Noninvasive ventilation versus conventional oxygen therapy after extubation failure in high-risk patients in an intensive care unit: a pragmatic clinical trial

INTRODUCTION

The failure of extubation after mechanical ventilation (MV) has a deleterious effect, since it increases the duration of ventilation, the risk of ventilator-associated pneumonia (VAP), stay in the intensive care unit (ICU), and mortality.\(^1\-^6\)

ABSTRACT

Objective: To determine the effectiveness of noninvasive ventilation versus conventional oxygen therapy in patients with acute respiratory failure after extubation failure.

Methods: A pragmatic clinical trial was conducted in an intensive care unit from March 2009 to September 2016. Patients on mechanical ventilation > 24 hours who developed acute respiratory failure after scheduled extubation were included and were assigned to noninvasive ventilation or conventional oxygen therapy. The primary objective was to reduce the reintubation rate. The secondary objectives were to improve respiratory parameters and reduce complications, the duration of mechanical ventilation, the intensive care unit stay, the hospital stay, and mortality in the intensive care unit, in the hospital, and 90 days after discharge. Factors correlated with reintubation were also analyzed.

Results: Of a total of 2,574 patients, 77 were analyzed (38 in the noninvasive ventilation group and 39 in the conventional oxygen therapy group). Noninvasive ventilation reduced the respiratory and cardiac rates more rapidly than conventional oxygen therapy. Reintubation was less common in the noninvasive ventilation group (12 (32%) versus 22 (56%) in the conventional oxygen therapy group, relative risk 0.58 (95%CI 0.34 - 0.97), p = 0.039). The rest of the parameters did not show significant differences. In the multivariate analysis, noninvasive ventilation protected against reintubation (OR 0.17 (95%CI 0.05 - 0.56), p = 0.004), while liver failure before extubation and the inability to maintain airway patency predisposed patients to reintubation.

Conclusion: The use of noninvasive ventilation in patients who failed extubation could be beneficial compared to conventional oxygen therapy.

Keywords: Noninvasive ventilation; Oxygen inhalation therapy; Extubation; Weaning; Respiration, artificial; Respiratory insufficiency

Clinical Trials register: NCT 03832387.

Conflicts of interest: None.

The present study has been presented at the XLIII Congreso de la Sociedad Española de Medicina Intensiva in Granada, June 2018.

Submitted on July 12, 2020
Accepted on November 22, 2020

Corresponding author:
Alberto Belenguer Muncharaz
Unidad de Cuidados Intensivos Hospital Universitario Dr. Peset
Av. Gaspar Aguilar, 90
E-460017 - Valencia, Spain
E-mail: belengueralberto8@gmail.com

Responsible editor: Alexandre Biasi Cavalcanti
DOI: 10.5935/0103-507X.20210059

This is an open access article under the CC BY license https://creativecommons.org/licenses/by/4.0/
Noninvasive ventilation (NIV) in patients with acute respiratory failure (ARF) improves breathing and gas exchange and therefore reduces the need for intubation, shortens the hospital stay, and lowers mortality.\(^{(7-9)}\) The use of NIV in weaning after MV is indicated for support in patients at risk of extubation failure.\(^{(7-10)}\) In contrast, NIV has not shown a benefit after extubation failure; therefore, there is currently no recommendation for its use in this situation.\(^{(9-12)}\)

Based on the benefits provided by NIV and despite the negative results of previous studies,\(^{(11,12)}\) the purpose of this study was to test the benefit of NIV over conventional oxygen therapy in patients who failed extubation. Our primary objective was to reduce the intubation rate. The secondary objectives were clinical improvement and reductions in complications, MV duration, ICU stay, hospital stay, and mortality in the ICU, in the hospital, and at 90 days. Factors correlated with reintubation were also analyzed.

**METHODS**

A pragmatic clinical trial was conducted in a medical-surgical ICU between March 2009 and September 2016. The study was approved by the Clinical Research Ethics Committee of the Hospital de La Plana. Informed consent was requested from the patients or their relatives. Patients ≥ 18 years of age with medical-surgical pathology who, after a first episode of MV > 24 hours, presented ARF within 48 hours after a scheduled extubation were included. Patients who presented structural neurological disease, toxic-metabolic coma with Glasgow coma scale value < 14 during weaning or neuromuscular disease, chronic obstructive pulmonary disease (COPD), chronic respiratory disease subsidiary to receiving NIV\(^{(10,13-16)}\) limitation of life support therapy, tracheotomy, spinal injury, scheduled surgery as subsidiary to receiving NIV,\(^{(10,13-16)}\) limitation of life support therapy, tracheotomy, spinal injury, scheduled surgery were excluded by the physician’s decision were not included. Lastly, patients who required urgent intubation within 48 hours after extubation or reconnection was made by the responsible physician. Patients with ARF during the 48 hours following extubation were evaluated for inclusion in the study by the attending physician. Extubation failure was considered when the following was observed: use of accessory muscles, paradoxical breathing, respiratory rate (RR) > 25 bpm or an increase greater than 50% over baseline for 2 hours, together with gasometric deterioration [partial pressure of oxygen - PaO\(_2\) < 65 mmHg or partial pressure of carbon dioxide (PaCO\(_2\)) > 45 mmHg (pH < 7.33)].\(^{(19)}\) Extubation failure was classified as\(^{(20)}\) a) airway pathology: postextubation stridor, excess secretions; b) pathology without airway involvement: pulmonary edema, hypoxemic and/or hypercapnic ARF, or encephalopathy. Patients who required urgent intubation within 48 hours after extubation were not included in the study. Lastly, patients excluded by the physician’s decision were not included.

After being deemed eligible for inclusion, each patient was assigned to a group, the study group (NIV) or the control group (conventional oxygen therapy), by opening a sealed envelope given them by the attending physician. Extubation failure was considered when the following was observed: use of accessory muscles, paradoxical breathing, respiratory rate (RR) > 25 bpm or an increase greater than 50% over baseline for 2 hours, together with gasometric deterioration [partial pressure of oxygen - PaO\(_2\) < 65 mmHg or partial pressure of carbon dioxide (PaCO\(_2\)) > 45 mmHg (pH < 7.33)].\(^{(19)}\) Extubation failure was classified as\(^{(20)}\) a) airway pathology: postextubation stridor, excess secretions; b) pathology without airway involvement: pulmonary edema, hypoxemic and/or hypercapnic ARF, or encephalopathy. Patients who required urgent intubation within 48 hours after extubation were not included in the study. Lastly, patients excluded by the physician’s decision were not included.

After being deemed eligible for inclusion, each patient was assigned to a group, the study group (NIV) or the control group (conventional oxygen therapy), by opening a sealed envelope given them by the attending physician. The simple randomization was carried out before the study began by a physician not belonging to the study, using a computerized system.

**Noninvasive ventilation**

The BiPAP® Vision (Respironics Inc., Murrysville, PA, USA) was used with oronasal and facial masks (Total face® and PerforMax®, respectively) (Respironics Inc., Murrysville, PA, USA), along with an active humidification system (MR850, Fischer & Payckel, Auckland, New Zealand). In addition, continuous positive airway pressure (CPAP) from a Boussignac
valve (Vygon®, Ecouen, France) was delivered through an oronasal mask. Procedure: (8) Once the patient was informed about the procedure, the type of mask was selected according to their anatomy, and the harness was placed. In the case of NIV, ventilation was initiated with progressive levels of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) until a minimum IPAP of 10 - 15cmH₂O and an EPAP of 5 - 6cmH₂O were reached in the first hour of support. In CPAP, the minimum initial PEEP level was 5cmH₂O, with progressive increases up to 10 - 15cmH₂O. The objective of pressures of both devices was to reduce dyspnea, the use of accessory muscles, paradoxical breathing, and RR. The FiO₂ from both devices was adjusted to obtain a oxygen saturation pulse oximeter (SaO₂) of 94 - 96%. After adaptation of the mask, it was adjusted to the face of the patient using adjustable straps.

**Conventional oxygen therapy**

The control group received oxygen therapy through a Venturi mask (FiO₂ of 0.5) or a non-rebreather mask connected to a high-flow flowmeter set to 30L/min O₂ (estimated FiO₂ of 1.0).

Both NIV/CPAP and oxygen therapy were maintained continuously until the patient experienced clinical and/or gasometric improvement. In the NIV/CPAP patients, pressure levels were progressively reduced until complete disconnection, at which time they were switched to a Venturi mask (FiO₂ 0.3 - 0.4). No need to reinstate such support due to clinical worsening in the following 48 hours after withdrawal of it was considered successful. Failure and indications of intubation followed established criteria in both groups. (9) The modifications of FiO₂ and levels of IPAP/EPAP or PEEP, as well as the time of orotracheal intubation, were performed according to the criteria set by the responsible physician. Patients received aspiration of secretions, postural changes, incentive spirometry, and bronchodilators at the discretion of the physician.

After inclusion in the study, demographic data, the cause of MV, (21) severity measured using the Simplified Acute Physiological Score (SAPS) 3, organ failure scale using the Sequential Organ Failure Assessment (SOFA) (22) (both at ICU admission), and comorbidities were recorded. Before extubation, the worst value of organ failure by SOFA was recorded, as was the type and duration of each sedative, analgesic, and neuromuscular blocking agents used. The duration from MV to first extubation, from the start of weaning to extubation, and from the last T-test, as well as the time from extubation to failure, were calculated.

Hemodynamic variables (mean arterial pressure - MAP, HR), respiratory (RR, SaO₂), and blood gas levels were collected at the time of extubation failure. Likewise, RR and HR were collected during the 1st, 2nd, and 8th hours after randomization to analyze the clinical improvement as estimated by the reductions in both parameters. After extubation failure, the following variables were collected: need for reintubation, tracheotomy, infections (pneumonia or tracheobronchitis associated with MV, urinary tract infection, bacteremia), (23) organ failure after allocation using the SOFA scale, (22) need for dialysis, need for surgery, and need for NIV or reintubation (both after the study period). The duration of the first MV period (until withdrawal of any of the devices under study), the duration of NIV or conventional oxygen therapy [time from allocation to withdrawal of ventilatory support (in the NIV group) and transition to Venturi mask, or a reduction in FiO₂ ≤ 0.4 (in the conventional oxygen therapy group)] was calculated, as were the overall duration of MV (considered complete withdrawal of any ventilation device or stoppage of high-concentration oxygen therapy), the ICU stay, and the hospital stay. Mortality in the ICU, in the hospital, and at 90 days was collected.

**Statistical analysis**

Based on previous results, (11,24) we thought that the need for intubation could be reduced by 32% (69% in the conventional oxygen therapy group versus 37% in the NIV group). The estimated sample needed was 35 subjects in each group, with a 95% confidence interval - 95%CI (1-α) and a power of 80%. The statistical tests used for quantitative variables were Student’s t-test or the Mann-Whitney U test, according to the normality of each variable. For qualitative variables, the chi-squared test was used with Fisher’s exact test. Differences were considered significant if p < 0.05. The relative risk (95%CI) of the variables under study and Cox regression for mortality at 90 days (together with the Kaplan-Meier cumulative survival) were calculated. The analysis was performed by intention-to-treat. With the aim of analyzing the influence of both groups on RR and HR, a multivariate analysis (with Bonferroni correction) of repeated samples was performed. A multivariate binary logistic regression analysis of the predictors of reintubation was performed, and the influence of NIV to avoid reintubation was analyzed. The inability to maintain airway patency was included, (25) as were those variables that were significant (p ≤ 0.05) before extubation failure (smoking, hepatic, renal, hemodynamic or hematological failure) plus the use of NIV or oxygen therapy. The data were analyzed in the statistical package SPSS 20.0.
RESULTS

During the study period, a total of 2,574 patients (Figure 1) were analyzed, of whom 663 were extubated on a scheduled basis. In 140 (21%) patients, extubation failed, and 77 were finally assigned. Sixty-three patients were not randomized for various reasons (39 by facultative decision and 15 by urgent intubation). After the trial, there were eight protocol breaks and four incorrect randomizations because they met one or more exclusion criteria, all of which were included in the final analysis (38 in NIV and 39 in conventional oxygen therapy).

Excluded = 1,860
MV < 24 hours = 674
Neurological disease = 605
Exitus = 386
COPD and chronic lung disease = 99
Readmission = 27
Tracheostomy = 24
Neuromuscular disease = 21
Spine injury = 13
Scheduled surgery < 48 hours = 9
Transfer to other center = 2

Excluded = 51
Tracheostomized = 28
Self-extubation = 13
Direct extubation without T-tube trial = 6
Use of NIV after planned extubation = 4

Unassigned patients = 63
Physician decision = 39
Urgent intubation = 15
Agitation = 4
LLST = 3
Urgent surgery = 2

Figure 1 - Flow diagram.
MV - mechanical ventilation; COPD - chronic obstructive pulmonary disease; LLST - limitation of life support therapy; NIV - noninvasive ventilation. * Incorrect inclusion: chronic obstructive pulmonary disease (two patients in the noninvasive ventilation group, one in the conventional oxygen therapy group), neuromuscular (one patient in the noninvasive ventilation group).
As shown in table 1, the majority of the sample was men, with an average age of > 60 years, who received MV mainly for ARF. As a sedative, a combination of propofol and midazolam was most often used. The median duration of MV was 13 - 14 days, and that of weaning was 4 days. Most patients were extubated after passing their first T-tube trial. The baseline characteristics at inclusion did not show significant differences, except for a higher percentage of smoking in the control group (44% versus 18% in the NIV group, p = 0.026). The main cause of extubation failure was ARF unrelated to airway management (74% in NIV versus 59% in control). There were no differences in the causes of extubation failure or in the clinical-gasometric variables at the time of failure or at the time of randomization (Table 2).

Table 1 - Demographic characteristics, comorbidities, and clinical parameters during the period of weaning from mechanical ventilation

|                          | NIV (n = 38) | Conventional oxygen therapy (n = 39) |
|--------------------------|-------------|------------------------------------|
| **Sex**                  |             |                                    |
| Male                     | 19 (50)     | 22 (56)                            |
| Age, years               | 66 (58 - 76)| 62 (49 - 73)                       |
| **BMI (kg/m²)**          | 29 ± 7      | 27 ± 6                             |
| **SOFA at ICU admission**| 2 (1 - 2)   | 2 (1 - 2)                          |
| **SAPS 3 at ICU admission**| 56 (51 - 67)| 58 (55 - 67)                       |
| **Comorbidities**        |             |                                    |
| Hypertension             | 21 (55)     | 17 (47)                            |
| Diabetes mellitus        | 13 (34)     | 10 (26)                            |
| Chronic renal failure    | 7 (18)      | 3 (8)                              |
| Chronic heart failure    | 4 (10)      | 3 (8)                              |
| Obstructive sleep apnea  | 2 (5)       | 1 (3)                              |
| Smoking                  | 7 (18)      | 17 (44)                            |
| Alcohol                  | 4 (10)      | 8 (20)                             |
| **Cause of mechanical ventilation** |         |                                    |
| ARF*                     | 25 (66)     | 24 (61)                            |
| Postoperative            | 12 (32)     | 12 (31)                            |
| Coma                     | 1 (2)       | 1 (8)                              |
| **Sedatives during mechanical ventilation (n = 54)** | | |
| None                     | 1/27 (4)    | 1/27 (4)                           |
| Propofol                 | 8/27 (30)   | 8/27 (30)                          |
| Midazolam                | 5/27 (18)   | 5/27 (18)                          |
| Propofol and midazolam   | 13/27 (48)  | 13/27 (48)                         |
| Morphine                 | 25/27 (93)  | 26/27 (96)                         |
| Cisatracurium            | 2/27 (7)    | 2/26 (8)                           |
| Propofol (days)          | 4 (2 - 5)   | 5 (3 - 7)                          |
| Midazolam (days)         | 8 (4 - 14)  | 9 (5 - 13)                         |
| **Parameters for weaning from mechanical ventilation** | | |
| Time from onset of MV to extubation (days) | 13 (4 - 19) | 14 (10 - 24) |
| Start time weaning to extubation (days) | 4 (2 - 7)   | 4 (2 - 10)                         |
| **Number of aspirations before the last T-tube trial (n = 68)** | | |
| None                     | 1/32 (3)    | 3/36 (8)                           |
| 1 aspiration             | 17/32 (53)  | 17/36 (47)                         |
| 2 aspirations            | 9/32 (28)   | 7/36 (19)                          |
| ≥ 3 aspirations          | 5/32 (15)   | 9/36 (25)                          |
| Strength to cough (n = 68) | 19/33 (58) | 25/35 (71)                        |
| Duration of last T-tube trial (hours) | 2 (1 - 3) | 2 (2 - 4) |
| Exubation in the first T-tube trial | 27 (71) | 21 (54) |

NIV - noninvasive ventilation; BMI - body mass index; SOFA - Sequential Organ Failure Assessment; ICU - intensive care unit; SAPS - Simplified Acute Physiology Score; ARF - acute respiratory failure; MV - mechanical ventilation. * Causes of acute respiratory failure in the noninvasive ventilation group (n = 25): pneumonia (n = 6), sepsis (n = 4), cardiopulmonary arrest (n = 5), acute postoperative respiratory failure (n = 2), acute edema of cardiogenic lung (n = 4), trauma (n = 2), bronchoaspiration (n = 2). Causes of acute respiratory failure in the conventional oxygen therapy group (n = 24): pneumonia (n = 6), sepsis (n = 3), cardiopulmonary arrest (n = 4), acute postoperative respiratory failure (n = 3), acute edema of cardiogenic lung (n = 2), trauma (n = 2), acute respiratory distress syndrome (n = 2), bronchoaspiration (n = 2). Results expressed as n (%), median and interquartile range (25-75) or mean ± standard deviation.
In the study group, NIV was used in 36 patients, and CPAP was used in two patients. The pressures used in NIV and CPAP in the first hour were IPAP 16 ± 5cmH₂O, EPAP 6 ± 2cmH₂O, and PEEP = 5cmH₂O. FiO₂ in the first hour did not show significant differences (0.54 ± 0.2 in the NIV group versus 0.56 ± 0.2 in the control group). In the first 8 hours of follow-up, significant reductions in RR (Figure 2) and HR (Figure 3) were observed in the NIV group versus the control group [(p = 0.003) and (p = 0.016), respectively].

Regarding the primary objective (Table 3), a lower percentage of reintubation was observed in the NIV group [12 (32%) versus 22 (56%) in the conventional oxygen therapy group, relative risk 0.58 (95%CI 0.34-0.97), p = 0.039]. In both groups, 50% of patients were reintubated for problems related to the airways (mainly due to poor management of secretions). The duration of support after extubation failure was greater in the NIV group [36 (20 - 79) hours versus 14 (3 - 39) hours in conventional oxygen therapy, p = 0.003]. Among the rest of the variables analyzed, a higher rate of complications, a longer duration of MV, and longer ICU and hospital stays were observed in the control group, without reaching significance. There were no significant differences in mortality at ICU discharge, at hospital discharge, or at 90 days (Table 3 and Figure 4). Nine (75%) of the 12 intubated patients in the NIV group developed multiorgan failure, causing their death (100%). The duration of ventilation within the NIV failure group was similar between survivors and nonsurvivors (Figure 5).

The analysis of the factors related to reintubation showed that the inability to maintain airway patency as a cause of extubation failure and the presence of hepatic failure (measured by SOFA) before extubation were determinants for reintubation. In contrast, the use of NIV prevented reintubation [odds ratio 0.17 (95%CI 0.05 - 0.56), p = 0.004] (Table 4).

### Table 2 - Cause of extubation failure and the hemodynamic and respiratory parameters at the time of randomization

|                          | NIV (n = 38) | Conventional oxygen therapy (n = 39) |
|--------------------------|--------------|-------------------------------------|
| **Time from extubation to postextubation ARF (hours)** | 7 (2 - 18) | 5 (1 - 28) |
| **Cause of extubation failure** |              |                                    |
| ARF not related to airway* | 28 (74)     | 23 (59) |
| Inability to maintain airway patency† | 10 (26)     | 16 (41) |
| **Clinical parameters at the time of ARF** |              |                                    |
| Respiratory rate > 25bpm  | 30 (79)      | 30 (77) |
| RR increase > 50% with respect to baseline | 23 (60)      | 22 (56) |
| PaO₂ < 65 mmHg            | 19 (50)      | 18 (46) |
| PaCO₂ > 45 mmHg           | 14 (37)      | 15 (38) |
| pH < 7.33                 | 18 (48)      | 18 (46) |
| PaO₂/FiO₂ < 250           | 23 (60)      | 26 (67) |
| Work of breathing         | 32 (84)      | 30 (77) |
| Mean arterial pressure (mmHg) | 94 ± 18     | 97 ± 18 |
| Heart rate (bpm)          | 107 ± 21     | 101 ± 25 |
| Respiratory rate (bpm)    | 32 ± 9       | 33 ± 10 |
| pH (mmHg)                 | 7.36 ± 0.11  | 7.38 ± 0.10 |
| PaCO₂ (mmHg)              | 48 ± 25      | 53 ± 63 |
| PaO₂/FiO₂                 | 187 ± 86     | 149 ± 59 |
| Lactate (mM/L)            | 1 ± 1        | 1 ± 2 |

NIV - noninvasive ventilation; ARF - acute respiratory failure; RR - respiratory rate; PaO₂ - arterial oxygen pressure; PaCO₂ - partial pressure of carbon dioxide; FiO₂ - fraction of inspired oxygen. * Causes of acute respiratory failure not related to the airways: NIV group: acute respiratory failure (n = 22), acute cardiogenic lung edema (n = 5), encephalopathy (n = 1); conventional oxygen therapy group: acute respiratory failure (n = 20), acute cardiogenic lung edema (n = 3); † causes of acute respiratory failure related to the airways: noninvasive ventilation group: poor management of secretions (n = 8), laryngomalacia (n = 2); conventional oxygen therapy group: poor management of secretions (n = 12), laryngomalacia (n = 4). Results expressed as median and interquartile range (25 - 75), n (%) or mean ± standard deviation.
Table 3 - Analysis of primary and secondary objectives achieved after extubation failure

| Objective                                      | NIV (n = 38) | Conventional oxygen therapy (n = 39) | p value | Relative risk (95%CI) |
|------------------------------------------------|--------------|-------------------------------------|---------|-----------------------|
| Reintubation                                   | 12 (32)      | 22 (56)                             | 0.039*  | 0.58 (0.34 - 0.97)    |
| Tracheectomy                                   | 7 (18)       | 10 (26)                             | 0.564*  | 0.79 (0.42 - 1.47)    |
| Tracheobronchitis or VAP†                      | 4 (10)       | 8 (20)                              | 0.347*  | 0.63 (0.27 - 1.46)    |
| Urinary tract infection‡                       | 7 (18)       | 10 (26)                             | 0.584*  | 0.79 (0.42 - 1.47)    |
| Bacteremia§                                    | 7 (18)       | 3 (8)                               | 0.309*  | 1.49 (0.92 - 2.40)    |
| Hemodynamic failure                           | 11 (29)      | 11 (28)                             | 1.000*  | 1.00 (0.62 - 1.67)    |
| Acute renal failure                           | 13 (34)      | 11 (28)                             | 0.628*  | 1.14 (0.72 - 1.82)    |
| Hepatic failure                               | 6 (16)       | 1 (3)                               | 0.056*  | 1.87 (1.26 - 2.78)    |
| Renal replacement therapy                     | 4 (10)       | 4 (10)                              | 1.000*  | 1.01 (0.48 - 2.11)    |
| Reintubation after 48 hours                    | 3 (8)        | 4 (10)                              | 1.000*  | 0.85 (0.35 - 2.08)    |
| NIV after 48 hours                            | 2 (5)        | 2 (5)                               | 1.000*  | 1.01 (0.37 - 2.77)    |
| Surgery after extubation                      | 1 (3)        | 3 (8)                               | 0.615*  | 0.49 (0.08 - 2.73)    |
| Duration of NIV or conventional oxygen therapy (hours) | 36 (20 - 79)  | 14 (3 - 39)                        | 0.003   |                      |
| Duration of first episode of MV (days)         | 12 (5 - 20)  | 14 (9 - 24)                        | 0.165   |                      |
| Overall duration of MV (days)                  | 14 (7 - 22)  | 14 (7 - 29)                        | 0.303   |                      |
| ICU stay (days)                                | 17 (10 - 30) | 27 (14 - 36)                       | 0.219   |                      |
| Hospital stay (days)                          | 39 (23 - 57) | 45 (31 - 58)                       | 0.347   |                      |
| Multorgan failure during evolution             | 9 (24)       | 7 (18)                              | 0.579*  | 1.18 (0.71 - 1.96)    |

Causes of multorgan failure

- Septic shock
- Decompensation of liver cirrhosis
- Hemorrhagic shock
- Refractory heart failure
- Maintained MOD#

| MOD# Causes | NIV (n = 38) | Conventional oxygen therapy (n = 39) | p value | Relative risk (95%CI) |
|-------------|--------------|-------------------------------------|---------|-----------------------|
| Septic shock | 2            | 3                                   |         |                       |
| Decompensation of liver cirrhosis             | 1            | 1                                   |         |                       |
| Hemorrhagic shock                             | 0            | 1                                   |         |                       |
| Refractory heart failure                      | 2            | 0                                   |         |                       |
| Maintained MOD#                                | 4            | 2                                   |         |                       |

Mortality in ICU | 9 (24) | 6 (15) | 0.404 | 1.28 (0.78 - 2.09)
Mortality 90-d** | 16 (42) | 9 (23) | 0.068 | 2.14 (0.94 - 4.85)
Hospital mortality | 16 (42) | 9 (23) | 0.092 | 1.51 (0.98 - 2.33)

NIV - noninvasive ventilation; 95%CI - 95% confidence interval; VAP - ventilator-associated pneumonia; MV - mechanical ventilation; ICU - intensive care unit; MOD - multorgan dysfunction. * Fisher’s exact test; † causes of tracheobronchitis or ventilator-associated pneumonia: noninvasive ventilation group: Pseudomonas aeruginosa (n = 3), methicillin-sensitive Staphylococcus aureus (n = 1); conventional oxygen therapy group: P. aeruginosa (n = 4), Escherichia coli (n = 2), Klebsiella pneumoniae (n = 1), methicillin-sensitive S. aureus (n = 1). ‡ causes of urinary tract infection: noninvasive ventilation group: Candida albicans (n = 2), Pseudomonas aeruginosa (n = 1), Candida tropicalis (n = 1); conventional oxygen therapy group: E. coli (n = 2), E. coli (n = 1), C. albicans (n = 2), Klebsiella ESBL, E. coli ESBL, and Staphylococcus hommic. § causes of bacteremia: noninvasive ventilation group: Staphylococcus epidermidis (n = 4), P. aeruginosa (n = 2), K. pneumoniae (n = 1); conventional oxygen therapy group: Staphylococcus epidermidis (n = 2), E. coli (n = 1). || causes of septic shock: noninvasive ventilation (n = 2), mesenteric ischemia (n = 1) and intestinal perforation (n = 1); conventional oxygen therapy (n = 3), mesenteric ischemia (n = 1), unknown cause (n = 2); # evolution of prolonged multorgan dysfunction during ICU stay. ** mortality at 90 days measured by Cox regression. Results expressed as n (%) or median and interquartile range.
Noninvasive ventilation versus conventional oxygen therapy after extubation failure

Figure 4 - Kaplan-Meier survival analysis comparing noninvasive ventilation versus conventional oxygen therapy at 90 days. NIV - noninvasive ventilation. Log rank test (p = 0.068). The table shows the number of subjects who survived during the study period.

|           | 10d | 20d | 30d | 60d | 90d |
|-----------|-----|-----|-----|-----|-----|
| NIV (n = 38) | 37  | 33  | 28  | 23  | 22  |
| Conventional oxygen therapy (n=39) | 39  | 37  | 36  | 31  | 30  |

Table 4 - Analysis of factors related to the need for reintubation after extubation failure

|                                | Number of OTI patients / number of patients (%) | Univariate analysis RR (95%CI) | p value | Multivariate analysis RR (95%CI) | p value |
|--------------------------------|-----------------------------------------------|-------------------------------|---------|----------------------------------|---------|
| NIV versus conventional oxygen therapy (n = 77) |                                              |                               |         |                                  |         |
| NIV                                           | 12/38 (32)                                   | 0.56 (0.32 - 0.96)           | 0.03    | 0.17 (0.05 - 0.56)               | 0.004   |
| Conventional oxygen therapy                 | 22/39 (56)                                   |                               |         |                                  |         |
| Smoking (n = 77)                             |                                              |                               |         |                                  |         |
| Yes                                           | 13/24 (54)                                   | 1.36 (0.83 - 2.24)           | 0.32    |                                  |         |
| No                                            | 21/53 (40)                                   |                               |         |                                  |         |
| Liver failure before extubation (n = 74)      |                                              |                               |         |                                  |         |
| Yes                                           | 8/9 (89)                                     | 2.22 (1.52 - 3.23)           | 0.01    | 16.31 (1.50 - 176.67)            | 0.005   |
| No                                            | 26/65 (40)                                   |                               |         |                                  |         |
| Renal failure before extubation (n = 74)      |                                              |                               |         |                                  |         |
| Yes                                           | 21/35 (60)                                   | 1.80 (1.07 - 3.02)           | 0.03    | 2.94 (0.85 - 10.11)              | 0.087   |
| No                                            | 13/39 (33)                                   |                               |         |                                  |         |
| Hemodynamic failure before extubation (n = 73)|                                              |                               |         |                                  |         |
| Yes                                           | 25/48 (52)                                   | 1.44 (0.80 - 2.60)           | 0.22    |                                  |         |
| No                                            | 9/25 (36)                                    |                               |         |                                  |         |
| Hematological failure before extubation (n = 73)|                                              |                               |         |                                  |         |
| Yes                                           | 12/17 (71)                                   | 1.79 (1.14 - 2.81)           | 0.02    | 1.38 (0.34 - 5.50)              | 0.648   |
| No                                            | 22/56 (39)                                   |                               |         |                                  |         |
| Failure of extubation due to inability to maintain airway patency (n = 77) | | | | | |
| Yes                                           | 15/24 (62)                                   | 1.74 (1.08 - 2.80)           | 0.04    | 5.14 (1.44 - 18.36)             | 0.012   |
| No                                            | 19/53 (36)                                   |                               |         |                                  |         |

OTI - orotracheal intubation; RR - relative risk; 95%CI - 95% confidence interval; NIV - noninvasive ventilation.
DISCUSSION

Noninvasive ventilation reduced the rate of reintubation after extubation failure, as well as in the rest of the target variables. In the multivariate analysis, NIV protected against reintubation. Until now, all studies had questioned its usefulness.\(^{10-12}\) Therefore, the results obtained in another study on daily clinical practice are relevant: Many of its participants had a high risk of extubation failure (> 65 years, overweight, previous cardiac pathology, prolonged MV (> 7 days) due to pneumonia, sepsis or cardiorespiratory arrest, and many secretions).\(^{26}\)

After the removal of the positive pressure generated by the MV, changes in the airway or in the cardiorespiratory system (including muscle function) that can lead to extubation failure often occur.\(^{26}\) As in our study, the most frequent causes of extubation failure are respiratory failure (65%) and the inability to protect the airway (10-20%).\(^{6}\) In respiratory failure (due to diaphragmatic weakness, fluid overload, or heart failure), the application of positive pressure (IPAP and EPAP) can be beneficial. Inspiratory positive airway pressure can provide support to the respiratory muscles (mainly the diaphragm), reducing energy expenditure, and EPAP/PEEP can act at two levels: 1) by increasing functional residual capacity, tidal volume, and oxygenation; and 2) by conditioning a reduction in preload in both ventricles and in the afterload of the left ventricle.\(^{26-28}\) We observed an important physiological response to NIV: a reduction in RR and HR with respect to those in the control group. Likewise, a small observational study showed improved respiratory parameters (RR, tidal volume) and blood gas, as well as a decrease in oxygen consumption and energy expenditure, after extubation failure when they used NIV and CPAP compared to oxygen therapy.\(^{29}\) In contrast, in the subgroup of patients who could not maintain airway patency, NIV was not effective, given the high rate of intubation observed (75%) and because it is a predictor of reintubation. We believe that the ability to maintain airway patency should be routinely assessed (cuff-leak test\(^{26,30}\) and secretion score\(^{26,31}\) together with respiratory trials\(^{32}\) to evaluate the need for NIV and respiratory physiotherapy after extubation. The benefit of NIV in patients with little ability to maintain airway patency (estimated by a peak cough flow < 70L/min) was reflected in an observational study, where it reduced the intubation rate compared to the control treatment (9% versus 35%) at 72 hours after extubation, p < 0.01.\(^{33}\) These results would support the use of NIV together with the aforementioned measures.

The NIV failure rate in observational studies ranges from 13% to 38%;\(^{24,25,29,34}\) in contrast, the failure rate has been higher in clinical trials, between 48% and 72%.\(^{11,12}\) The main characteristics of our study, which could explain the different results, are the following: First, we did not include COPD patients, given the benefit of NIV to them.\(^{10,13,15,16}\) Second, in the study by Esteban et al.,\(^{12}\) NIV rescue was investigated in patients in the control group (n = 28), where an NIV failure rate of 25% was observed, in line with the results of observational studies.\(^{24,25,29,34}\) Third, the levels of IPAP/EPAP in the study by Keenan et al.,\(^{11}\) were lower (IPAP 10 ± 2cmH\(_2\)O, EPAP 5 ± 1cmH\(_2\)O) than those used here (IPAP 16 ± 5cmH\(_2\)O, EPAP 6 ± 2cmH\(_2\)O). In various studies, the main cause of reintubation is the persistence of dyspnea as a sign of muscle fatigue.\(^{4,12}\) Therefore, it would be necessary to provide an adequate pressure level (> 15cmH\(_2\)O pressure support) that can reduce muscle fatigue and dyspnea in order to avoid reintubation.\(^{28,29}\) The levels of IPAP used in our study are in line with those recommended,\(^{27,28}\) which could have influenced the results obtained.

Surprisingly, despite the reduction in the intubation rate in the NIV group, a nonsignificant reduction was observed in the rest of the objectives analyzed. The shorter duration of conventional oxygen therapy stands out, probably due to the failure to control the signs of respiratory fatigue, as shown in figures 2 and 3, which led to earlier intubation. The longer duration of support in NIV, the presence of complications after the study period, and the small sample size may have made the improvements in the NIV group not as evident.

Figure 5 - Comparison of the duration of noninvasive ventilation between survivors and nonsurvivors who required orotracheal intubation.

NIV - noninvasive ventilation. p = 0.315.
Like various studies, this study observed an increase in mortality related to NIV failure, which was striking at 90 days and at hospital discharge. Perhaps more than the failure of NIV as a mortality factor, it could be the high number of patients who developed multiorgan failure due to complications associated with their underlying pathology (a fact also observed in the oxygen therapy group) that led to death. This theory would be supported by the long time elapsed from randomization to death of most of the nonsurvivors (20 - 30 days). We believe that these factors were related to mortality in the ICU, where the differences in mortality were centered on three patients (24% versus 15%); on the other hand, mortality in the hospital would not be influenced by the device used. Along these lines, an editorial that analyzed the results of a clinical trial showed that NIV success [relative risk 1.66 (95%CI 0.51 - 5.37)] or NIV failure did not influence mortality [relative risk 1.77 (95%CI 0.95 - 3.30)]. Likewise, an observational study found no increase in mortality associated with failure after the use of NIV (29% versus 27% without NIV, p = 0.77). Another factor that has been correlated with mortality is the prolongation of ventilation in those patients who have failed NIV. In contrast, we did not verify this relationship, nor did two other observational studies in hypoxemic patients, observed similar numbers of complications at the time of intubation and similar mortality rates.

Regarding the predictive factors of reintubation, we found that the inability to maintain airway patency and a previous decompensated liver disease were determinants of reintubation. As we pointed out at the beginning of the Discussion, the role of NIV in the inability to maintain airway patency has yet to be determined; therefore, we should expect the failure of NIV in patency-failure patients. In contrast, NIV proved beneficial over oxygen therapy as a means to prevent reintubation, which would answer the question that drove this study.

The role of high-flow nasal oxygen therapy (HFNOT) has been relevant in recent years. Although its use as support in weaning has been studied, its efficacy in subjects who fail extubation has not yet been proven. A recent clinical trial supports the use of NIV together with HFNOT versus HFNOT alone to avoid extubation failure in patients at risk. At the time of this study, HFNOT was not available in our center.

The main weaknesses of this study are the long period of patient enrollment due to its being a single-center study with strict exclusion criteria, the low failure rate probably due to the prolongation of MV, and, finally, the use of NIV right after extubation failure in candidates who were not included in the study at the discretion of the attending physician. This last subset of patients would have had a faster inclusion, which would have shortened the timeframe of the study. On the other hand, the high rate of respiratory failure not related to the airways in the NIV group could have influenced the findings of the superiority of NIV over oxygen therapy. Protocol breaks (six in the oxygen therapy group) could also have influenced the results in favor of NIV, and could the low use of CPAP.

**CONCLUSION**

Noninvasive ventilation in patients who fail extubation could be beneficial compared to conventional oxygen therapy.
ventilación no invasiva [12 (32%) versus 22 (56%) en grupo oxigenoterapia convencional, RR 0,58 (IC95% 0,34 - 0,97), p = 0,039], el resto de los parámetros no mostró diferencias significativas. En el análisis multivariante, la ventilación no invasiva prevenía la reintubación [OR 0,17 (IC95% 0,05 - 0,56), p = 0,004], mientras que el fracaso hepático previo a la extubación y la incapacidad para mantener vía aérea permeable predisponían a la reintubación.

Conclusión: El empleo de la ventilación no invasiva en pacientes que fracasa la extubación podría ser beneficiosa frente a la oxigenoterapia convencional.

Descriptores: Ventilación no invasiva; Terapia por inhalación de oxígeno; Extubación traqueal; Destete; Respiración artificial; Insuficiencia respiratoria

Registro Clinical Trials: NCT 03832387.

REFERENCES

1. Esteban A, Alia I, Gordo F, Fernández R, Solosna JF, Valverdú I, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med. 1997;156(2 Pt 1):459-65.

2. Valverdú I, Calaf N, Subirana M, Net A, Benito S, Mancebo J. Clinical characteristics, respiratory functional parameters, and outcome of a two-hout T-piece trial in patients weaning from mechanical ventilation. Am J Respir Crit Care Med. 1998;158(6):1855-62.

3. Pefiuelas O, Frutos-Vivar F, Fernández C, Anzueto A, Epstein SK, Apezteguia C, González M, Nin N, Raymondos K, Tomicic V, Desmery P, Arabi Y, Pelosi P, Kuper M, Jibaja M, Matamis D, Ferguson ND, Esteban A; Ventila Group. Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. Am J Respir Crit Care Med. 2011;184(4):430-7.

4. Frutos-Vivar F, Esteban A, Apezteguia C, González M, Arabi Y, Restrepo MI, et al. Outcome of reintubated patients after scheduled extubation. J Crit Care. 2011;26(5):502-8.

5. Menon N, Joffe AM, Deem S, Yanez ND, Grabinsky A, Dagal AH, et al. Occurrence and complications of tracheal reintubation in critically ill adults. Respir Care. 2012;57(10):1555-63.

6. Thille AW, Boissy F, Ben Ghezala H, Razai K, Melkonto-Dessap A, Brun-Buisson Ch. Risk factors for and prediction by caregivers of extubation failure in ICU patients: a prospective study. Crit Care Med. 2015;43(3):613-20.

7. Organized jointly by the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Société de Réanimation de Langue Francaise, and approved by ATS Members Of The Steering Committee, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof S Members Of The Task Force. Official ERS/ATS clinical practice guidelines: noninvasive positive pressure ventilation in acute respiratory failure. Eur Respir J. 2002;57(1):192-211.

8. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navales P, Members Of The Steering Committee, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof S Members Of The Task Force. Official ERS/ATS clinical practice guidelines: noninvasive ventilation in acute respiratory failure. Eur Respir J. 2017;50(2):1345-55.

9. British Thoracic Society Standards of Care Committee. Non-invasive ventilation in acute respiratory failure. Thorax. 2002;57(1):192-211.

10. Hoebeke P, Verbrugghe V, Testa A, Calvayrac D, Goffin K, Bistoni F, et al. Randomized, controlled trial. Ann Intern Med. 1999;131(5):374-82.

11. Esteban A, Frutos-Vivar F, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguia C, Nightingale P, Arroliga AC, Tobin MJ; Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA. 2002;287(3):345-55.

12. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ disfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-10.

13. Ganev JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16(3):128-40.

14. Nava S, Gregoretti C, Fantulla F, Squadroni E, Grassi M, Carlucci A, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005;33(11):2465-70.

15. Ferrer M, Valencia M, Nicolas JM, Bernard O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006;173(2):164-70.

16. Ferrer M, Sellarés J, Valencia M, Carrillo A, Gonzalez G, Badia JR, et al. Non-invasive ventilation after extubation in hypcapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet. 2009;374(9695):1082-8.

17. Esteban A, Frutos F, Tobin MJ, Alia I, Solosna FE, Valverdú I, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med. 1995;332(6):345-50.

18. Esteban A, Alia I, Tobin MJ, Gil A, Gordo F, Valverdú I, et al. Effects of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med. 1999;159(2):512-8.

19. Boles JM, Bion J, Connors A, Herring M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. Eur Respir J. 2007;29(5):1033-56.

20. Epstein SK, Ciubotaru RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. Am J Respir Crit Care Med. 1998;158(2):489-93.

21. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguia C, Nightingale P, Arroliga AC, Tobin MJ. Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA. 2002;287(3):345-55.

22. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-10.

23. Ganev JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16(3):128-40.

24. de Santos LS, Barcone C, Santar N, Romano G, Dell Corte A, Vicch M, et al. Noninvasive positive-pressure ventilation for extubation failure after cardiac surgery: pilot safety evaluation. J Thorac Cardiovasc Surg. 2009;137(2):342-6.

25. Liu Y, An Z, Chen J, Liu Y, Tang Y, Han Q, et al. Risk factors for noninvasive ventilation failure in patients with post-extubation acute respiratory failure after cardiac surgery. J Thorac Dis. 2018;10(6):3319-28.

26. Maggiore SM, Battilana M, Serano L, Petrini F, Deye N, Lellouche F, Taille S, Demoule A, Fraticelli A, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-10.

27. Ganev JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16(3):128-40.

28. L’Her E, Deye N, Lellouche F, Taille S, Demoule A, Fraticelli A, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-10.
29. Kilger E, Briegel J, Haller M, Frey L, Schelling G, Stoll C, et al. Effects of noninvasive positive pressure ventilatory support in non-COPD patients with acute respiratory insufficiency after early extubation. Intensive Care Med. 1999;25(12):1374-80.

30. Engoren M. Evaluation of the cuff-leak test in a cardiac surgery population. Chest. 1999;116(4):1029-31.

31. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med. 2000;161(5):1530-6.

32. Terzi N, Lofaso F, Masson R, Beuret P, Normand H, Dumanowski E, et al. Physiological predictors of respiratory and cough assistance needs after extubation. Ann Intensive Care. 2018;8(1):18.

33. Duan J, Han X, Huang S, Bai L. Noninvasive ventilation for avoidance of reintubation in patients with various cough strength. Crit Care. 2016;20(1):316.

34. Yamauchi LY, Figueiroa M, da Silveira LT, Travaglia TC, Bernardes S, Fu C. Noninvasive positive pressure ventilation after extubation: features and outcomes in clinical practice. Rev Bras Ter Intensiva. 2015;27(3):252-9.

35. Carrillo A, Gonzalez-Diaz G, Ferrer M, Martinez-Quintana ME, Lopez-Martinez A, Llamas N, et al. Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. Intensive Care Med. 2012;38(3):458-66.

36. Hess DR, Stelfox HT, Schmidt U. Noninvasive positive-pressure ventilation: a silver bullet for extubation failure? Respir Care. 2007;52(11):1454-6.

37. Mosier JM, Sakles JC, Whitmore SP, Hypes CD, Hallett DK, Hawbaker KE, et al. Failed noninvasive positive-pressure ventilation is associated with an increased risk of intubation-related complications. Ann Intensive Care. 2015;5:4.

38. Thille AW, Contou D, Fragnoli C, Córdoba-Izquierdo A, Boissier F, Brun-Buisson C. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. Crit Care. 2013;17(6):R269.

39. Xu Z, Li Y, Zhou J, Li X, Huang Y, Liu X, et al. High-flow nasal cannula in adults with acute respiratory failure and after extubation: a systematic review and meta-analysis. Respir Res. 2018;19(1):202.

40. Thille AW, Muller G, Gacouin A, Coudray R, Decavéle M, Sonneville R, Beloncle F, Girault C, Dangers L, Lauterette A, Cabasson S, Rouzé A, Vivier E, Le Meur A, Ricard JD, Razai K, Barberet G, Lebert C, Ehrmann S, Sabatier C, Bourenne J, Pradel G, Bailly P, Terzi N, Dellamonica J, Lacave G, Danin PE, Nanadoumgar H, Gibelin A, Zanre L, Deye N, Demoule A, Maamar A, Nay MA, Robert R, Ragot S, Frat JP; HIGH-WEAN Study Group and the REVA Research Network. Effect of postextubation high-flow nasal oxygen with noninvasive ventilation vs high-flow nasal oxygen alone on reintubation among patients at high risk of extubation failure: a randomized clinical trial. JAMA. 2019;322(15):1465-75.