Association of independent risk factors with post-extubation failure in patients undergoing mechanical ventilation weaning

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Abstract

Introduction: Even with an adequate mechanical ventilation weaning (MVW) protocol, the procedure fails in 15 to 30 % of cases. **Objective:** To assess the association between independent risk factors (IRFs) and post-extubation failure in patients undergoing MVW in an intensive care unit. **Method:** Longitudinal, prospective, analytical cohort study in patients on mechanical ventilation for more than 24 hours and who were extubated. Pre-extubation reports of hemoglobin, albumin, phosphorus, waist-hip ratio and SOFA score were obtained. Extubation failure was defined as resumption of mechanical ventilation within 48 hours or less. **Results:** 123 patients were extubated, out of whom 74 were males (60 %); average age was 50 ± 18 years. Extubation failure occurred in 37 (30 %). Hypoalbuminemia was associated as an independent risk factor in 29 (23.8 %, $RR = 1.43$, 95 % $CI = 1.11-1.85$) and hypophosphatemia was in 18 (14.6 %, $RR = 2.98$, 95 % $CI = 1.66-5.35$); two or more IRFs were observed in 22.7 % ($RR = 1.51$, 95 % $CI = 1.14-2.00$). **Conclusions:** Identifying independent risk factors prior to MVW can help reduce the risk of extubation failure and associated morbidity and mortality.

KEY WORDS: Weaning. Mechanical ventilation. Extubation failure. Independent risk factors.

Asociación de factores de riesgo independientes con fracaso posextubación en pacientes desconectados de la ventilación mecánica

Resumen

Introducción: Aun con adecuado protocolo de desconexión de la ventilación mecánica (DVM), el procedimiento falla en 15 a 30 % de los casos. **Objetivo:** Evaluar la asociación entre factores de riesgo independientes y fracaso posextubación en pacientes con DVM en una unidad de cuidados intensivos. **Método:** Estudio de cohorte, longitudinal, prospectivo, analítico, que incluyó pacientes sometidos a ventilación mecánica por más de 24 horas y que fueron extubados. Se obtuvieron reportes preextubación de hemoglobina, albúmina, fósforo, índice cintura-cadera y puntuación SOFA. Se definió como fracaso de extubación al reinicio de la ventilación mecánica en 48 horas o menos. **Resultados:** Se extubaron 123 pacientes, 74 hombres (60 %); la edad promedio fue de 50 ± 18 años. Ocurrió fracaso de extubación en 37 (30 %). Como factores de riesgo independientes se asoció hipoalbuminemia en 29 (23.8 %, $RR = 1.43$, $IC\ 95\ \% = 1.11-1.85$) e hipofosfatemia en 18 (14.6 %, $RR = 2.98$, $IC\ 95\ \% = 1.66-5.35$); se observaron dos o más factores de riesgo independientes en 22.7 % ($RR = 1.51$, $IC\ 95\ \% = 1.14-2.00$). **Conclusiones:** Identificar los factores de riesgo independientes antes de la DVM puede ayudar a reducir el fracaso de la extubación y la morbimortalidad asociada.

PALABRAS CLAVE: Desconexión. Ventilación mecánica. Fracaso de extubación. Factores de riesgo independientes.

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Introduction

Mechanical ventilation (MV) is used to provide ventilatory support to patients that, due to some pathology or intoxication by biological, chemical or physical agents, experience acute respiratory failure with severe alterations in gas exchange (dysoxia) and who do not manage to cover metabolic oxygen demands, with imminent danger of life loss.^{1,2}

Weaning from MV continues to be an important problem in intensive care units.^{3,4} Unnecessary delay in MV discontinuation increases complications, morbidity and mortality, and hospital costs.^{5,6} Even with an adequate MV disconnection protocol, extubation failure (EF) persists in 15 to 30 % of cases.^{7,8} European guidelines include an arterial oxygen partial pressure/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) value ≥ 150 mm Hg among the criteria to evaluate weaning from mechanical ventilation.^{9,10}

EF is defined as the need for ventilatory mechanical support during the first 48 hours post-extubation; extubation is considered successful if tolerated longer than this period.^{11,12}

EF-related risk factors have been investigated and reported in different studies;^{13,14} among them, obesity restricts rib cage mobility and modifies lung volumes during mechanical ventilation, thus increasing EF risk three times.¹⁵⁻¹⁷

In Mexico, a combined prevalence of overweight and obesity of 72.5 % was reported in 2016 in 20-year old and older adults.¹⁸

Intensive care unit patients present with anemia of different degrees; those with hemoglobin < 7.5 g/dL have been reported to have twice the risk of EF.¹⁹ Similarly, due to an increased metabolic response to trauma and intestinal protein loss, these patients develop hypoalbuminemia, which is associated three times more with prolonged mechanical ventilation.²⁰ Hypophosphatemia is a common electrolyte disorder in intensive care units and is associated with weakness of the diaphragm and intercostal muscles, which causes a decrease in spontaneous breathing tidal volume and doubles EF risk.^{21,22}

The present investigation was carried out with the purpose to find out if the association of anemia, hypoalbuminemia, hypophosphatemia and visceral obesity, which are considered independent risk factors, increases the risk of EF in intensive care unit patients in whom mechanical ventilation is withdrawn, an association that has been little investigated.

Method

A prospective, longitudinal cohort of patients admitted to the Intensive Care Unit of Mexican Institute of Social Security La Raza National Medical Center Specialty Hospital "Antonio Fraga Mouret" was studied between May 1, 2018 and May 1, 2019. The project was authorized by the local investigation committee, with registration number 2018-3501-047.

After the patients or legal representatives signed the informed consent letter, those on MV weaning protocol were included if they met the following inclusion criteria: age 16 to 75 years, on MV for more 24 hours and less than 20 days with the pressure support ventilation, continuous positive airway pressure and synchronized intermittent mechanical ventilation modalities; with waist-hip ratio measurement, and hemoglobin, albumin and phosphorus report prior to extubation; surgical and non-surgical patients; with sequential organ failure evaluation and Sequential Organ Failure Assessment (SOFA) score ≤ 9 .

Patient weaning from MV and extubation were indicated by the treating physician. Once the patient was extubated, pre-extubation arterial blood gas was recorded, as well as albumin, hemoglobin and phosphorus levels and patient evolution for the first 12, 24 and 48 hours. Extubation tolerance or not was assessed by the attending physician on duty, who decided if the patient should be re-intubated or not.

Successful extubation was recorded if the patient tolerated it for more than 48 hours and EF if the patient was reintubated in a ≤ 48 hour period. The cause of reintubation, tracheostomy performance, length of stay and the reason for discharge were recorded.

At the end, extubation outcome association with independent risk factors was analyzed. Figure 1 shows the research design.

Categorical variables frequencies and percentages were calculated and bivariate analysis was carried out with Pearson's chi-square test $p < 0.05$.

Quantitative variables with normal distribution mean, standard deviation and 95 % confidence intervals (CI) were determined; freely distributed variables median and interquartile ranges (IQR) were obtained. Finally, a multiple logistic regression analysis was performed and the beta exponential was calculated to find out EF risk.²³

Results

One hundred and twenty-three participants who were weaned from mechanical ventilation and who met

Figure 1. Research development algorithm. MV = mechanical ventilation, HECMN La Raza ICU (Unidad de Cuidados Intensivos del Hospital de Especialidades, Centro Médico Nacional La Raza) = La Raza National Medical Center Specialty Hospital Intensive Care Unit, PSV = pressure support ventilation, CPAP = continuous positive airway pressure, SIMV = synchronized intermittent mechanical ventilation.

the inclusion criteria were studied, out of which 64 were men (60 %) and 49 women (40 %), with a mean age of 55 ± 15.9 years and 44 ± 18.4 years, respectively. With regard to anthropometric characteristics, mean height was found to be 1.68 ± 0.077 cm and 1.56 ± 0.075 cm, mean weight was 80 ± 15.0 kg and 73 ± 14.7 kg, waist-hip ratio was 1.0 ± 0.21 and 0.87 ± 0.17 , respectively, for men and women. Visceral obesity was observed in 33 men (26.8 %) and 28 women (22.7 %).

Surgical causes for intensive care unit admission were recorded in 74 patients (60 %), including abdominal sepsis in 23 (19 %), thoracic surgery postoperative period in 14 (12 %), exploratory laparotomy in 13 (11 %) and nephrectomy postoperative period in five (4 %). Non-surgical causes were recorded in 49 patients (40 %), which included nosocomial pneumonia in 12 (10 %), acute coronary syndrome in 10 (9 %), acute respiratory distress syndrome in six (5 %) and community-acquired pneumonia in six (5 %).

Patients had a mean SOFA score of 6 ± 2 at intensive care unit admission; reasons for admission and demographic data are shown in table 1.

Biochemical and arterial blood gas parameters were recorded prior to extubation (Table 2).

In 78 patients (63.4 %), the time on MV was found to range from one to five days; in 33 (26.8 %), from 6 to 11 days; and in 12 (9.7 %), from 12 to 18 days. As for MV modalities prior to extubation, pressure support ventilation was recorded in 57 patients (46.3 %), with EF in 18 (14.6 %), RR = 1.09, 95 % CI = 0.64-1.87; continuous positive airway pressure was recorded in 55 (44.7%), with EF in 16 (13 %), RR = 0.95, CI 95 % = 0.55-1.65; and synchronized intermittent mechanical ventilation in 11 (8.9 %), with EF in three (2.4 %), RR = 0.89, 95 % CI = 0.32-2.45. During the MV weaning protocol, 113 patients (91 %) were switched to T-tube, out of which 34 (26.8 %) experienced EF (RR = 1.00, 95 % CI = 0.89-1.12). T-tube was not indicated in 10 patients, out of which three (2.4 %) developed EF (RR = 0.99, 95 % CI = 0.27-3.64). Risk factors of the study population that experienced EF are shown in table 3.

In the present investigation, 37 patients were extubated with a $\text{PaO}_2/\text{FiO}_2$ ratio < 200 (30 %), out of which 12 % experienced EF.

Even when an adequate protocol was implemented for weaning from MV, EF occurred in 37 patients

Table 1. Demographic characteristics of 123 patients weaned from mechanical ventilation and reasons for admission to the intensive care unit

Variable	Males (n = 74, 60 %)		Females (n = 49, 40 %)	
	n	%	n	%
Age				
> 60 years	43	35	25	20
< 60 years	31	25.2	24	19.5
Visceral obesity	33	26.8	28	22.8
Sedentary lifestyle	60	48.8	34	27.6
Smoking	48	39	11	8.9
Systemic arterial hypertension	37	30	18	14.6
Type 2 diabetes	25	20.3	14	11.4
Acute coronary syndrome	15	12.2	2	1.8
Chronic kidney failure	8	6.5	5	4.1
Immune disease	3	2.4	5	4.1
Chronic obstructive pulmonary disease	5	4.1	1	0.8
Surgical causes	44	36	30	25
Abdominal sepsis	13	10.6	10	8.1
Post-thoracic surgery	8	6.5	6	4.9
Exploratory laparotomy	7	5.7	6	4.9
Non-surgical causes	30	25	19	16
Nosocomial pneumonia	8	6.5	4	3.3
Acute coronary syndrome	9	7.3	1	0.8
ARDS	3	2.4	3	2.4

ARDS = acute respiratory distress syndrome.

(30 %), with no significant difference between genders (RR = 1.11, 95 % CI = 0.82-1.50, p = 0.485).

A logistic regression analysis of the independent risk factors considered in EF was carried out; the results are shown in table 4. Independent risk factors that were included were hypoalbuminemia, hypophosphatemia and association of two or more risk factors (p = 0.013):

$$y = -0.302 + (0.913) + (1.33) + (0.788)$$

The highest probability of EF was 37 %.

The main causes that justified reintubation in the study population within the first 12 to 48 hours post-extubation are shown in figure 2.

Of the patients who experienced EF, 17 (14 %) were discharged without MV, 11 (9 %) with MV, 10 with tracheostomy (8 %) and one with MV in the patient's best interest. Mortality in these patients was 8 %, with an hospital stay time of seven days (IQR = 4-12).

One hundred and fourteen patients (92 %) were discharged due to improvement of their condition.

Discussion

In the analyzed cohort, patients extubated using a MV weaning protocol showed no significant differences in baseline conditions. Hypoalbuminemia and hypophosphatemia were independent risk factors for EF, and the association of two or more independent risk factors increased the probability of EF by 37 %, both in surgical and non-surgical patients.

Hypoalbuminemia occurred with a high frequency and was identified as an independent risk factor for EF. Hypoalbuminemia is common in patients at intensive care units, is caused by different factors and is associated with longer hospital stay, higher EF risk and higher mortality. The results of this research strengthen those found in other studies regarding the association of hypoalbuminemia and higher EF risk.²⁰

Hypophosphatemia was found to be a common electrolyte disorder in patients admitted to intensive care units and turned out to be an independent risk factor for EF, which are similar findings to those reported in

Table 2. Biochemical and arterial blood gas characteristics of the population prior to extubation

Variable	Males	Females
Hemoglobin, 8 to 10 g/dL*	10.14 ± 2.06	10.14 ± 1.69
Albumin < 3 g/dL*	2.60 ± 0.71	2.75 ± 0.92
Phosphorus < 2.5 g/dL*	3.14 ± 1.39	2.91 ± 1.05
FiO ₂ (%)	42 ± 9.4	42 ± 9.2
PEEP (mm Hg)	4.5 ± 0.86	4.8 ± 0.76
pH	7.43 ± 0.06	7.43 ± 0.06
PaO ₂ (mm Hg)	96.8 ± 26.7	98.6 ± 34.7
PaCO ₂ (mm Hg)	33.9 ± 6.33	33.4 ± 9.64
HCO ₃ (mm Hg)	23.3 ± 5.15	22.5 ± 4.64
Respiratory index	1.12 ± 0.75	1.03 ± 0.69
Lactate (mg/dL)	1.82 ± 1.66	1.64 ± 0.62
PaO ₂ /FiO ₂ (mm Hg)	246 ± 75.5	239 ± 63.7
Time on MV (days)	4.5 ± 3.6	5.6 ± 4.4

*Independent risk factors.

FiO₂ = fraction of inspired oxygen, PEEP = positive end of expiration pressure, PaO₂ = arterial pressure of oxygen, PaCO₂ = arterial pressure of carbon dioxide, HCO₃ = bicarbonate, PaO₂/FiO₂ = arterial oxygen pressure to fraction of inspired oxygen ratio, MV = mechanical ventilation.

international literature, where hypophosphatemia is referred to be associated with longer time of stay in intensive care units and higher EF risk.^{21,22}

In our research, there was a strong risk for EF when more than two independent risk factors were associated, unlike other studies where these risk factors were separately analyzed.

Different analyses report that hemoglobin levels < 7 g/dL are associated with a high risk of post-extubation failure; in our research, no association was found between mean hemoglobin levels of 10.14 ± 2.06 g/dL and EF risk, which is consistent with the extubation criteria recommendation that hemoglobin levels should be ≥ 8 g/dL.^{19,20}

Visceral obesity in the present investigation was observed more frequently in men, although no association of gender with EF was identified. Several reviews refer an association between general obesity and EF; however, there are few studies reporting the association of visceral obesity and EF risk.^{16,17}

Comorbidities such as sedentary lifestyle, smoking, type 2 diabetes, systemic arterial hypertension, acute coronary syndrome and chronic kidney failure were more common in men, while immune comorbidities were more prevalent in women; on the other hand,

Causes of failure to wean from mechanical ventilation		
Cause	Frequency	Percentage
Poor management of secretions	20	17
Neurological impairment	9	8
Excessive use of breathing muscles work	4	4
Hypoxemia	3	2
Laryngospasm	1	1

Figure 2. Reintubation events and percentage grouped by causes.

surgical and non-surgical causes of admission were more common in men. No association was found between admission causes and EF risk.

Regarding the MV modality prior to extubation, no significant difference was found between pressure support ventilation, continuous positive airway pressure, synchronized intermittent mechanical ventilation and EF. There are few prospective cohort studies that address MV modality and its association with EF.^{3,4}

In our study, we observed higher EF frequency in patients with a PaO₂/FiO₂ ratio ≤ 200 mm Hg; therefore, we differ from the European guidelines recommendation^{9,10} and we suggest that patients with a PaO₂/FiO₂ ratio ≤ 200 mm Hg should not be extubated.

The main causes that justified reintubation in our study population were similar to those reported in the literature.^{4,6} The frequency of EF agreed with that described in some retrospective multicenter studies, where it was reported to range from 15 to 30 %.⁶⁻⁸ Once independent risk factors are identified, we consider they should be corrected prior to extubation in order to reduce the percentage of EF.

As reported in other studies, post-extubation failure was strongly associated with an increase in morbidity and mortality.^{13,14}

Table 3. Risk factors in intensive care unit patients who were weaned from mechanical ventilation

Variables	EF < 48 hours (n = 37)		Successful extubation (n = 86)		RR	95 % CI	p
	n	%	n	%			
Male gender	24	20	50	41	1.11	0.82-1.50	0.485
Age > 60 years	21	17	47	39	1.03	0.73-1.46	0.829
Surgical factors	20	17	54	44	1.28	0.75-2.19	0.366
Visceral obesity	21	17	40	66	1.22	0.85-1.75	0.297
Albumin < 3 g/dL*	29	24	47	39	1.43	1.11-1.85	0.013
Hb, 8 to 10 g/dL	18	15	42	34	1.00	0.46-2.17	0.98
Phosphorus < 2.5 mg/dL*	18	15	14	12	2.98	1.66-5.35	0.000
Two or more IRF*	28	23	43	35	1.51	1.14-2.00	0.008
Time on MV, 6-11 days*	15	12	13	10	1.85	1.10-3.13	0.024
PaO ₂ /FiO ₂ < 200*	15	12	22	18	1.74	1.00-3.01	0.051
Pressure support ventilation	18	15	39	32	1.09	0.64-1.87	0.113
CPAP	16	13	39	32	0.95	0.55-1.65	0.046
SIMV	3	2	8	6.5	0.89	0.32-2.45	0.045

*There is association.

EF = post-extubation failure, Hb = hemoglobin, MV = mechanical ventilation, PaO₂/FiO₂ = pre-extubation arterial oxygen pressure to fraction of inspired oxygen ratio, IRF = independent risk factors, PSV = pressure support ventilation, CPAP = continuous positive airway pressure, SIMV = synchronized intermittent mechanical ventilation, CI = confidence interval, RR = relative risk. p < 0.05.

Table 4. Independent risk factors in the logistic regression model for post-extubation failure in patients admitted to an intensive care unit

Variable	Beta	SE	OR	95% CI
Visceral obesity	0.048	0.444	1.049	0.85-1.75
Hemoglobin, 8 to 10 g/dL	-0.794	0.586	0.452	0.46-2.17
Albumin < 3 mg/dL*	0.913	0.556	2.492	1.11-1.85
Phosphorus < 2.5 mg/dL*	1.337	0.510	3.807	1.66-5.35
Two or more IRF*	0.788	0.723	2.200	1.14-2.00
Constant	-0.302	0.482	0.739	

*Risk factor.

IRF = independent risk factors, SE = standard error, OR = Beta exponential, CI = confidence interval.

The study limitations consisted of variability in the criteria of the extubation protocol, which resulted in a large number of subjects being extubated with PaO₂/FiO₂ > 150 mm Hg but < 200 mm Hg. As a consequence, EF risk was higher. Since the follow-up of study subjects ended at the conclusion of the 48 hours that followed extubation, it was not possible to know

if subsequently they had to be re-intubated at hospitalization area.

As strengths of our research, it should be mentioned that it contributes to the knowledge on the frequency of EF in our population and some independent risk factors that favor it, which will serve as a starting point for future studies aimed at reducing EF risk.

Conclusions

The presence of hypoalbuminemia or hypophosphatemia increases EF risk in intensive care unit patients who are extubated, and the risk is doubled when two or more independent risk factors are associated. Identification of these independent risk factors prior to extubation may have a potential clinical usefulness for making the decision in the extubation process and reducing the risk of reintubation.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures that were followed adhered to the ethical standards of the responsible human experimentation committee and to the World Medical Association and the Declaration of Helsinki guidelines.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Written informed consent was obtained from patients; this document is in possession of the authors.

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