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Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients
A Randomized Clinical Trial

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IMPORTANCE High-flow conditioned oxygen therapy delivered through nasal cannulae and noninvasive mechanical ventilation (NIV) may reduce the need for reintubation. Among the advantages of high-flow oxygen therapy are comfort, availability, lower costs, and additional physiopathological mechanisms.

OBJECTIVE To test if high-flow conditioned oxygen therapy is noninferior to NIV for preventing postextubation respiratory failure and reintubation in patients at high risk of reintubation.

DESIGN, SETTING, AND PARTICIPANTS Multicenter randomized clinical trial in 3 intensive care units in Spain (September 2012-October 2014) including critically ill patients ready for planned extubation with at least 1 of the following high-risk factors for reintubation: older than 65 years; Acute Physiology and Chronic Health Evaluation II score higher than 12 points on extubation day; body mass index higher than 30; inadequate secretions management; difficult or prolonged weaning; more than 1 comorbidity; heart failure as primary indication for mechanical ventilation; moderate to severe chronic obstructive pulmonary disease; airway patency problems; or prolonged mechanical ventilation.

INTERVENTIONS Patients were randomized to undergo either high-flow conditioned oxygen therapy or NIV for 24 hours after extubation.

MAIN OUTCOMES AND MEASURES Primary outcomes were reintubation and postextubation respiratory failure within 72 hours. Noninferiority margin was 10 percentage points. Secondary outcomes included respiratory infection, sepsis, and multiple organ failure, length of stay and mortality; adverse events; and time to reintubation.

RESULTS Of 604 patients (mean age, 65 [SD, 16] years; 388 [64%] men), 314 received NIV and 290 high-flow oxygen. Sixty-six patients (22.8%) in the high-flow group vs 60 (19.1%) in the NIV group did not require reintubation (absolute difference, −3.7%; 95% CI, −9.1% to ∞); 78 patients (26.9%) in the high-flow group vs 125 (39.8%) in the NIV group experienced postextubation respiratory failure (risk difference, 12.9%; 95% CI, 6.6% to ∞). Median time to reintubation did not significantly differ: 26.5 hours (IQR, 14-39 hours) in the high-flow group vs 21.5 hours (IQR, 10-47 hours) in the NIV group (absolute difference, −5 hours; 95% CI, −34 to 24 hours). Median postrandomization ICU length of stay was lower in the high-flow group, 3 days (IQR, 2-7) vs 4 days (IQR, 2-9; P=.048). Other secondary outcomes were similar in the 2 groups. Adverse effects requiring withdrawal of the therapy were observed in none of patients in the high-flow group vs 42.9% patients in the NIV group (P < .001).

CONCLUSIONS AND RELEVANCE Among high-risk adults who have undergone extubation, high-flow conditioned oxygen therapy was not inferior to NIV for preventing reintubation and postextubation respiratory failure. High-flow conditioned oxygen therapy may offer advantages for these patients.

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Supplemental content

CME Quiz at jamanetworkcme.com and **CME Questions** page 1594

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Three noninvasive methods to increase oxygenation after extubation are available: conventional oxygen therapy, high-flow conditioned oxygen therapy, and noninvasive ventilation (NIV). Compared with conventional oxygen therapy, high-flow conditioned oxygen therapy improves oxygenation and comfort after extubation and prevents postextubation respiratory failure and reintubation in general populations of critically ill patients[1] and in patients at low risk of reintubation.[2] However, the evidence supporting its use in patients at high risk of reintubation is inconclusive.

The clinical benefits of high-flow conditioned oxygen therapy include improved oxygenation and secretions management.[1,2] However, other, poorly understood mechanisms may contribute to the beneficial effect, such as increased end-expiratory lung volume,[3] reduced work of breathing,[4] and hemodynamic improvements secondary to increases in lung volume that cannot be explained solely by low airway pressure[5,6] and counterbalance of intrinsic positive end-expiratory pressure (PEEP).

The evidence supporting NIV to prevent postextubation respiratory failure and reintubation is weak,[7,8] although 2 meta-analyses[7,8] concluded that early use of NIV can decrease reintubation rates. However, these studies included trials involving both general and high-risk populations, and patients at high-risk of reintubation accounted for only 35% of the total weight in the meta-analyses. In both meta-analyses, the odds ratios (ORs) and 95% CIs were not statistically significant, but the studies may have been underpowered. Two studies comparing NIV to conventional oxygen therapy in critically ill patients at high risk of reintubation found that NIV was more effective.[9,10] However, to our knowledge, no meta-analyses of NIV including only patients at high risk of reintubation have been published.[9-13] Despite the inconclusive evidence supporting NIV to prevent postextubation respiratory failure and reintubation, the use of NIV after extubation has increased up to 10% in the last 15 years.[14,15]

Compared with NIV, high-flow conditioned oxygen therapy has some advantages,[1] such as greater patient comfort, lower costs, greater availability, and some additional pathophysiological mechanisms not offered with NIV (eg, conditioning the air). Furthermore, high-flow conditioned oxygen therapy could avoid some recently highlighted adverse effects of NIV (eg, increased tidal volume) that could lead to worse outcome in patients with acute respiratory failure.[16]

This trial was conducted to test the hypothesis that delivering high-flow conditioned oxygen therapy through nasal prongs immediately after planned extubation is noninferior to NIV in reducing reintubation and postextubation respiratory failure in patients at high risk of reintubation.

Key Points

Question Is high-flow nasal cannula noninferior to noninvasive ventilation for preventing reintubation and postextubation respiratory failure?

Findings In this multicenter randomized noninferiority clinical trial that included 604 adults, the proportion requiring reintubation was 22.8% with high-flow therapy vs 19.1% with noninvasive ventilation, and postextubation respiratory failure was observed in 26.9% with high-flow therapy vs 39.8% with noninvasive ventilation, reaching the noninferiority threshold.

Meaning High-flow nasal cannula immediately after scheduled extubation was not inferior to noninvasive mechanical ventilation for risk of reintubation and postextubation respiratory failure in patients at high risk of reintubation.

Methods

From September 2012 to October 2014, a randomized noninferiority trial was conducted at 3 intensive care units (ICUs) in Spain (the trial registry includes 2 separate analyses, the low-risk group was reported elsewhere).[2] The study protocol (available in Supplement 1) was approved by the departments of health of the regional governments to which these hospitals are affiliated (Madrid and Castilla–la Mancha). The ethics committee at each center approved the trial, and all patients or their relatives provided written informed consent.

Patients

All adult patients receiving mechanical ventilation for more than 12 hours who were ready for scheduled extubation were screened (trial protocol in Supplement 1). Exclusion criteria were do-not-resuscitate orders, tracheostomies, hypercapnia during the spontaneous breathing trial, accidental extubation, or self-extubation.

Patients fulfilling at least 1 of the following criteria were considered at high-risk of extubation failure: age older than 65 years[9,10]; heart failure as the primary indication for mechanical ventilation[9,10]; moderate to severe chronic obstructive pulmonary disease[17]; an Acute Physiology and Chronic Health Evaluation II (APACHE II) score higher than 12 on extubation day[9,10]; body mass index of more than 30 (calculated as weight in kilograms divided by height in meters squared)[2,18]; airway patency problems, including high risk of developing laryngeal edema (eAppendix 2 in Supplement 2)[9]; inability to deal with respiratory secretions (inadequate cough reflex or suctioning >2 times within 8 hours before extubation)[9]; difficult or prolonged weaning, in brief, a patient failing the first attempt at disconnection from mechanical ventilation[9]; 2 or more comorbidities (eAppendix 3 in Supplement 2)[9]; and mechanical ventilation for more than 7 days.[19]

The following variables recorded at inclusion were age, sex, APACHE II score within the first 24 hours of admission, and primary diagnosis; at extubation, the variables recorded were arterial blood gases, APACHE II score, and administration of steroids; in the 72 hours after extubation, the variables recorded were extubation-related complications, nasal septum and skin trauma as surrogates for adverse events, reasons for reintubation, and time to reintubation; and at discharge, the variables recorded were ICU and hospital lengths of stay and mortality.

Weaning Protocol

The weaning protocol included daily screening for weaning readiness according to the following criteria[20]: recovery from

the precipitating illness; respiratory criteria (PaO_2:FIO_2 [partial pressure of oxygen, atrial:fraction of inspired oxygen] ratio >150 with FIO_2 ≤0.4, PEEP <8 cm H_2O, and arterial pH >7.35); and clinical criteria (absence of electrocardiographic signs of myocardial ischemia, no vasoactive drugs, or only low doses of dopamine [<5 µg/kg/min], heart rate <140/min, hemoglobin >8 g/dL, temperature <38°C, no need for sedatives, presence of respiratory stimulus, and appropriate spontaneous cough). Patients fulfilling these criteria underwent a spontaneous breathing trial with either T-tube or 7 cm H_2O of pressure support for 30 to 120 minutes. Standard criteria for failure of the breathing trial were used (eAppendix 1 in Supplement 2). Patients who tolerated the spontaneous breathing trial were reconnected with the previous ventilator settings for rest and clinical evaluation of airway patency, respiratory secretions, and upper airway obstruction (eAppendix 2 in Supplement 2).

Randomization

Patients who passed the breathing trial and underwent scheduled extubation were randomized to receive NIV or high-flow oxygen by concealed allocation with a random number generator (simple randomization) through a telephone call center.

Interventions

High-flow oxygen (Optiflow, Fisher and Paykel Healthcare) was applied immediately after extubation through specific nasal cannula. Flow was initially set at 10 L/min and titrated upwards in 5-L/min steps until patients experienced discomfort. Temperature was initially set to 37°C, unless reported too hot by patients, and FIO_2 was regularly adjusted to the target peripheral capillary oxygen saturation (SPO_2) of greater than 92%. After 24 hours, high-flow was stopped and, if necessary, patients received conventional oxygen therapy.

Full face mask NIV (BiPAP Vision; Respironics Inc) was continuously delivered immediately after extubation for a scheduled period of 24 hours after extubation. Afterward, NIV was withdrawn and oxygen was administered by Venturi mask. Both PEEP and inspiratory pressure support were adjusted to target a respiratory rate of 25/min and adequate gas exchange (arterial oxygen saturation [SaO_2] 92%, with pH of 7.35). The FIO_2 was adjusted to maintain SPO_2 at less than 92%. Sedatives to increase tolerance to NIV were not allowed.

Both groups were treated by the same medical, nursing, and respiratory therapy staff (excluding the investigators) and received similar medical management.

Outcomes

The primary outcomes were reintubation within 72 hours after extubation and postextubation respiratory failure. Predefined criteria for immediate respiratory-related reintubation included any of the following: 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 less than 50/min with loss of alertness, and severe hemodynamic instability unresponsive to fluids and vasoactive drugs; patients who developed persistent postextubation respiratory failure (eAppendix 4 in Supplement 2) were also reintubated. Nonrespiratory-related reasons for reintubation were needed for emergency surgery or low level of consciousness (decrease in Glasgow Coma Scale [GCS] >2 points or GCS <9 points) with $PaCO_2$ less than 45 mm Hg.

Postextubation respiratory failure within 72 hours of extubation was defined as the presence and persistence of any of the following criteria: respiratory acidosis (pH <7.35 with $PaCO_2$ >45 mm Hg), SPO_2 less than 90% or PaO_2 less than 60 mm Hg at FIO_2 higher than 0.4, respiratory rate more than 35/min, decreased level of consciousness (GCS >1 point decrease), agitation, or clinical signs suggestive of respiratory muscle fatigue or increased work of breathing, such as the use of respiratory accessory muscles, paradoxical abdominal motion, or retraction of the intercostal spaces.[21]

Secondary outcomes were respiratory infection (ventilator-associated pneumonia or ventilator-associated tracheobronchitis) (eAppendix 5 in Supplement 2), sepsis or multiple organ failure, ICU and hospital length of stay and mortality, and the reason for failure of assigned treatment if applicable, including patient comfort requiring withdrawal of the therapy for more than 6 hours and nasal septum or skin trauma. Delayed reintubation was the main safety concern, and time to reintubation was measured as a safety surrogate. Rescue therapy with NIV for postextubation respiratory failure was not allowed in the high-flow oxygen therapy group.

Statistical Analysis

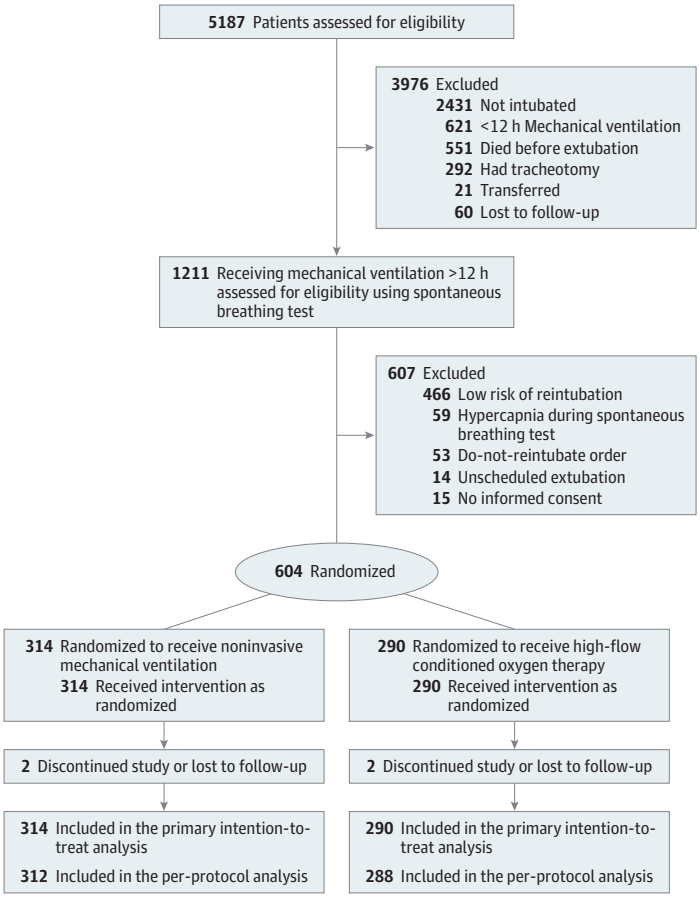
Because reported reintubation rates in high-risk patients receiving NIV range from 9% to 32%,[9-13] the sample size was estimated assuming a baseline reintubation rate of 20% to 25% for each therapy and a predefined noninferiority margin of 10% for the high-flow group. The noninferiority design included a unilateral 95% CI analysis with a statistical power of 80%, and a maximum tolerated patient loss rate of 15%. These conditions required 300 participants per study group.

The noninferiority analyses were performed on both a per-protocol and an intention-to-treat bases for primary outcomes only. To assess the probability of reintubation and postextubation respiratory failure, noninferiority was established if the limit of the 1-sided 95% CI (Newcombe hybrid-score type) for the between-group difference in treatment failure rates was less than 10%. This noninferiority margin was based on data reported by Nava et al[9] and Ferrer et al[10] and considerations of clinical relevance.

To test whether the marginal odds ratio (OR) and its 1-sided 95% CI of high-flow oxygen was similar to the OR conditioned to covariables and its 1-sided 95% CI, multivariable logistic regression was used. The independent variables tested in the model were high-flow, hospital, and all variables associated with reintubation with $P < .10$ (eAppendix 6 in Supplement 2).

Time to reintubation was assessed by Kaplan-Meier curves. For the analysis of secondary outcomes and post hoc analyses, Fisher exact, *t*, and Mann-Whitney *U* tests were used. Significance was set at .05; SPSS version 13.0 (SPSS Inc) was used for all analyses.

Figure 1. Flowchart of Participants in a Study of Postextubation High-Flow Conditioned Oxygen vs Noninvasive Mechanical Ventilation for Preventing Reintubation in High-Risk Patients



Results

During the study period, 1211 weanable patients were screened; 604 (49.8%) of these were randomized: 290 to the high-flow conditioned oxygen therapy group and 314 to the NIV group (**Figure 1**). There were 2 dropouts in each group. Demographic and clinical characteristics of patients in the 2 groups were similar (**Table 1**), except for a lower incidence of heart failure as a risk factor for reintubation in the high-flow conditioned oxygen therapy group (5.5% vs 9.9% in the NIV group) and a higher incidence of surgical diagnosis at admission (43.8% vs 33.4% in the NIV group).

Primary Outcomes

According to the preestablished definition, high-flow oxygen therapy was noninferior to NIV, with reintubation occurring in 60 patients (19.1%) in the NIV group and 66 patients (22.8%) in the high-flow group (risk difference, −3.7%; 95% CI, −9.1% to ∞; **Table 2**). Additionally, the multivariable analysis (eAppendix 6 in Supplement 2) confirmed that the marginal OR of 1.25 (95% CI, 0 to 1.74) was similar to the OR conditioned to covariables (OR, 1.23; 95% CI, 0 to 1.76). After nonrespiratory-related reintubations were excluded, the difference in reintubation rate was 50 patients (15.9%) in the NIV group vs 49 patients (16.9%) in the high-flow group (absolute difference, 1; 95% CI, −4.9 to 6.9; **Table 3**).

Figure 2 shows the Kaplan-Meier curve for all-cause-related reintubations. One patient in the high-flow group needed delayed reintubation for respiratory causes within the first 7 days; this patient was included in the per-protocol analysis (eAppendix 7 in Supplement 2).

After extubation, more patients experienced respiratory failure in the NIV group (125 [39.8%]) than in the high-flow group (78 [26.9%]; risk difference, 12.9%; 95% CI, 6.6% to ∞).

Secondary Outcomes

Median time to reintubation was not significantly different in the 2 groups: 26.5 hours (interquartile range [IQR], 14-39) in the high-flow group vs 21.5 hours (IQR, 10-47) in the NIV group (absolute difference, −5 hours; 95% CI, −34 to 24 hours). Table 2 reports the causes for respiratory failure and reintubation after extubation. Hypercapnic respiratory failure accounted for 6 reintubations (2%) in the high-flow group and 8 (2.5%) in the NIV group (P = .63). Median ICU length of stay after randomization was lower in the high-flow group, 3 days (IQR, 2 to 7) vs 4 days (IQR, 2 to 9; P = .048). Other secondary outcomes were similar in the 2 groups (Table 2).

Table 1. Patient Baseline Characteristics

	No. (%)	
	Noninvasive Mechanical Ventilation (n = 314)	High-Flow Conditioned Oxygen Therapy (n = 290)
Age, mean (SD), y	64.4 (15.8)	64.6 (15.4)
Men	202 (64.3)	186 (64.1)
APACHE II, median (IQR)[a]		
ICU admission	16 (14-21)	16 (13.8-22)
Extubation	10 (8-12)	11 (8-12)
Length of MV before extubation, median (IQR), d	4 (2-8)	4 (2-9)
Comorbidities[b]		
Body mass index >25[c]	74 (23.6)	74 (25.5)
Arterial hypertension	176 (56.1)	165 (56.9)
Heart disease	102 (32.5)	94 (32.4)
Neurologic disease	73 (23.2)	83 (28.6)
COPD	70 (22.3)	54 (18.6)
Other respiratory disease	0	88 (30.3)
Diabetes mellitus	90 (28.7)	89 (30.7)
Cancer	65 (20.7)	48 (16.6)
Vascular disease	22 (7)	21 (7.2)
Renal failure	37 (11.8)	42 (14.5)
Hepatic disease	29 (9.2)	31 (10.7)
Other comorbid conditions	38 (12.1)	43 (14.8)
High-risk factors for reintubation		
>65 y	182 (58)	166 (57.2)
Heart failure as the primary indication for MV	31 (9.9)	16 (5.5)
COPD	65 (20.7)	51 (17.6)
APACHE II >12 on extubation day[a]	128 (40.8)	131 (45.2)
Body mass index >30[c]	62 (19.7)	63 (21.7)
Airway patency problems	10 (3.2)	7 (2.4)
Inability to deal with respiratory secretions	66 (21)	66 (22.8)
Difficult or prolonged weaning[d]	87 (27.7)	73 (25.2)
≥2 Comorbidities	218 (69.4)	204 (70.3)
Prolonged mechanical ventilation	120 (38.2)	101 (34.8)
High-risk factors, median (IQR), No.	3 (2-4)	3 (2-4)
Diagnosis at admission[e]		
Medical	186 (59.2)	154 (53.1)
Respiratory primary failure	121 (38.5)	98 (33.8)
ARDS[f]	26 (8.3)	27 (9.3)
Respiratory infection	48 (15.3)	37 (12.8)
Exacerbated COPD	33 (10.5)	15 (5.2)
Airway patency problem	6 (1.9)	7 (2.4)
Other	8 (2.5)	12 (4.1)
Nonrespiratory primary failure	65 (20.7)	56 (19.3)
Cardiologic	51 (16.2)	39 (13.4)
Neurologic	6 (1.9)	11 (3.8)
Other	8 (2.5)	6 (2.1)
Trauma	33 (10.5)	19 (6.6)
Traumatic brain injury	18 (5.7)	10 (3.4)
Surgical	105 (33.4)	127 (43.8)
Scheduled	15 (4.8)	27 (9.3)
Urgent	90 (28.7)	100 (34.5)

(continued)

Table 1. Patient Baseline Characteristics (continued)

	No. (%)	
	Noninvasive Mechanical Ventilation (n = 314)	High-Flow Conditioned Oxygen Therapy (n = 290)
Type of surgery		
Vascular	5 (1.6)	2 (0.7)
Trauma	3 (0.9)	4 (1.4)
Thoracic	2 (0.6)	3 (1)
Abdominal	44 (14)	63 (21.7)
Facial	1 (0.3)	4 (1.4)
Neurosurgery	39 (12.4)	41 (14.1)
Other	12 (3.8)	5 (1.7)
>1 type	6 (1.9)	5 (1.7)
Baseline physiologic variables from spontaneous breathing trial prior to extubation, mean (SD)		
Pao_2:Fio_2, mm Hg	194 (37)	191 (34)
$Paco_2$, mm Hg	39 (3.2)	41 (2.2)
Arterial pH	7.4 (0.2)	7.39 (0.3)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation.

[a] APACHE II score was calculated from 17 variables. Scores range from 0 to 71 points, with higher scores indicating more severe disease.

[b] Comorbidities were categorized based on the Charlson Comorbidity Index (eAppendix 4 in Supplement 2).

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Definitions according to the Sixth International Consensus Conference on Intensive Care Medicine.[19]

[e] Patients can have more than 1 diagnosis.

[f] Defined according to the American European Consensus Definition. These patients are included under current mild, moderate or severe ARDS diagnosis.

Adverse Events

All patients tolerated high-flow conditioned oxygen therapy; none reported nasal mucosa or skin trauma. In the NIV group, the total time under NIV was 14 hours (IQR, 8-23; Table 3).

Discussion

In this study involving critically ill patients at high risk of reintubation, the postextubation respiratory failure rate was lower in the high-flow conditioned oxygen therapy group than in the NIV group, and high-flow conditioned oxygen therapy was noninferior to NIV at preventing reintubation.

In this study, the reintubation and postextubation respiratory failure rates were similar to those reported in previous studies for patients treated with conventional oxygen,[9,10] but the reintubation rate in NIV patients (19%) was slightly higher than in these same studies (11%-16%).[9,10] Various factors might help explain this difference. The 24-hour protocol in the present study could represent an underuse of both NIV and high-flow conditioned oxygen therapy compared with more prolonged protocols.[1,9] Second, not allowing the administration of sedatives to increase NIV tolerance may have reduced the treatment time under NIV (IQR, 8-23 hours). Moreover, the patients in the present study had more risk factors for reintubation.[9] In addition, since some investigators advocated an extended period for reintubation for patients under NIV or high-flow conditioned oxygen therapy,[22] patients in the present study were followed up until hospital discharge to ensure that delayed reintubation was recorded, whereas shorter follow-up in other studies might have underestimated reintubation rates by missing delayed episodes.

The protocol in the present study called for switching to conventional oxygen therapy in both groups after 24 hours. This requirement was imposed mainly because 24 hours is the standard monitoring period before ICU discharge in our health system, and high-flow conditioned oxygen therapy was unavailable on the wards. However, some data suggest that more prolonged high-flow conditioned oxygen therapy could improve outcomes in critically ill patients after extubation. First, the Kaplan-Meier curves in the present study (Figure 2 and **Figure 3**) show a sudden increase in reintubation shortly after switching to conventional oxygen therapy. Second, in a general population of critically ill patients randomized to receive either high-flow conditioned oxygen therapy or conventional oxygen for 48 hours, Maggiore et al[1] found persistent improvement in oxygenation and comfort parameters and achieved a lower reintubation rate (3.8%) than in the present study.

Intermediate respiratory support therapies such as NIV and high-flow conditioned oxygen therapy have traditionally raised safety concerns.[23,24] These therapies might increase the risk of worse outcomes, including death, by delaying reintubation because apparent improvement in patient comfort and gasometric variables could mask deterioration. In the present study, time to reintubation was similar in the 2 groups (26.5 hours in the high-flow conditioned oxygen therapy vs 21.5 hours in the NIV group, $P = .43$), probably because of the switch to conventional oxygen after 24 hours. These data suggest that, when used as preventive therapies, the efficacy of both NIV and high-flow conditioned oxygen therapy should be coun-

Table 2. Primary and Secondary Outcomes

	No. (%)		
	Noninvasive Mechanical Ventilation (n = 314)	High-Flow Conditioned Oxygen Therapy (n = 290)	Difference Between Groups (95% CI)[a]
Primary outcome			
All-cause reintubation[b]	60 (19.1)	66 (22.8)	−3.7 (−9.1 to ∞)[c]
Postextubation respiratory failure[b]	125 (39.8)	78 (26.9)	12.9 (6.6 to ∞)[c]
Secondary Outcomes			
Causes of postextubation respiratory failure			*P* = .89[d]
Respiratory acidosis[e]	21 (6.7)	11 (3.8)	
Hypoxia[f]	19 (6.1)	12 (4.1)	
Unbearable dyspnea	26 (8.3)	21 (7.2)	
Decreased level of consciousness	7 (2.2)	4 (1.4)	
Inability to clear secretions	52 (16.6)	30 (10.3)	
Causes for reintubation			*P* = .28[d]
Cardiorespiratory arrest	3 (1)	3 (1)	
Agitation	1 (0.3)	3 (1)	
Inability to clear secretions	20 (6.4)	13 (4.5)	
Hemodynamic impairment[g]	10 (3.2)	14 (4.8)	
Persistent postextubation respiratory failure[f]	16 (5.1)	16 (5.5)	
Nonrespiratory causes for reintubation			
Surgery	4 (1.3)	2 (0.7)	
Low level of consciousness[h]	6 (1.9)	15 (5.2)	
Adverse events[i]	135 (42.9)	0 (0)	*P* < .001
Sepsis	4 (1.3)	6 (2.1)	−0.8 (−3.3 to 1.5)[d,j]
Multiorgan failure	5 (1.6)	5 (1.7)	−0.1 (−2.6 to 2.2)[d,j]
Respiratory infection	34 (10.8)	23 (7.9)	2.9 (−1.8 to 7.6)[j]
Ventilator-associated tracheobronchitis	18 (5.7)	11 (3.8)	1.9 (−1.6 to 5.5)[j]
Ventilator-associated pneumonia	17 (5.4)	12 (4.1)	1.3 (−2.3 to 4.8)[j]
Time to reintubation, median (IQR), h	21.5 (10 to 47)	26.5 (14 to 39)	−5 (−34 to 24)[j,k]
ICU length of stay, median (IQR), d	4 (2 to 9)	3 (2 to 7)	1 (−0.1 to 2.1)[k,l]
Hospital length of stay, median (IQR), d	26 (16 to 37)	23 (14 to 46)	3 (−6.8 to −0.8)[k,l]
Mortality			
ICU	18 (5.7)	19 (6.6)	−0.8 (−4.9 to 3.1)[j]
Hospital	56 (17.8)	59 (20.3)	−2.5 (−8.8 to 3.8)[d,j]

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] Data are expressed as difference (95% CI) except as otherwise indicated.

[b] Per-protocol analysis: all-cause reintubation 60 of 312 (19.2%) vs 66 of 288 (22.9%), respectively,−3.7 (−9.2 to ∞); postextubation respiratory failure 124 of 312 (39.7%) vs 76 of 288 (26.4%), respectively, 13.3 (6.5 to ∞). The rest of the results were obtained with an intention-to-treat analysis.

[c] One-sided 95% CI noninferiority analysis for primary outcomes.

[d] Fisher exact test.

[e] Respiratory acidosis: pH lower than 7.35 with $Paco_2$ less than 45 mm Hg; hypoxia: Spo_2 less than 90% or Pao_2 less than 60 mm Hg at Fio_2 greater than 0.4.

[f] Patients reintubated for persistent postextubation respiratory failure included 6/290 (2%) and 8/314 (2.5%) reintubated secondary to hypercapnia (*P* = .63) (eAppendix 4 in Supplement 2).

[g] Heart rate less than 50/min with loss of alertness or severe hemodynamic instability (systolic blood pressure, <90 mm Hg for >30 min) unresponsive to fluids and vasoactive drugs.

[h] Criteria for reintubation secondary to low level of consciousness: decrease in Glasgow Coma Scale score >2 points or score <9 points with $Paco_2$<45 mm Hg.

[i] Adverse events requiring treatment discontinuation for 25% or more of the per-protocol time (18 hours).

[j] Bilateral 95% CI for secondary and exploratory outcomes.

[k] Mann-Whitney *U* test.

[l] Time analyzed since randomization in survivors. Total ICU length of stay was 10.5 (5-19) vs 9 (4-19) days, respectively (absolute difference, 1.5 days; 95% CI, −4.4 to 1.4; *P* = .23).

terbalanced against safety. Prolonging postextubation high-flow conditioned oxygen therapy or NIV to 48 hours could improve extubation success,[9,10] but protocols with variable duration based on clinical parameters instead of fixed periods increase the risk of delayed reintubation in cases with unperceived deterioration.[24]

Various mechanisms that explain the improved rate of successful extubation with high-flow conditioned oxygen therapy have been reported: reduced hypoxia,[1,2] reduced work of breathing and respiratory muscle fatigue,[3,6,9] improved management of respiratory secretions, and reduction in upper airway obstruction episodes attributed to conditioning the inspired gas.[1,2] The significant reduction in the Fio_2 required by patients to maintain the target Spo_2 with high-flow conditioned oxygen therapy in the present study supports a reduction in hypoxia. Greater hypoxemia in the NIV group could be

Table 3. Exploratory Outcomes and Between-Group Differences in Physiologic Variables

	Noninvasive Mechanical Ventilation (n = 314)	High-Flow Conditioned Oxygen Therapy (n = 290)	Difference Between Groups (95% CI)[a]
Exploratory outcomes, No. (%)			
Respiratory-caused reintubation	50 (15.9)	49 (16.9)	1 (−4.9 to 6.9)
Physiologic variables			
FIO_2 12 h postextubation, median (IQR)	40 (35 to 50)	35 (30 to 40)	5 (−1.7 to 8.3)[b]
Gas-flow 12 h postextubation, mean (SD), L/min		50 (5)	
Length of NIV, median (IQR), h	14 (8-23)		
PaO_2:FIO_2, mean (SD), mm Hg[c]	104 (32)	99 (2)	*P* = .83[b]
$PaCO_2$, mean (SD), mm Hg[c]	47 (2.8)	46 (3.1)	*P* = .67[b]
Arterial pH, mean (SD)[c]	7.37 (0.03)	7.38 (0.05)	*P* = .57[b]

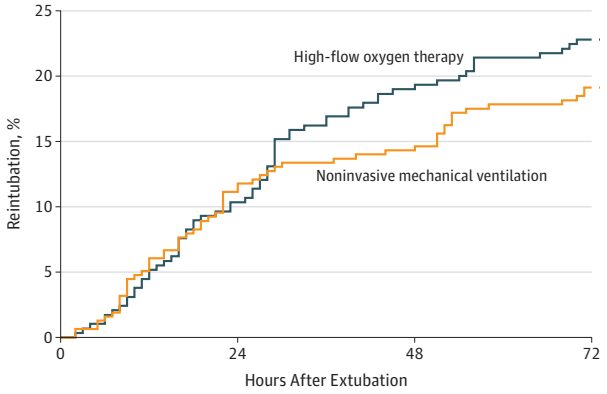
Abbreviations: IQR, interquartile range; NIV, noninvasive mechanical ventilation.

[a] Data are expressed as difference (95% CI) except as otherwise indicated.

[b] Mann-Whitney *U* test.

[c] Analysis including postextubation respiratory failure and reintubated patients only.

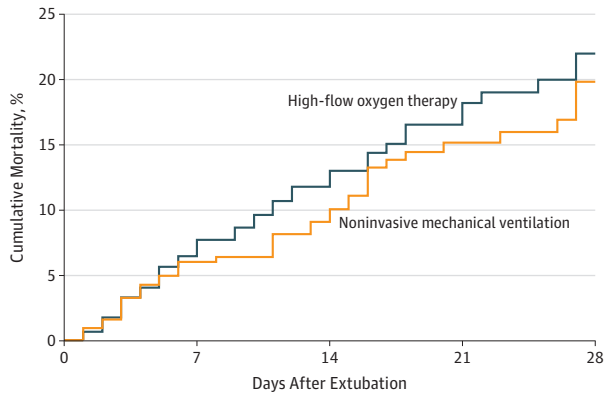
Figure 2. Kaplan-Meier Analysis of Time From Extubation to Reintubation



No. at risk

High-flow oxygen therapy	290	260	234	223
Noninvasive mechanical ventilation	314	279	269	253

Figure 3. Kaplan-Meier Analysis of Time From Extubation to Death



No. at risk

High-flow oxygen therapy	282	223	144	101	78
Noninvasive mechanical ventilation	309	261	187	112	79

Patients censored in the first 24 hours are not included.

explained by the lower actual time under effective preventive NIV due to withdrawal for discomfort. In addition, the 50 L/min of flow tolerated by high-risk patients is clearly higher than the 30 L/min of flow tolerated by low-risk patients,[2] reinforcing the idea that the flow tolerated by patients is a marker of severity.

There is still not much information about the role of high-flow conditioned oxygen therapy in managing hypercapnia, except for the mechanism of dead-space washout. The present study supports a possible role of high-flow conditioned oxygen therapy in managing hypercapnia after extubation. Postextubation respiratory failure due to hypercapnia showed a trend toward a higher rate in the NIV than in the high-flow conditioned oxygen therapy group (6.7% vs 3.8%, respectively), although this difference was not translated to the rates of hypercapnia as the reason for reintubation (2% vs 2.5%, respectively). There is a possible explanation for these results: the time under NIV (IQR, 8-23 hours) suggests that discomfort could have been the reason for postextubation respiratory failure in some patients because $PaCO_2$ improves without any respiratory support in most patients.

Limitations of the Study

One possible limitation in the current study is the criteria used to select patients who were at high risk of reintubation. No prospectively validated model that accurately predicts extubation failure is available. Recently, Thille et al,[22] prospectively analyzed risk factors for reintubation and reported a multivariable model including only cough strength, duration of mechanical ventilation, and cardiac dysfunction. The present study considered a wider variety of risk factors, mainly those used in previous randomized trials on preventive NIV after extubation[9,10] or confirmed in several studies,[25-28] excluding physiological variables at extubation.[22] A sensitivity analysis to rule out a possible bias that could have led to inclusion of patients not at high risk of reintubation was done (eAppendix 7 in Supplement 2) and confirmed the results in the main analysis.

Two key issues regarding the design of noninferiority trials deserve mention[29]: the choice of the active control and the selection of the noninferiority boundary. It could be argued that the evidence supporting the use of NIV as the active control is relatively limited, given the results of the 2 meta-analyses.[7,8] Nevertheless, a clinical practice guideline focused on this topic[30] suggested that NIV may be used in patients at high risk of reintubation in expert centers and states that grade 2B evidence supports this recommendation. In addition, recently are being published new studies supporting NIV over conventional oxygen therapy in high-risk patients.[31]

When selecting the noninferiority boundary, both statistical reasoning and clinical judgment are used. First, it is usually recommended that the limit for the size of the effect should be less than the lower limit of the 95% CI of the previously observed effect of the active control (NIV) vs placebo (conventional oxygen therapy in this case).[32] It is extremely difficult to estimate the difference in risk from other studies because the failure rates of both NIV[9-12,33] and conventional oxygen[9-13,34] reported vary widely (8%-32% and 8%-25%, respectively). No published data about the reintubation rate in patients who are at high risk of reintubation treated with high-flow conditioned oxygen therapy were available at the start of the present study, although the rates reported in recent studies range from 4% to 17%.[1,33,34] Thus, we decided to use the mean reintubation rate of NIV failing patients in the 5 trials[9,10,12,13,33] and the reintubation rate of high-flow conditioned oxygen therapy failing patients from the study reporting the worst results.[34] Second, from a clinical point of view, our noninferiority boundary is concordant with previous noninferiority trials testing the effect of high-flow conditioned oxygen therapy compared with NIV,[17,33] with boundaries up to 20%. These margins to clinically accept noninferiority, in our opinion are closely related with the evidence supporting the use and clinical acceptance of the active control for the indication tested in the trial.[35] In the case of this study, as mentioned earlier, there is no strong evidence for that indication, as reflected by the slow increase in the clinical use of NIV for these patients in the recent years.

Another limitation of this study is that attending teams could not be blinded to the study group; however, to reduce this unavoidable bias, investigators were excluded from clinical decisions, but it is not possible to totally exclude this bias.

Conclusions

Among high-risk adults who have undergone extubation, high-flow conditioned oxygen therapy was not inferior to NIV for preventing reintubation and postextubation respiratory failure. High-flow conditioned oxygen therapy may offer advantages for these patients.

ARTICLE INFORMATION

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Author Contributions: Dr Hernandez had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Hernandez, Cuena, Fernández.
Acquisition, analysis, or interpretation of data: Hernandez, Vaquero, Colinas, Cuena, González, Canabal, Sanchez, Rodriguez, Villasclaras.
Drafting of the manuscript: Hernandez, Vaquero, Colinas, Cuena, Canabal, Sanchez, Rodriguez.
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Administrative, technical, or material support: Hernandez, Vaquero, Canabal, Villasclaras, Fernández.
Study supervision: Hernandez, Colinas, González, Canabal, Sanchez, Rodriguez, Villasclaras, Fernández.

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