-14)	14 (7-19)	0.05
Hospital length of stay, days	17 (10-22)	18 (12-25)	0.09
ICU mortality	4 (3.6%)	7 (6.3%)	0.35
ICU mortality in reintubated patients	4 (44%)	7 (41%)	0.99
Hospital mortality	7 (6.3%)	9 (8.1%)	0.60

ICU = intensive care unit; HFO = high flow oxygen therapy.

flow > 35 L/min at 12-h after extubation was highly associated with reintubation (9 (13%) vs. 0 (0%) patients, p < 0.01). Additionally, gas-flow showed a near-linear relationship with reintubation rate: 0/43 (0%) at flow < 35 L/min, 1/41 (2.4%) at flow 35-39 L/min and 8/27 (30%) with flow > 39 L/min, p < 0.01 (Figure 3). Tolerance to higher gas-flow was highly related to COPD diagnosis (p < 0.01) and APACHE II at ICU admission (p < 0.01).

The univariable analysis of variables associated with reintubation is shown in table 3, the multivariable analysis for all-cause reintubation in table 4 and multivariable analysis for respiratory-cause reintubation in table 5. The HFO appeared as a protector for reintubation (OR 0.31, 95% CI 0.10-0.95, p = 0.04). Among high risk criteria for reintubation, only APACHE II at extubation (OR 1.06, 95% CI 1.01-1.12, p = 0.04) and length of MV (OR 1.16, 95% CI 1.03-1.30, p = 0.01) appeared significant in the multivariate analysis.

Development of hypercapnia after extubation was the clinical variable most strongly related to reintubation (OR 51.20, 95% CI 11.55-226.63, p < 0.01). Interestingly, we observed a trend toward a reduced reintubation rate in hypercapnic patients when using HFO: 50% (4/8) vs. 85% (6/7), p = 0.18. The model showed an area under the ROC curve of 0.89 (95% CI 0.77-0.94).

Discussion

The major finding of this study is that HFO is independently associated with reintubation reduction in our multivariate analysis.

The variable most strongly related to an increased risk for reintubation was development of hypercapnia after extubation. In the subgroup of patients who developed hypercapnia after extubation, we found a trend towards a lower reintubation rate in patients receiving HFO (50% vs 85% in controls, p = 0.2); however, HFO did not prevent

Table 3: Univariable analysis of factors associated with all-cause reintubation. Data are expressed as mean±SD, median (interquartile range), or number and percentage (%).

	Failed extubation n = 26	Successful extubation n = 196	P
At least one high risk factor for reintubation	18 (69.2%)	114 (58.2%)	0.28
Heart disease	10 (38.4%)	35 (17.8%)	< 0.01
APACHE II > 12 at extubation	20 (76.9%)	83 (42.3%)	< 0.01
Length of mechanical ventilation > 10 days before extubation	20 (76.9%)	88 (44.9%)	< 0.01
Hypercapnia after extubation	11 (42.3%)	4 (2.1%)	< 0.01
Laryngeal edema after extubation	3 (11.5%)	1 (0.5%)	< 0.01
FiO_2 > 35% at 12-h after extubation	24 (92.3%)	88 (44.9%)	< 0.01
Gas-flow (only HFO), L/min	34 ± 3.9	40 ± 2.5	0.09
Gas-flow (only HFO) > 35 L/min at 12-h after extubation	9 (34.6%)	0 (0%)	0.01

APACHE = acute physiology and chronic health evaluation; HFO = high flow oxygen therapy; ICU = intensive care unit.

Table 4: Multivariate analysis of factors associated with all-cause reintubation.

Variables	Odds Ratio (95% CI)	P
High flow oxygen therapy	0.31 (0.10-0.95)	0.04
Hypercapnia after extubation	51.20 (11.55-226.63)	< 0.01
APACHE II > 12 at extubation	1.06 (1.01-1.12)	0.04
Length of mechanical ventilation, per day	1.16 (1.03-1.30)	0.01
Constant	0.09	< 0.01

Table 5: Multivariate analysis of factors associated with respiratory-cause reintubation.

Variables	Odds Ratio (95% CI)	p
High flow oxygen therapy	0.25 (0.06-0.99)	0.04
Hypercapnia after extubation	44.93 (9.58-210.59)	< 0.01
APACHE II >12 at extubation	1.05 (0.98-1.13)	0.15
Length of mechanical ventilation, per day	1.17 (1.02-1.34)	0.01
Constant	0.04	< 0.01

hypercapnia (7% vs 6%, p = 0.9), as suggested by Maggiore et al [10]. These findings are difficult to interpret in light of previous evidence. The evidence supporting the use of higher pressurization devices like noninvasive ventilation to prevent post-extubation respiratory failure in selected patients who develop hypercapnia during the spontaneous breathing trial is strong [3,15], but the evidence for using these devices to treat post-extubation hypercapnic respiratory failure is weaker [17]. Furthermore, in two other studies [18,19], post hoc analysis of hypercapnic patients failed to demonstrate significant reductions in the reintubation rate for noninvasive ventilation used to treat even mild (pH < 7.35) post-extubation hypercapnic respiratory failure. This complex scenario precludes any conclusion for this specific subgroup of patients until more information is available.

Not all the pre-defined factors for high risk of reintubation used to match the cohorts were confirmed in our study. The stratification of the risk for reintubation is complex. Although numerous factors have been described [20-22], subsequent studies have failed to confirm many of them, and no definitive model has yet to be established. Our study included no neurocritical patients [23], so we aimed to eliminate potential confounders by matching patients on a wide spectrum of risk factors (mainly those used by Ferrer [15] and Nava [24]). Risk factors selected by our univariate analysis were hypercapnia, airway patency problems (including laryngeal edema), MV longer than 7 days, heart disease, and APACHE II > 12 points on the day of extubation; however, only APACHE II on the day of extubation and MV length remained significant in the multivariate analysis, suggesting that not all the high risk factors selected are equally associated with a real increase in the risk of reintubation. In addition, in the multivariate analysis centered on reintubation due to respiratory causes, the APACHE II score was not significant, thus underlining the unpredictable etiology of reintubation due to non-respiratory causes.

The linear relationship between gas-flow and reintubation suggests that the higher the gas-flow tolerated by the patient, the greater the respiratory failure and the greater the risk of reintubation.

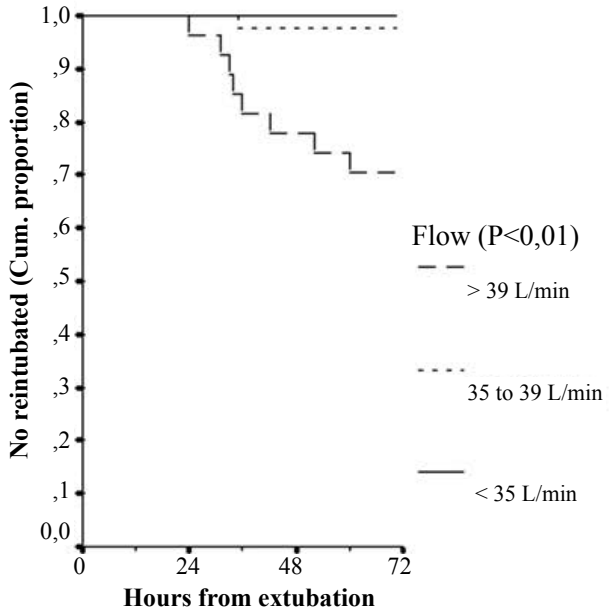

Figure 3: Kaplan-Meier curve for reintubation according to gas flow in HFO group.

Setting flow according to patient tolerance leads to higher flows than setting by oxygenation, even when HFO is indicated for acute hypoxemic respiratory failure [25]. In addition, tolerance to higher gas-flow was significantly associated with other variables associated with reintubation in the univariate analysis (COPD diagnosis, APACHE II at ICU admission and FiO_2 at 12-h after extubation), supporting this hypothesis.

The apparent greater improvement observed in the low risk group merits some consideration. At first glance, the classification criteria used may have a low discriminating value, as suggested by the small difference in the reintubation rates between the subgroups within the control group (17% in high risk and 13% in low risk). An alternative explanation is that the beneficial effect of HFO is small and only able to reverse low-intensity complications.

Whether HFO can prevent laryngeal edema after extubation could not be determined due to our low incidence (4% in the control group vs. 0% in the HFO group), but both low level PEEP and gas conditioning can reduce inspiratory effort and dryness of the upper airways, so this is a very interesting possibility.

One concern related to using HFO as a preventive measure is the possibility of delaying reintubation, with its associated morbidity and mortality [26], as reported previously for NIMV [19]. The time to reintubation was significantly longer in the HFO group (35 h vs. 12 h in the control group), suggesting that the withdrawal of HFO unmasked respiratory insufficiency. Nevertheless, ICU mortality tended to be lower in HFO patients and was very similar among patients requiring reintubation in the two groups. However, there are

some data suggesting that increasing time under high-flow therapy up to 48 hours, could improve outcomes in critically ill patients after extubation [10]. Additionally, our observation that hypercapnia after extubation, and that high FiO2 and high gas-flow al 12-h after extubation, are markers of failure may help to reduce the risk of delaying reintubation in the future.

Limitations of the Study

Some specific points of our protocol could limit the extrapolation of our conclusions. First, in any study with historical controls, the comparability between groups is always debatable. Although we used a wide number of reported risk factors for extubation failure to select historical controls and the resulting data was comparable, unrecorded variables could affect extubation outcome. Another issue is whether a temporary trend may reduce comparability. In our study, both groups were consecutive, without any time-lag in between them, and our reintubation rate was fairly stable in the three years comprising the period from which controls were selected (13/70 (18.6%), 16/107 (14.9%), and 15/89 (16.8%), p = 0.1). Moreover, co-interventions other than HFO remained unchanged in our ICU during the two study periods.

Second, we cannot identify which component of the HFO system is most important for its beneficial effect. The CPAP effect is higher at higher gas flow, but in our patients higher gas flow was associated with higher reintubation rates. Hence, despite the higher CPAP effect, HFO was unable to reverse respiratory insufficiency in patients asking for more flow, which is probably a marker of much greater severity. The dead-space washout may reduce ventilatory needs, but our design did not allow for comparisons of minute ventilation, respiratory rate, or dyspnea between groups. Improved humidification can also play a beneficial role, but bedside bronchial ciliary movement or mucus viscosity measurements were not available.

We conclude that routine clinical use of HFO was associated with a reduction in the reintubation rate. The multicenter randomized controlled trial necessary to confirm these results is currently recruiting patients (ClinicalTrials.gov Identifier: NCT01191489).

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Author contributions

Dr. Hernandez: contributed to the conception, coordination, design, and interpretation of the study, as well as to drafting, critical revision, reading, and approval of the manuscript; **Dr. Pardo, Dra. Gonzalez, Dra. Villasclaras, Dra. García and Dra. De la Fuente**: contributed to coordination and interpretation of the study, as well as to critical revision, reading, and approval of the manuscript; **Dr. Cuena**: contributed to statistical analyses and interpretation of the study, as well as to critical revision, reading, and approval the manuscript; **Dra. Vaquero, and Dr. Fernandez**: contributed to interpretation of the study, and to drafting, critical revision, reading, and approval of the manuscript.

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