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Associations of positive end-expiratory pressure (PEEP) with extubation failure and clinical outcomes in invasively ventilated patients with acute brain injury: A secondary analysis of the ENIO study

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A R T I C L E   I N F O

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A B S T R A C T

Background: Invasive mechanical ventilation (IMV) is crucial for managing acute brain injury (ABI) patients, yet the effects of positive end-expiratory pressure (PEEP) on outcomes are not well understood. This study aimed to evaluate the relationship between PEEP levels and risk of extubation failure as well as intensive care unit (ICU) mortality in ABI patients.
Methods: This post-hoc analysis of the ENIO study included 1512 ABI patients from the ENIO cohort, excluding those without available data on PEEP at day 1 and who never received an extubation trial. PEEP levels were recorded at days 1, 3, 7, and on the day of extubation. Logistic regression assessed the association between PEEP and extubation failure, while Cox proportional hazards regression analyzed ICU mortality.
Results: Among 1154 included patients, extubation failure occurred in 21.2 % and ICU mortality was 3.7 %. Higher median PEEP at days 1, 3, and 7 was independently associated with increased odds ratio (OR) of extubation failure (OR = 1.13; 95 %CI = 1.01–1.26; $p = 0.0294$). At the time of extubation, higher PEEP was also significantly associated with extubation failure (OR = 1.13; 95 %CI = 1.02–1.25; p = 0.0218) and ICU mortality (Hazard Ratio, HR = 1.38; 95 %CI = 1.12–1.69; p = 0.0026). However, at sensitivity analyses adjusted for acute respiratory distress syndrome (ARDS), PEEP was no longer significantly associated with outcomes, while ARDS itself was an independent predictor of extubation failure.
Conclusions: Extubating ABI patients at higher PEEP levels was associated with an increased risk of extubation failure and ICU mortality. However, this association likely reflects underlying respiratory pathology or disease severity. Our findings suggest that PEEP level may serve as a surrogate marker for extubation readiness, rather than a modifiable risk factor, and highlight the need for individualized assessment prior to extubation.

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1. Introduction

Patients with acute brain injury (ABI) may require invasive mechanical ventilation (IMV) to improve systemic and cerebral oxygenation and carefully control carbon dioxide levels [1]. However, these patients often require long periods of IMV due to depressed neurological status, which can impair airway patency, swallow ability, gag reflexes, and respiratory drive [2]. Conventional IMV for patients with ABI may conflict with lung protective ventilation strategies [3], potentially exacerbating pulmonary and systemic inflammation and increasing the risk of ventilator-induced lung injury (VILI) [4].

Among IMV parameters, positive end-expiratory pressure (PEEP) is considered one of the most critical variables for brain physiology. From a lung perspective, PEEP enhances oxygenation and promotes lung recruitment, while minimizing the harmful effects of the cyclical opening and closing of alveolar units [5]. However, PEEP can also reduce cardiac output and increase physiological dead space, leading to intracranial arterial vasodilatation and increased cerebral blood volume. Additionally, PEEP can raise intrathoracic and intra-abdominal pressure, which may impact intracranial pressure (ICP) and cerebral perfusion pressure (CPP) [6,7]. Historically, concerns regarding these pathophysiological effects led to the widespread use of zero PEEP strategy in ABI patients [8]. However, with a growing understanding of pulmonary and cerebral physiology, recent guidelines recommend PEEP levels like those used in the general ICU population [4,9]. Nonetheless, the PROLABI trial did not demonstrate any benefit in low vs higher PEEP in ABI patients [10], raising concerns about the safety of lung-protective strategies in this population. Given the unique physiological challenges of ABI patients, including altered cerebral perfusion and the risk of secondary brain injury, appropriate PEEP selection is essential [7].

This is a secondary analysis of the ENIO trial, aimed to describe the use of PEEP in ABI patients and assess its association with extubation failure and ICU mortality at multiple time points throughout their care. We hypothesized that in patients with ABI, higher PEEP during IMV is associated with an increased rate of extubation failure and higher ICU mortality compared to lower PEEP levels.

2. Methods

2.1. Study design and consent

This is a *post-hoc* analysis of the ENIO study (NCT03400904) [2], a prospective multi-center international observational cohort study, endorsed and promoted by the PROtective VEntilation Network, European Society of Intensive Care Medicine, Society of Critical Care Medicine, French Society of Anesthesiology and Critical Care (SFAR), and Colegio Mexicano de Medicina Critica. Groupe Nantais d'Éthique dans le Domaine de la Santé, IRB No. 7/11/2017, provided the initial permission. The local ethics committees at each participating center granted permission to conduct the ENIO study. In accordance with local laws and regulations, both written and verbal informed consent was given to participate in the ENIO study. The Medical Research Involving Human Subjects Act (WMO) and the Declaration of Helsinki's tenets guided the ENIO investigation [11]. Data management, monitoring, and reporting of the study were performed in accordance with the ICH-GCP Guidelines [12]. The ENIO study and this *post-hoc* analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [13], *Supplementary Material (SM) Item S1*.

2.2. Study endpoints and definitions

The primary endpoint was extubation failure, defined as the need for reintubation within 5 days after an extubation attempt. Secondary endpoints were ICU mortality and the description of PEEP trajectories and variability. Extubation failure was defined as the need for reintubation within 5 days after an extubation attempt, as defined in the ENIO study [2].

Visual pursuit is defined as the ability of the eyes to smoothly follow a moving object. ARDS was defined according to the Berlin definition [14].

At each time-points (Day 1, 3, 7, and the Day of Extubation), patients were dichotomized according to a PEEP level > 5 cmH_2O and ≤ 5 cmH_2O. Definition for low-PEEP ≤ 5 cmH_2O was previously adopted in patients without acute respiratory distress syndrome (ARDS) in the RELAx trial [15]. Considering that in the trial High-PEEP was defined as >8 cmH_2O, and that our median PEEP value at day 1,3,7 was 5.5 cmH_2O, we decided to binary classify patients using PEEP>5 cmH_2O and ≤ 5 cmH_2O [15].

2.3. Patients and data collection

The inclusion and exclusion criteria of the ENIO study have been previously published [2]. Eligible participants for the ENIO study were neurocritical care patients aged 18 or older, with a Glasgow Coma Score (GCS) of 12 or lower before intubation, requiring IMV for at least 24 h, and undergoing an extubation trial. Exclusion criteria included individuals under 18 or pregnant, those with spinal cord injuries above T4, resuscitated postcardiac arrest, certain neuromuscular conditions, or who died before extubation. Additionally, patients withdrawing life-sustaining treatment within 24 h, those with severe respiratory comorbidities or major chest trauma, and those with prior tracheostomy were also excluded. Patients who died without an attempt at ventilation liberation were not eligible. For this post-hoc study, we excluded patients without available data on PEEP at day 1 and those who were never extubated.

Demographic and baseline information [age, body mass index, (BMI), medical history] and origin injury data [traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), ischemic stroke (IS), central nervous system (CNS) infection, and brain tumor] were obtained from the ENIO dataset. Neuro-surgical management [decompressive craniectomy, ICP monitoring, external ventricular drainage (EVD), posterior fossa injury, use of therapeutic hypothermia, neurosurgery]; airway management data [tracheostomy placement, extubation success]; and severity of brain injury [GCS, episode of anisocoria, GCS motor score]; in-ICU events and outcomes [reintubation within 5 days from extubation, in-ICU and in-hospital mortality, length of stay in ICU, ventilator-associated pneumonia (VAP), ARDS].

Data on days 1, 3, and 7, and at extubation included: ventilatory setting and blood gas analysis [ventilator mode (pressure assist, pressure control, volume assist, pressure support), respiratory rate (breaths/min), PEEP (cmH_2O), tidal volume (mL and mL/kg of predicted body weight [PBW]), arterial partial pressure of oxygen (PaO_2, mmHg) to fraction of inspired oxygen (FiO_2), arterial pH (pHa), arterial partial pressure of carbon dioxide ($PaCO_2$, mmHg), Driving pressure (calculated as Pplat - PEEP, cmH_2O) [16]], sedation strategy [midazolam, propofol, dexmedetomidine, pentothal], and use of neuromuscular blockers. All data were collected around 8:00 AM.

2.4. Statistical analyses

Continuous variables are presented as mean $\pm$ standard deviation (SD) or medians and interquartile ranges [IQR], while categorical variables are expressed as numbers with percentages (%). Independent *t*-tests or Mann-Whitney *U* tests were conducted for continuous variables, and Chi-square tests were used for categorical variables, as appropriate. The assumptions of normality and homogeneity of variances were assessed prior to performing *t*-tests.

Logistic regression analyses were performed to assess the association between PEEP levels and the likelihood of extubation failure. The forced entry strategy for regression analysis was adopted, with predictors selected based on clinical plausibility and previous evidence. To examine the relationship between PEEP and extubation failure, a logistic regression model was developed using the median PEEP value across days 1, 3, and 7 for each patient. The median PEEP value was calculated, and this value was included as the primary predictor in the model. The following predictors were included in the model: age, gender, BMI, type of brain injury, GCS motor score at ICU admission, episode of anisocoria, and presence of visual pursuit. At extubation, the following predictors were included: GCS motor score the day of extubation, age, gender, PEEP before extubation, type of brain injury, ability to perform visual pursuit, ability to coughing (weak, moderate, vigorous), and cuff leak test. ARDS presence was also tested in a separate model as sensitivity analysis. PEEP was managed both as dichotomic and continuous variable. The overall model fit and the significance of individual coefficients were assessed, and variance inflation factors (VIF) were evaluated to detect multicollinearity among the independent variables. The logistic regression results were reported as odds ratios [OR] with 95 % confidence intervals [CIs], with predictor significance determined using the Wald test. For each model, we tested the inclusion of ICU site (center) as a random intercept using mixed-effects logistic regression to account for potential center-level variation in extubation practices. Model performance was compared using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

To assess the relationship between PEEP and ICU-mortality, a single Cox regression model was constructed using the median PEEP value across days 1, 3, and 7 for each patient. The following predictors were included based on clinical relevance: age, gender, GCS motor score, presence of visual pursuit, median PEEP across day 1,3,7, and episodes of anisocoria. The cumulative probability of survival was estimated using Kaplan-Meier survival curves. The log-rank test was applied to compare survival distributions between groups. Hazard ratios [HR] for each predictor were calculated, along with their corresponding 95 %CIs. The assumptions of proportional hazards were assessed using Schoenfeld residuals. Model fit was evaluated through concordance indices, and the null hypothesis estimate was reported. The significance of predictors within the Cox model was assessed using Z statistics, and *p*-values were derived from the Wald test. All statistical analyses were performed using JASP® software (version 0.19.3) and R® software, with a significance level set at $p < 0.05$ for all tests.

3. Results

3.1. General characteristics of the study cohort

Of the 1512 ENIO patients screened, 358 were excluded due to missing day-1 PEEP data and absence of extubation, leaving 1154 included: 485 (42 %) in the PEEP >5 cmH_2O group and 669 (58 %) in the PEEP ≤5 cmH_2O group at day 1. Median PEEP values [IQR] were 5 [IQR: 5–6] cmH_2O on day 1, 6 [IQR: 5–7] cmH_2O on day 3, 6 [IQR: 5–8] cmH_2O on day 7, and 5 [IQR: 5–6] cmH_2O at time of extubation (Fig. 1). Ventilatory settings and sedation practices at day 1 are shown in *SM Item S2*, while country-specific PEEP distributions are reported in *SM Item S3*.

Compared to the PEEP ≤5 cmH_2O group, patients in the PEEP >5 cmH_2O group had significantly higher BMI (27 [IQR: 23–29] vs. 25 [IQR: 22.5–28] kg/m^2, $p = 0.0016$), more ARDS during ICU stay (11.7 % vs. 6.8 %, $p = 0.0036$), less decompressive craniectomy (13.61 % vs. 17.96 %; $p = 0.0471$), and longer duration of invasive mechanical ventilation (median 8 [IQR: 4–15] days vs. 6 [IQR: 3–12] days; $p = 0.0158$), and ICU length of stay (median 14 [IQR: 7–25] days vs. 12 [IQR: 7–20] days; $p = 0.0018$). No significant differences were observed in the duration of non-invasive ventilation (median 2 [IQR: 1–4] days in both groups; $p = 0.8969$) or oxygen therapy (median 2 [IQR: 1–3] days in both groups; $p = 0.2065$). ICU mortality was 4.2 % in the higher PEEP group versus 3.3 % in the lower PEEP group ($p = 0.4441$), while in-hospital mortality was 8.1 % overall, with no differences between groups ($p = 0.9766$), see Table 1.

3.2. Association between PEEP and extubation failure

In the multivariable logistic regression model, higher median PEEP at days 1,3,7 (continuous variable) was significantly associated with increased odds of extubation failure (OR = 1.13, 95 %CI = 1.01–1.26, $p = 0.0294$). Age was an independent predictor of extubation failure, while the presence of TBI, visual pursuit, and higher GCS motor score were associated with decreased risk of extubation failure, see Table 2 *and SM Item S4*. When PEEP was modeled as a binary variable, PEEP>5 cmH_2O was no longer independently associated with an increased odds of extubation failure, see *SM Item S5*. In a posthoc analysis of main multivariable logistic regression model, we calculated the predicted probability of extubation failure across the full observed range of extubation PEEP while holding all other covariates at their mean or reference values and derived 95 %CI for each PEEP level, see Fig. 2. Including ICU site as a random intercept did not improve model fit for median PEEP at day 1,3,7, with degenerate estimates indicating negligible center-level variability, see *SM Item S6*.

At the time of extubation, median 7 days [IQR: 3–13.5], higher PEEP (continuous variable) was independently associated with an increased likelihood of extubation failure (OR = 1.13 95 %CI = 1.02–1.25, $p = 0.0218$), as well as the presence of weak cough (Table 3 *and SM Item S7)*. The presence of TBI and visual pursuit were associated with decreased risk of extubation failure. The results were confirmed when PEEP was modeled as a binary variable, with PEEP>5 cmH_2O remaining independently associated with an increased likelihood of extubation failure (*SM Item S8).* Adding ICU site as a random effect to the extubation PEEP model resulted in a singular fit, supporting the use of a fixed-effects model, see *SM Item S9.*

3.3. Sensitivity analysis in patients with ARDS

SM Item S10 shows the median PEEP values at days 1, 3, 7, and the day of extubation in patients with and without ARDS. PEEP levels were significantly higher in patients with ARDS than those without ARDS at all time points. PEEP values, stratified according to the severity of ARDS (mild, moderate, severe), are reported in *SM Item S11*. In the sensitivity multivariate logistic regression analysis including ARDS as a covariate, median PEEP at day 1,3,7 was no longer significantly associated with extubation failure; however, the presence of ARDS during ICU stay was independently associated with higher odds of extubation failure (OR = 2.51 95 %CI = 0.44–1.40, $p < 0.001$), *SM Item S12*.

After adjusting for the presence of ARDS, higher PEEP at extubation was no longer associated with extubation failure; however, the presence of ARDS during ICU stay was independently associated with higher odds of extubation failure (OR = 2.10 95 %CI = 0.23–1.25, $p = 0.0043$), *SM Item S13*.

3.4. Association between PEEP and ICU-mortality

Median PEEP at days 1, 3, 7 (continuous variable) was not associated with ICU-mortality. However, age and the inability to perform visual pursuit were associated with an increased hazard of ICU-mortality, see *SM Item S14*. When PEEP was modeled as binary variable, the non-association with ICU-death was consistent, *SM Item S15*. Kaplan—Meier curves for survival in the overall cohort and according to PEEP as binary variable are reported in Fig. 3.

Higher levels of PEEP the day of extubation (continuous variable) were independently associated with increased ICU-mortality risk (HR = 1.38 95 %CI = 1.12–1.69, $p = 0.0026$). Higher patient age was also associated with an increased risk of death, while a higher GCS motor

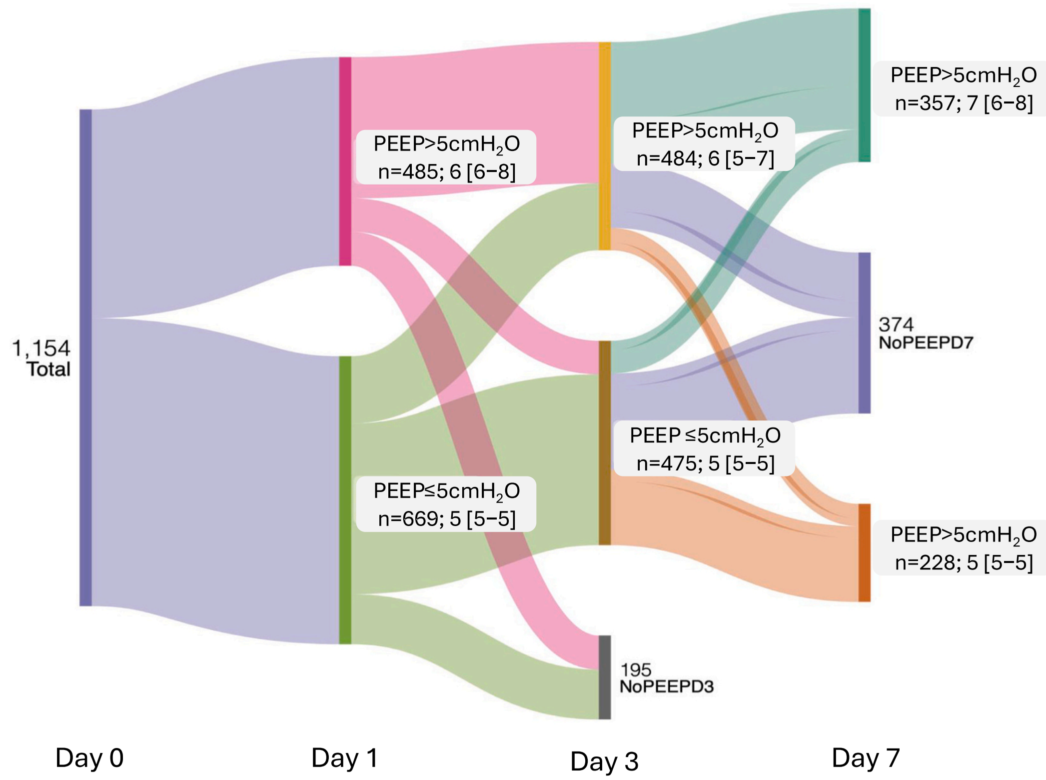

Fig. 1. Sankey plot (alluvial plot) for PEEP distribution over Days.
Number of patients with available PEEP data are reported over Days with respective median (25th—75th percentiles) PEEP values at each timepoint (Day 0 = Intensive Care Unit admission, 1, 3, 7). The figure was done with the online free software SankeyMATIC ®.

score at extubation, and the presence of visual pursuit were significantly associated with lower risk of death, see *SM Item S16*. When PEEP was modeled as binary variable, the association with ICU-death was lost, *SM Item S17*.

4. Discussion

The findings of this study can be summarized as follows: (a) PEEP levels in patients with ABI remained around 5–6 cmH_2O throughout their ICU stay, with minimal variability across countries; (b) higher PEEP levels at extubation (and specifically >5 cmH_2O) and median of PEEP at day 1,3,7 were independently associated with an increased likelihood of extubation failure and the presence of ARDS; (c) ICU mortality was associated with PEEP levels at extubation, but not median of PEEP at days 1,3,7; (d) the presence of ARDS during ICU stay was independently associated with increased risk of extubation failure, regardless of PEEP level.

The main strengths of this study are the robust methodology and extensive data collection as part of the ENIO study [2], an international multicenter cohort, with high-quality and comprehensive data collection, enhancing the reliability of findings. The inclusion of a large and diverse cohort of ABI patients improves the generalizability of results across various clinical settings. Furthermore, the use of advanced statistical modeling, including logistic regression and Cox proportional hazards models, allows for a more nuanced understanding of the relationship between PEEP, extubation failure, and mortality.

4.1. General characteristics of the study cohort

Our study aligns with the IMV trends of the last decade in ABI patients, suggesting a global effort to standardize IMV strategies in this population. As reported by Tejerina et al., in 2004, PEEP was kept <5 cmH_2O in 72 % and between 5 and 10 cmH_2O in 24 % of patients. By 2010, these proportions shifted to 58 % and 36 % of patients, respectively, and by 2016, to 56 % and 40 % of patients, respectively [4]. Our findings, reflecting IMV practices from 2017 to 2020, indicate a continued trend toward increasing PEEP levels over time, in agreement with lung-protective IMV strategies. However, recent data from the PROLABI trial (2024), challenge the assumption that higher PEEP levels are beneficial in ABI patients. This trial compared a lung-protective ventilatory strategy—characterized by lower tidal volumes and higher PEEP levels—to a conventional ventilatory approach. The lung-protective strategy was associated with increased mortality, a lower rate of IMV weaning, a higher incidence of ARDS, and poorer neurological outcomes [10]. In our study, higher PEEP levels likely reflect the management of respiratory complications such as ARDS, which was present in 9.2 % of patients. In line with current ARDS guidelines [3,9,17,18], patients with more severe lung injury at admission may require higher PEEP levels to improve oxygenation and lung recruitment. In accordance with previous findings, patients who received higher PEEP also had concomitantly lower tidal volumes and higher respiratory rates [19]. Our results highlight the need for a personalized approach when applying lung-protective IMV settings in ABI patients. While higher PEEP may benefit lung function, its potential physiological effects on cerebral hemodynamics must be carefully considered. These findings underscore the importance of individualized ventilatory strategies tailored to the patient's underlying pathology.

4.2. Association between PEEP and extubation failure

While PEEP is known to improve oxygenation by recruiting collapsed alveoli [5], our findings indicate that each 1 cmH_2O increase in PEEP on the day of extubation raises the odds of extubation failure by approximately 13 % (OR = 1.13 95 %CI = 1.02–1.25, $p = 0.0218$). Particularly, for PEEP >5 cmH_2O the risk of extubation failure is confirmed. Similarly, the WEAN-SAFE study found a 6 % increase in weaning failure

Table 1
Baseline characteristics, demographics, and ICU outcomes of the overall population and according to the PEEP value at ICU Day 1.

	Overall n = 1154	PEEP > 5 cmH_2O n = 485	PEEP ≤ 5 cmH_2O n = 669	P-value
Demographics				
Age, years, median [25th; 75th]	54 [36; 66]	54 [37; 65]	54 [35; 66]	0.6604
Gender, n (%)				0.6850
Male	780 (67.59)	331 (68.25)	449 (67.12)	
Female	374 (32.41)	154 (31.75)	220 (32.88)	
BMI, kg/m^2, median [25th; 75th]	25 [23; 29]	27 [23; 30]	25 [22.5; 28]	0.0016
Country, n (%)				
Argentina	41 (3.55)	4 (0.82)	37 (5.53)	<0.001
Bangladesh	2 (0.17)	0 (0.00)	2 (0.30)	
Belgium	18 (1.56)	0 (0.00)	18 (2.69)	
Canada	12 (1.04)	2 (0.41)	10 (1.49)	
France	607 (52.60)	257 (52.99)	350 (52.32)	
Greece	14 (1.21)	4 (0.82)	10 (1.49)	
India	19 (1.65)	6 (1.24)	13 (1.94)	
Italy	56 (4.85)	33 (6.80)	23 (3.44)	
Japan	19 (1.65)	11 (2.27)	8 (1.20)	
Libyan	8 (0.69)	5 (1.03)	3 (0.45)	
Mexico	145 (12.56)	68 (14.02)	77 (11.51)	
Netherlands	45 (3.90)	15 (3.09)	30 (4.48)	
Qatar	11 (0.95)	2 (0.41)	9 (1.34)	
Switzerland	63 (5.46)	31 (6.39)	32 (4.78)	
United Kingdom	44 (3.81)	15 (3.09)	29 (4.33)	
United States	5 (0.43)	0 (0.00)	5 (0.75)	
Uruguay	27 (2.34)	25 (5.15)	2 (0.30)	
Baseline comorbidities				
Pulmonary disease, n (%)	44 (3.82)	22 (4.55)	22 (3.29)	0.2716
Heart Failure, n (%)	36 (3.12)	16 (3.31)	20 (2.99)	0.7606
Hypertension, n (%)	340 (29.49)	145 (29.90)	195 (29.15)	0.7658
Active smoking, n (%)	252 (21.99)	106 (21.99)	146 (21.99)	0.9988
Diabetes mellitus, n (%)	133 (11.54)	63 (13.02)	70 (10.46)	0.1805
History of malignancy, n (%)	52 (4.51)	23 (4.75)	29 (4.33)	0.7362
Cause of ICU admission				
TBI, n (%)	569 (49.31)	230 (47.42)	339 (50.67)	0.2757
ICH, n (%)	375 (32.50)	152 (31.34)	223 (33.33)	0.4755
SAH, n (%)	204 (17.68)	90 (18.56)	114 (17.04)	0.5051
Ischemic Stroke, n (%)	102 (8.84)	44 (9.07)	58 (8.67)	0.8121
CNS infection, n (%)	50 (4.33)	24 (4.95)	26 (3.89)	0.3817
Brain Tumor, n (%)	61 (5.29)	30 (6.19)	31 (4.63)	0.2449
Other, n (%)	20 (1.73)	7 (1.44)	13 (1.95)	0.5186
Neurologic characteristics				
GCS total, mean (SD) median [25th; 75th]	6.99 (2.63) 7 [5; 9]	6.89 (2.62) 7 [5; 9]	7.05 (2.63) 7 [5; 9]	0.3089
Anisocoria, n (%)	299 (25.98)	127 (26.29)	172 (25.75)	0.8350
Intracranial probe, n (%)	523 (45.40)	219 (45.15)	304 (45.58)	0.8869
EVD, n (%)	337 (29.23)	137 (28.25)	200 (29.94)	0.5327
Posterior fossa injury, n (%)	66 (5.73)	25 (5.17)	41 (6.14)	0.4833
Therapeutic hypothermia, n (%)	47 (4.08)	23 (4.74)	24 (3.59)	0.3299
Barbiturate coma, n (%)	58 (5.03)	28 (5.77)	30 (4.49)	0.3254
Neurosurgery, n (%)	437 (37.90)	184 (37.94)	253 (37.87)	0.9824
Decompressive craniectomy, n (%)	186 (16.13)	66 (13.61)	120 (17.96)	0.0471
ICU outcome				
VAP, n (%)	434 (37.94)	196 (40.92)	238 (35.79)	0.0778
Tracheobronchitis, n (%)	107 (9.41)	51 (10.71)	56 (8.47)	0.2014
ARDS, n (%)	101 (8.84)	56 (11.72)	45 (6.77)	0.0036
Reintubation, n (%)	243 (21.24)	111 (23.13)	132 (19.88)	0.1853
Tracheostomy required, n (%)	93 (8.16)	45 (9.45)	48 (7.23)	0.1759
IMV duration, days, median [25th; 75th]	7 [3; 13.5]	8 [4; 15]	6 [3; 12]	0.0158
Non-IMV duration, days, median [25th; 75th]	2 [1; 4]	2 [1; 4]	2 [1; 5]	0.8969
Oxygen duration, days, median [25th; 75th]	2 [1; 3]	2 [1; 3]	2 [1; 3]	0.2065
ICU LOS, days, median [25th; 75th]	13 [7; 22]	14 [7; 25]	12 [7; 20]	0.0018
In-ICU mortality, n (%)	42 (3.70)	20 (4.20)	22 (3.33)	0.4441
In-hospital mortality, n (%)	91 (8.10)	38 (8.07)	53 (8.12)	0.9766

Data are reported as median (interquartile range, IQR) for standardization in reporting. P values are calculated using the t-tests or Mann-Whitney U tests, and the Chi-square test as appropriate. BMI = body mass index; TBI = traumatic brain injury; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage; CNS = central nervous system; GCS = Glasgow coma scale; EVD = external ventricular derivation; VAP = ventilator-associated pneumonia; ARDS = acute respiratory distress syndrome; IMV = invasive mechanical ventilation; ICU = intensive care unit; LOS = length of stay.

Table 2
Logistic regression: predictors of extubation failure (median PEEP day 1,3,7 as primary predictor).

Variable	OR (95 % CI)	p-value
Median PEEP day 1,3,7 (cmH_2O)	1.13 (1.01–1.26)	0.0294
Patient age (years)	1.01 (1.00–1.02)	0.0436
GCS motor score at ICU admission	0.96 (0.82–0.98)	0.0224
BMI (kg/m^2)	1.00 (0.96–1.03)	0.7866
Traumatic Brain Injury	0.54 (0.37–0.78)	0.0010
Intracranial Hemorrhage	1.34 (0.96–1.86)	0.0861
Visual pursuit	0.68 (0.47–0.98)	0.0395
Gender (female)	0.79 (0.56–1.11)	0.1757
Episode of anisocoria	1.00 (0.70–1.41)	0.9790
Aneurysmal hemorrhage	0.81 (0.52–1.25)	0.3324

Extubation failure coded as (1); OR = odds ratio; CI = confidence interval; BMI = body mass index; GCS = Glasgow Coma Scale.

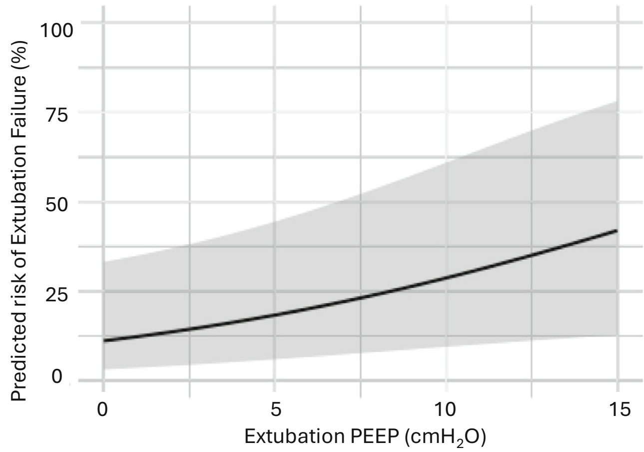

Fig. 2. Predicted probability of extubation failure across extubation PEEP levels with 95 % confidence intervals from multivariable logistic regression. Predicted probability of extubation failure across the observed range of extubation PEEP levels (cmH_2O), derived from the multivariable logistic regression model in a posthoc analysis. All other covariates were held at their mean (continuous variables) or reference (categorical variables) values. The solid curve represents the predicted risk of extubation failure, while the shaded area indicates the 95 % confidence interval. The y-axis represents the predicted probability expressed as a percentage.

Table 3
Logistic regression: predictors of extubation failure (PEEP at extubation as primary predictor).

Variable	OR (95 % CI)	p-value
PEEP at extubation (cmH_2O)	1.13 (1.02–1.25)	0.0218
Traumatic Brain Injury	0.47 (0.32–0.68)	0.0010
Intracranial Hemorrhage	1.26 (0.89–1.77)	0.1933
Cuff leak test	0.97 (0.69–1.37)	0.8724
Visual pursuit	0.65 (0.43–0.98)	0.0389
Cough none	3.24 (0.85–12.32)	0.0839
Cough weak	2.30 (0.62–8.50)	0.2107
Cough vigorous	1.38 (0.37–5.15)	0.6303
Patient age (years)	1.00 (0.99–1.01)	0.4928
GCS motor score at extubation	0.96 (0.79–1.18)	0.7075
Gender (female)	0.77 (0.54–1.10)	0.1538

Extubation failure coded as (1); OR = odds ratio; CI = confidence interval; GCS = Glasgow Coma Scale.

odds per 1 cmH_2O rise in PEEP (OR = 1.06, 95 % CI = 1.0–1.11, p = 0.036). After excluding 1079 patients with neurological conditions, the association remained consistent, with a 7 % increase in weaning failure odds per 1 cmH_2O increment in PEEP. These findings highlight the potential risks of higher PEEP levels at extubation, underscoring the importance of reassessing PEEP before discontinuing mechanical ventilation [20].

The impact of PEEP on extubation failure may be exacerbated in patients with hemodynamic instability, particularly if the increased work of breathing post-extubation is underestimated [21–24]. Our analysis revealed significant associations between median PEEP at days 1, 3, and 7 and extubation failure, suggesting that not only the level but also the duration of exposure to elevated PEEP—or the “dose” of PEEP over the recovery period—may be critical. This appears particularly relevant for ABI patients, who may have altered respiratory drive and impaired airway reflexes, making them more vulnerable to the prolonged effects of high PEEP [2,25].

Weaning from invasive mechanical ventilation in ABI patients typically considers the patient’s neurological status, ventilator settings, physiological parameters, and clinical judgment, often preceded by a spontaneous-breathing trial (SBT) [26]. Various SBT techniques exist, ranging from pressure-support ventilation to non-assisted methods [27,28]. A recent protocol reported that using a 10-15 cmH_2O of positive pressure during cuff deflation improves weaning success [29,30]. A meta-analysis comparing positive-pressure and suctioning techniques suggested that positive-pressure weaning was associated with a lower, albeit not statistically significant, risk of complications including desaturation, airway obstruction, pneumonia, aspiration, atelectasis, and reintubation [31]. Considering the worldwide variability in weaning practice, the ideal ventilator settings, including PEEP and pressure support levels during SBT and extubation, is a topic of continuous debate [20,26].

Brain injury presents significant challenges during the weaning and extubation phases [2]. In ABI patients, reintubation rates are approximately 21 % after extubation. Strong predictors of extubation success include TBI, vigorous cough, intact gag reflex, and a GCS motor score of 6. Although recent studies, including the ENIO study, explore the impact of different ventilatory strategies on weaning success in ABI patients, the role of PEEP remains uncertain [2]. PEEP significantly affects brain physiology and cerebral hemodynamics, particularly in patients with compromised cerebral autoregulation, increasing vulnerability to perfusion variations [7,32–35], contributing to cerebral hemodynamics and ICP [36,37].

Interestingly, preserved cognitive function, such as the ability to track objects visually, appears to be a protective factor against extubation failure, suggesting that better neurological status enhances weaning success [6,38–40]. Evidence supports using cognitive and motor assessments to determine extubation readiness, emphasizing the need for individualized weaning protocols based on neurological evaluations [2]. This highlights the importance of a multidisciplinary approach in managing ABI patients, involving intensivists, neurologists, neurosurgeons, and respiratory therapists.

In patients with ARDS, our data suggest that higher PEEP at the time of extubation is not independently associated with extubation failure. Instead, it is the presence of ARDS itself that confers a higher risk. This may reflect the fact that elevated PEEP is often necessary in ARDS to maintain adequate oxygenation and alveolar recruitment and does not independently worsen outcomes when used appropriately. Conversely, the pathophysiological severity of ARDS—rather than PEEP per se—may compromise respiratory mechanics, gas exchange, and the success of extubation [41,42].

4.3. Association between PEEP and ICU-Mortality

Median PEEP at day 1,3,7 was not associated with ICU mortality; however, higher PEEP levels at extubation were associated with an increased risk of ICU mortality. Specifically, each 1 cmH_2O increase in PEEP at extubation was associated with a 38 % rise in the hazard of ICU mortality. This was not confirmed for PEEP >5 cmH_2O when dichotomizing PEEP into two groups, suggesting a dose-response relationship may be more informative than binary thresholds. This finding underscores a limitation of categorical thresholds in ventilatory decision-making. A cutoff such as >5 cmH_2O may fail to capture the gradual and cumulative risk associated with increasing PEEP levels, especially at the time of extubation when patients may be more vulnerable to the hemodynamic and respiratory consequences of elevated intrathoracic pressure and ICP [6,9,33]. It also suggests that patients with only moderately elevated PEEP may still carry increased risk, which is masked when grouped with lower-risk individuals under a single binary definition. Rather than relying on arbitrary cutoffs, these results support a continuous and individualized interpretation of PEEP values, especially in the context of extubation readiness. PEEP at this stage may reflect unresolved lung injury or ongoing ARDS, which could independently contribute to poor outcomes. A nuanced approach that accounts for both the absolute level and trajectory of PEEP, rather than fixed thresholds, may improve risk stratification and guide safer weaning practices [43,44]. The demographics of the study population show a

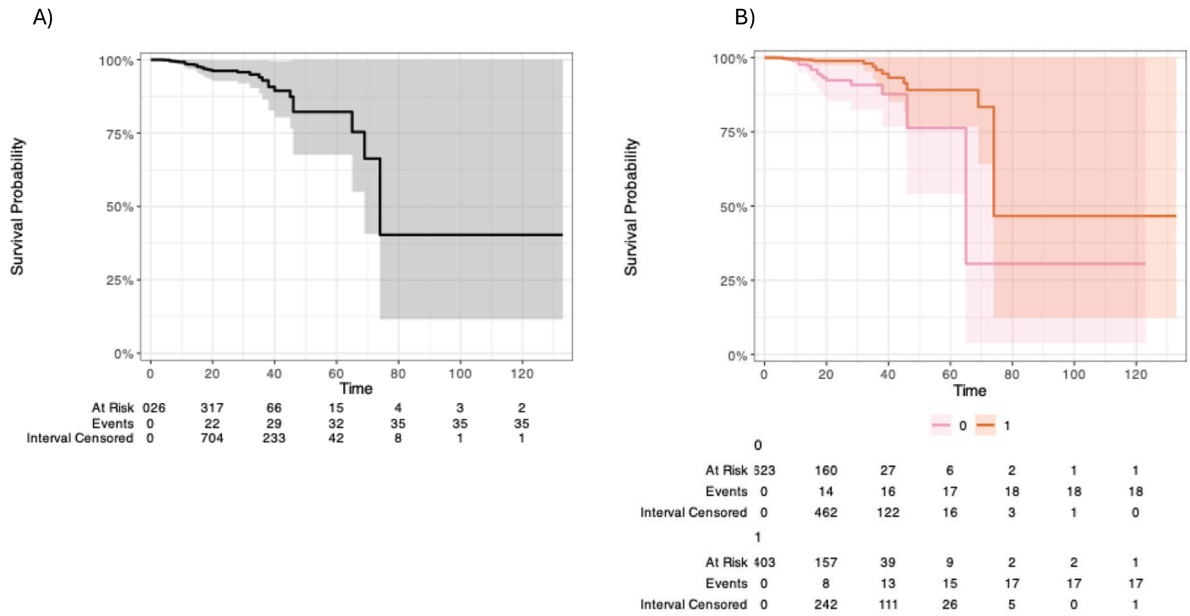

Fig. 3. ICU Survival Probability Over Time: Overall and Stratified by Extubation PEEP Levels.
A) Kaplan–Meier survival curve showing ICU survival probability over time. The curve incorporates interval-censored data and displays the number of events and patients at risk at each time point. Survival probability is shown on the y-axis, and time (in days) on the x-axis. B) Kaplan–Meier survival curves stratified by a binary variable (stratum PEEP$<$5 cmH_2O vs PEEP$\geq$5 cmH_2O), showing ICU survival probability over time. The plot displays interval-censored events and the number of patients at risk at successive time points for each stratum. Survival probability is plotted on the y-axis, and time (in days) on the x-axis. Shaded areas represent confidence intervals.

mean age of 52 years with a predominance of males. Increased age, lower GCS motor score at extubation, and the inability to perform visual pursuits were independently associated with increased ICU-mortality, emphasizing the need for comprehensive assessments beyond ventilatory settings [5,8,31].

4.4. Limitations

Despite its strengths, the study has limitations. The retrospective nature of the post-hoc analysis may introduce bias, as the original study design did not specifically intend to investigate the relationship between PEEP levels and extubation failure. Additionally, the variability in clinical practices across different centers may affect the consistency of PEEP application and monitoring. The observational design also limits the ability to draw causal inferences, and confounding variables, despite adjustments, may still influence the results. Moreover, due to the structure of the original ENIO dataset, we could not account for potential confounding conditions such as pneumonia, pulmonary embolism, or cardiac injury, which may have influenced extubation outcomes. A key analytical limitation is the use of binary categorization for PEEP levels (e.g., $>$5 cmH_2O vs. $\leq$5 cmH_2O), which may obscure clinically relevant dose-response effects. The absence of an association when PEEP is dichotomized, despite a significant effect when modeled as a continuous variable, highlights the potential loss of granularity and sensitivity inherent in threshold-based approaches. Moreover, while higher PEEP levels were associated with extubation failure, this relationship may reflect underlying disease severity—particularly the presence of ARDS—rather than a direct causal effect, highlighting the potential for residual confounding despite multivariable adjustment. Unfortunately, the cause of extubation failure was frequently missing in the ENIO dataset, precluding reliable subgroup analyses by airway vs non-airway failure. Finally, the absence of long-term outcome data post-ICU discharge may limit our understanding of the overall impact of PEEP on patient neurological recovery and quality of life.

5. Conclusions

Our results indicate that elevated PEEP levels at extubation are associated with a higher risk of extubation failure and ICU mortality; however, this association is not independent of ARDS. Instead, the presence of ARDS during ICU stay emerged as a key driver of extubation failure. These findings suggest that PEEP may act more as a surrogate marker of underlying disease severity rather than as a direct causal factor.

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Consent for publication

Not applicable.

Ethics approval and consent to participate

Groupe Nantais d'Éthique dans le Domaine de la Santé, IRB No. 7/11/2017, provided the initial permission. The local ethics committees at each participating center granted permission to conduct the ENIO study. In accordance with local laws and regulations, both written and verbal informed consent was given to participate in the ENIO study.

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Declaration of competing interest

The author Denise Battaglini (DB) declares lecturer for ESTOR, not related to this work. The author Chiara Robba (CR) declares consulting or advisory for DB, not related to this work. The other authors declare no competing financial interests or personal relationships. All authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2025.155274.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to privacy reasons but are available from the corresponding author on reasonable request.

References

[1] Hawryluk GWJ, Aguilera S, Buki A, Bulger E, Citerio G, Cooper DJ, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle international severe traumatic brain injury consensus conference (SIBICC). Intensive Care Med 2019;45:1783–94. https://doi.org/10.1007/s00134-019-05805-9.

[2] Cinotti R, Mijangos JC, Pelosi P, Haenggi M, Gurjar M, Schultz MJ, et al. Extubation in neurocritical care patients: the ENIO international prospective study. Intensive Care Med 2022. https://doi.org/10.1007/s00134-022-06825-8.

[3] Robba C, Camporota L, Citerio G. Acute respiratory distress syndrome complicating traumatic brain injury. Can opposite strategies converge? Intensive Care Med 2023;49:583–6. https://doi.org/10.1007/s00134-023-07043-6.

[4] Tejerina EE, Pelosi P, Robba C, Peñuelas O, Muriel A, Barrios D, et al. Evolution over time of Ventilatory management and outcome of patients with neurologic disease. Crit Care Med 2021;49:1095–106. https://doi.org/10.1097/ccm.0000000000004921.

[5] Battaglini D, Roca O, Ferrer R. Positive end-expiratory pressure optimization in ARDS: physiological evidence, bedside methods and clinical applications. Intensive Care Med 2024;50:762–5. https://doi.org/10.1007/s00134-024-07397-5.

[6] Giardina A, Cardim D, Ciliberti P, Battaglini D, Ball L, Kasprowicz M, et al. Effects of positive end-expiratory pressure on cerebral hemodynamics in acute brain injury patients. Front Physiol 2023:14. https://doi.org/10.3389/fphys.2023.1139658.
[7] Zunino G, Battaglini D, Godoy DA. Effects of positive end-expiratory pressure on intracranial pressure, cerebral perfusion pressure, and brain oxygenation in acute brain injury: Friend or foe? A scoping review. Journal of Intensive Medicine 2023. https://doi.org/10.1016/j.jointm.2023.08.001. Online ahead of print.
[8] Koutsoukou A, Perraki H, Raftopoulou A, Koulouris N, Sotiropoulou C, Kotanidou A, et al. Respiratory mechanics in brain-damaged patients. Intensive Care Med 2006;32:1947–54. https://doi.org/10.1007/s00134-006-0406-0.
[9] Robba C, Poole D, McNett M, Asehnoune K, Bösel J, Bruder N, et al. Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus. Intensive Care Med 2020;46: 2397–410. https://doi.org/10.1007/s00134-020-06283-0.
[10] Mascia L, Fanelli V, Mistretta A, Filippini M, Zanin M, Berardino M, et al. Lung-protective mechanical ventilation in patients with severe acute brain injury: a multicenter randomized clinical trial (PROLABI). Am J Respir Crit Care Med 2024; 210:1123–31. https://doi.org/10.1164/rccm.202402-0375OC.
[11] General assembly of the World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent 2014;81:14–8.
[12] Dixon JR. The international conference on harmonization good clinical practice guideline. Qual Assur 1999;6:65–74. https://doi.org/10.1080/105294199277860.
[13] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806–8. https://doi.org/10.1136/bmj.39335.541782.AD.
[14] Ranieri V, Rubenfeld G, Thompson B, Ferguson N, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307:2526–33. https://doi.org/10.1001/jama.2012.5669.
[15] Algera AG, Pisani L, Serpa Neto A, den Boer SS, Bosch FFH, Bruin K, et al. Effect of a lower vs higher positive end-expiratory pressure strategy on ventilator-free days in ICU patients without ARDS: a randomized clinical trial. JAMA - Journal of the American Medical Association 2020. https://doi.org/10.1001/jama.2020.23517.
[16] Wahlster S, Sharma M, Taran S, Town JA, Stevens RD, Cinotti R, et al. Associations between driving pressure and clinical outcomes in acute brain injury: a subanalysis of ENIO. Am J Respir Crit Care Med 2024;209:1400–4. https://doi.org/10.1164/rccm.202402-0402LE.
[17] Picetti E, Pelosi P, Taccone FS, Citerio G, Mancebo J, Robba C. VENTILatOry strategies in patients with severe traumatic brain injury: the VENTILO survey of the European Society of Intensive Care Medicine (ESICM). Crit Care 2020;24:158. https://doi.org/10.1186/s13054-020-02875-w.
[18] Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med 2023;49:727–59. https://doi.org/10.1007/s00134-023-07050-7.
[19] Taran S, Stevens RD, Perrot B, McCredie VA, Cinotti R, Asehnoune K, et al. Incidence and outcomes of acute respiratory distress syndrome in brain-injured patients receiving invasive ventilation: a secondary analysis of the ENIO study. J Intensive Care Med 2024;39:136–45. https://doi.org/10.1177/08850666231194532.
[20] Pham T, Heunks L, Bellani G, Madotto F, Aragao I, Beduneau G, et al. Weaning from mechanical ventilation in intensive care units across 50 countries (WEAN SAFE): a multicentre, prospective, observational cohort study. Lancet Respir Med 2023;11:465–76. https://doi.org/10.1016/S2213-2600(22)00449-0.
[21] Banner MJ, Kirby RR, Kirton OC, DeHaven CB, Blanch PB. Breathing frequency and pattern are poor predictors of work of breathing in patients receiving pressure support ventilation. Chest 1995;108:1338–44. https://doi.org/10.1378/chest.108.5.1338.
[22] Mortamet G, Nardi N, Groleau V, Essouri S, Fauroux B, Jouvet P, et al. Impact of spontaneous breathing trial on work of breathing indices derived from esophageal pressure, electrical activity of the diaphragm, and oxygen consumption in children. Respir Care 2019;64:509–18. https://doi.org/10.4187/respcare.06351.
[23] Tulaimat A, Patel A, Wisniewski M, Gueret R. The validity and reliability of the clinical assessment of increased work of breathing in acutely ill patients. J Crit Care 2016;34:111–5. https://doi.org/10.1016/j.jcrc.2016.04.013.
[24] Apigo M, Schechtman J, Dhliwayo N, Al Tameemi M, Gazmuri RJ. Development of a work of breathing scale and monitoring need of intubation in COVID-19 pneumonia. Crit Care 2020;24:477. https://doi.org/10.1186/s13054-020-03176-y.
[25] Karanjia N, Nordquist D, Stevens R, Nyquist P. A clinical description of Extubation failure in patients with primary brain injury. Neurocrit Care 2011;15:4–12. https://doi.org/10.1007/s12028-011-9528-5.
[26] Akella P, Voigt LP, Chawla S. To Wean or not to Wean: a practical patient focused guide to ventilator weaning. J Intensive Care Med 2022;37:1417–25. https://doi.org/10.1177/08850666221095436.
[27] Burns KEA, Raptis S, Nisenbaum R, Rizvi L, Jones A, Bakshi J, et al. International practice variation in weaning critically ill adults from invasive mechanical ventilation. Ann Am Thorac Soc 2018;15:494–502. https://doi.org/10.1513/AnnalsATS.201705-410OC.
[28] Tobin MJ. Extubation and the Myth of “Minimal Ventilator Settings”. Am J Respir Crit Care Med 2012;185:349–50. https://doi.org/10.1164/rccm.201201-0050ED.
[29] Andreu M, Bertozzi M, Bezzi M, Borello S, Castro D, Di Giorgio V, et al. Comparison of two Extubation techniques in critically ill adult subjects: the ExtubAR randomized clinical trial. Respir Care 2022;67:76–86. https://doi.org/10.4187/respcare.09276.
[30] Andreu MF, Dotta ME, Bezzi MG, Borello S, Cardoso GP, Dib PC, et al. Safety of positive pressure Extubation technique. Respir Care 2019;64:899–907. https://doi.org/10.4187/respcare.06541.
[31] Shimada K, Inokuchi R, Iwagami M, Tanaka M, Tamiya N. Comparison of Postextubation complications between positive-pressure and suctioning techniques: a systematic review. Respir Care 2023;68:429–36. https://doi.org/10.4187/respcare.10326.
[32] Li HP, Lin YN, Cheng ZH, Qu W, Zhang L, Li QY. Intracranial-to-central venous pressure gap predicts the responsiveness of intracranial pressure to PEEP in patients with traumatic brain injury: a prospective cohort study. BMC Neurol 2020; 20:234. https://doi.org/10.1186/s12883-020-01764-7.
[33] Battaglini D, Delpiano L, Masuello D, Leme Silva P, Rocco PRM, Matta B, et al. Effects of positive end-expiratory pressure on brain oxygenation, systemic oxygen cascade and metabolism in acute brain injured patients: a pilot physiological cross-sectional study. J Clin Monit Comput 2023. https://doi.org/10.1007/s10877-023-01042-0.
[34] Citerio G, Robba C, Rebora P, Petrosino M, Rossi E, Malgeri L, et al. Management of arterial partial pressure of carbon dioxide in the first week after traumatic brain injury: results from the CENTER-TBI study. Intensive Care Med 2021;47:961–73. https://doi.org/10.1007/s00134-021-06470-7.
[35] Dimitri GM, Beqiri E, Placek MM, Czosnyka M, Stocchetti N, Ercole A, et al. Modeling brain-heart crosstalk information in patients with traumatic brain injury. Neurocrit Care 2022;36:738–50. https://doi.org/10.1007/s12028-021-01353-7.
[36] Huynh T, Messer M, Sing RF, Miles W, Jacobs DG, Thomason MH, et al. Positive end-expiratory pressure alters intracranial and cerebral perfusion pressure in severe traumatic brain injury. J Trauma 2002;53:488–93.
[37] Robba C, Ball L, Nogas S, Battaglini D, Messina A, Brunetti I, et al. Effects of positive end-expiratory pressure on lung recruitment, respiratory mechanics and intracranial pressure in mechanically ventilated brain injured patients. Front Physiol 2021;12:711273. Doi: 10.3389-fphys.2021.711273.
[38] Boone MD, Jinadasa SP, Mueller A, Shaefi S, Kasper EM, Hanafy KA, et al. The effect of positive end-expiratory pressure on intracranial pressure and cerebral hemodynamics. Neurocrit Care 2017;26:174–81. https://doi.org/10.1007/s12028-016-0328-9.
[39] Robba C, Bragazzi NL, Bertuccio A, Cardim D, Donnelly J, Sekhon M, et al. Effects of prone position and positive end-expiratory pressure on noninvasive estimators of ICP. J Neurosurg Anesthesiol 2017;29:243–50. https://doi.org/10.1097/ANA.0000000000000295.
[40] Mascia L, Grasso S, Fiore T, Bruno F, Berardino M, Ducati A. Cerebro-pulmonary interactions during the application of low levels of positive end-expiratory pressure. Intensive Care Med 2005;31:373–9. https://doi.org/10.1007/s00134-004-2491-2.
[41] McNamara L, Baedorf Kassis E. Optimal positive-end expiratory pressure weaning in acute respiratory distress syndrome patients. Curr Opin Crit Care 2024;30:85–8. https://doi.org/10.1097/MCC.0000000000001122.
[42] Aldabayan YS, Tolba AA, Alrajeh AM, Ahmed AT, Mahgoub AA, Glalah AAA, et al. Factors affecting mechanical ventilator weaning success and 28-day survival among patients with acute respiratory distress syndrome secondary to COVID-19. SAGE Open Nurs 2023:9. https://doi.org/10.1177/23779608231187248.
[43] von Düring S, Parhar KKS, Adhikari NKJ, Urner M, Kim SJ, Munshi L, et al. Understanding ventilator-induced lung injury: the role of mechanical power. J Crit Care 2025;85:154902. https://doi.org/10.1016/j.jcrc.2024.154902.
[44] Nieman G, Kollisch-Singule M, Ramcharran H, Satalin J, Blair S, Gatto LA, et al. Unshrinking the baby lung to calm the VILI vortex. Crit Care 2022;26:242. https://doi.org/10.1186/s13054-022-04105-x.

Glossary

ABI: Acute Brain Injury
ARDS: Acute Respiratory Distress Syndrome
BMI: Body Mass Index
CI: Confidence Interval
CNS: Central Nervous System
CPP: Cerebral Perfusion Pressure
ENIO: Extubation strategies in Neuro-Intensive care unit patients, and associations with Outcomes
EVD: External Ventricular Drainage
FiO_2: fraction of inspired oxygen
GCS: Glasgow Coma Score
HR: Hazard Ratio
LOS: Length of Stay
ICH: Intracranial Hemorrhage
ICP: Intracranial Pressure

IMV: Invasive Mechanical Ventilation
IQR: Interquartile Range
IS: Ischemic Stroke
OR: Odds Ratio
$PaCO_2$, mmHg: arterial partial pressure of carbon dioxide
PaO_2: Arterial Partial Pressure of Oxygen
PBW: Predicted Body Weight
PEEP: Positive End-Expiratory Pressure
pHa: arterial pH
SAH: Subarachnoid Hemorrhage
SD: Standard Deviation
SpO_2: Saturation of Peripheral Oxygen
TBI: Traumatic Brain Injury
VAP: Ventilator-Associated Pneumonia
VIF: Variance Inflation Factors