

# STRATEGIES, PREDICTORS, AND OUTCOMES OF WEANING AND EXTUBATION IN MECHANICALLY VENTILATED PATIENTS: A COMPREHENSIVE SYSTEMATIC REVIEW OF EVIDENCE

**JALAL SAEED ALQAHTANI**

Respiratory Department, National Guard Hospital, Riyadh, Saudi Arabia.

**AHMED HAMAD ALAQEILY**

Respiratory Department, National Guard Hospital, Riyadh, Saudi Arabia.

**KHALAF AWAYED ALANAZI**

Respiratory Department, National Guard Hospital, Riyadh, Saudi Arabia.

**ALI NASSER AL ALIANI**

Respiratory Department, National Guard Hospital, Riyadh, Saudi Arabia.

**OTHMAN KHALID ABAHOUSSIN**

Respiratory Department, National Guard Hospital, Riyadh, Saudi Arabia.

**THAMER AWADH ALANAZI**

Respiratory Department, National Guard Hospital, Riyadh, Saudi Arabia.

**YASSER AL SHAMMARI**

Respiratory Department, National Guard Hospital, Riyadh, Saudi Arabia.

## Abstract

Background: Mechanical ventilation is an essential component of critical care but is associated with complications such as ventilator-induced diaphragm dysfunction, prolonged weaning, and increased mortality. Identifying effective strategies to optimize liberation from mechanical ventilation remains a priority to improve patient outcomes. Objectives: This systematic review aimed to evaluate evidence on weaning and extubation strategies, predictive parameters, and pathophysiological mechanisms influencing extubation outcomes in critically ill patients. Methods: Following PRISMA guidelines, a comprehensive literature search of PubMed, Scopus, and Web of Science was conducted up to 2024. Eligible studies included randomized controlled trials, observational studies, crossover trials, and narrative reviews assessing ventilation strategies, extubation outcomes, or predictors of successful weaning. Two independent reviewers performed screening, data extraction, and risk of bias assessment. Results: Nine studies met inclusion criteria, comprising seven randomized controlled trials, one crossover trial, and one narrative review. Sample sizes ranged from 23 preterm infants to 604 critically ill adults. Structured weaning protocols, such as spontaneous awakening and breathing trials, were associated with increased ventilator-free days, reduced ICU stay, and lower mortality. Lactate-guided therapy facilitated earlier liberation and reduced hospital mortality. Post-extubation noninvasive ventilation (NIV) reduced reintubation in high-risk and obese patients, while high-flow nasal cannula (HFNC) was non-inferior in broader populations and better tolerated. In neonates, cardiorespiratory variability measures predicted extubation success with moderate accuracy. The narrative review underscored unique challenges in obese patients, advocating individualized ventilatory strategies. Conclusion: Evidence supports the use of structured weaning protocols, risk-stratified use of NIV or HFNC, and physiologic predictors to optimize extubation outcomes. Preventive strategies against respiratory muscle dysfunction and tailored approaches for high-risk groups,

including obese and neonatal patients, are essential. Future research should refine predictive models and evaluate interventions targeting ventilator-induced diaphragm dysfunction.

**Keywords:** Mechanical Ventilation, Weaning, Extubation, Noninvasive Ventilation, High-Flow Nasal Cannula, Predictors, Systematic Review.

## INTRODUCTION

Mechanical ventilation is a cornerstone of modern critical care, providing lifesaving support for patients who cannot maintain adequate oxygenation or ventilation. Despite its therapeutic benefits, prolonged ventilatory support is associated with multiple complications, including ventilator-induced diaphragm dysfunction, weaning failure, and poor long-term outcomes. Understanding the interplay between respiratory physiology, underlying disease processes, and ventilation strategies is crucial in optimizing patient outcomes and guiding evidence-based practice.

Critical illness-associated diaphragm weakness represents one of the most significant barriers to successful liberation from mechanical ventilation. It may pre-exist or develop during intensive care, most commonly as a result of sepsis and sustained ventilatory support. This condition is consistently associated with prolonged mechanical ventilation, difficult weaning, and increased mortality. Advances in bedside techniques for assessing diaphragmatic function and emerging interventions, such as inspiratory muscle training and pharmacological therapies, offer potential avenues for improving outcomes, though evidence on their clinical effectiveness remains limited (Dres et al. 2017).

The complexity of ventilatory management is further underscored by the multidisciplinary nature of care. While mechanical ventilation is most often managed by physicians and respiratory therapists, pharmacists also play an important role within the critical care team. Their contributions extend to medication optimization, minimizing drug-disease interactions, and supporting institutional weaning protocols. Integration of pharmacological considerations into ventilatory care has been shown to enhance safety, reduce complications, and optimize weaning success (Pinto et al. 2021).

Acute respiratory distress syndrome (ARDS) exemplifies the clinical challenges associated with mechanical ventilation. ARDS arises from inflammatory injury to the alveolar-capillary barrier, leading to pulmonary edema, decreased lung compliance, and severe hypoxemia. It is responsible for approximately one in ten ICU admissions and one in four cases of mechanical ventilation, with mortality in severe cases reaching 60%. Management emphasizes lung-protective ventilation strategies, including low tidal volume and high positive end-expiratory pressure, as well as prone positioning in selected patients. Successful recovery requires timely recognition of weaning readiness and careful transition from ventilatory support to spontaneous breathing (Saguil et al. 2020).

Mechanistic studies further illuminate the physiological consequences of prolonged mechanical ventilation. Experimental evidence demonstrates that sustained ventilatory support induces rapid diaphragmatic atrophy and contractile dysfunction, collectively described as ventilator-induced diaphragm dysfunction (Levine et al. 2008; Shanely et al. 2002).

These findings provide biological plausibility for clinical observations of difficult weaning and highlight the urgent need for interventions targeting preservation of respiratory muscle function. Similarly, translational and clinical investigations underscore the importance of individualized approaches, accounting for patient heterogeneity, comorbidities, and disease-specific characteristics (Dres et al. 2017).

Collectively, the evidence underscores the dual challenge of mechanical ventilation: providing adequate life support while minimizing iatrogenic harm. By synthesizing findings from clinical, experimental, and multidisciplinary perspectives, this review aims to clarify the impact of ventilation strategies on patient outcomes and to highlight opportunities for optimizing liberation from mechanical support.

## METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed across electronic databases including PubMed, Scopus, and Web of Science, covering studies published from inception to 2024. The search strategy combined controlled vocabulary and free-text terms related to “mechanical ventilation,” “driving pressure,” “weaning,” “extubation,” and “ventilation outcomes.” Additional records were identified by manual screening of reference lists from included articles and relevant reviews.

Eligible studies were randomized controlled trials, observational cohort studies, and experimental investigations that evaluated ventilation strategies, extubation outcomes, or predictors of liberation from mechanical ventilation in adult or neonatal populations. Studies focusing exclusively on pediatric non-ICU populations or those without patient-centered outcomes were excluded. Narrative reviews were considered only if they provided mechanistic or contextual evidence relevant to clinical practice.

Two independent reviewers screened titles and abstracts for relevance. Full texts of potentially eligible studies were retrieved and assessed according to prespecified inclusion and exclusion criteria. Discrepancies were resolved through discussion or adjudication by a third reviewer. Data extraction was performed using a standardized form that included study design, sample size, patient demographics, methodology, interventions, and primary outcomes. Extracted data were cross-checked for accuracy.

The primary outcome of interest was extubation success, defined as the absence of reintubation within 48–72 hours or up to 7 days after extubation, depending on study definitions. Secondary outcomes included ventilator-free days, ICU and hospital length of stay, mortality, and physiological predictors of extubation readiness such as rapid shallow breathing index, diaphragmatic function, or cardiorespiratory variability.

For experimental studies, mechanistic outcomes related to ventilator-induced diaphragm dysfunction were considered. Risk of bias was assessed using the Cochrane risk-of-bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies.

Quality appraisal was conducted independently by two reviewers, with disagreements resolved by consensus. Due to clinical heterogeneity in populations and interventions, a narrative synthesis was undertaken. Where possible, findings were grouped according to patient subgroup (high-risk adults, obese patients, preterm neonates) and intervention type (noninvasive ventilation vs. high-flow nasal cannula, structured weaning protocols, physiologic predictors).

## RESULTS

A total of nine studies met the inclusion criteria, comprising seven randomized controlled trials (RCTs), one randomized crossover trial, and one narrative review. These studies addressed different aspects of ventilatory management, weaning, and extubation outcomes in critically ill populations, including adults with obesity, neurological and general ICU patients, as well as extremely preterm infants. The main characteristics and outcomes of the included studies are summarized in Tables 1 and 2.

Sample sizes varied across the included studies, ranging from 23 extremely preterm infants (Latremouille et al. 2022) to 604 critically ill adults at high risk for reintubation (Hernández et al. 2016). Adult populations were predominantly middle-aged to elderly, with median ages between 60–65 years (Hernández et al. 2016, 2022, 2024; Jansen et al. 2010). The majority of participants were male (45–64%). Specific high-risk subgroups included obese patients with BMI >30 (Hernández et al. 2024; De Jong et al. 2020), patients with multiple risk factors for extubation failure (Hernández et al. 2022), and neurological ICU patients requiring prolonged mechanical ventilation (Fan et al. 2015). Pediatric evidence came from a crossover trial in preterm infants undergoing their first extubation (Latremouille et al. 2022). One trial (Daniels et al. 2015) explored feeding practices in infants, relevant to respiratory development and outcomes but outside the ICU context.

Several studies compared post-extubation support strategies. Two RCTs demonstrated that noninvasive ventilation (NIV) with active humidification reduced reintubation rates compared to high-flow nasal cannula (HFNC) in patients at very high risk (23.3% vs 38.8%) (Hernández et al. 2022) and showed a favorable trend in obese patients at intermediate risk (23.6% vs 33.3%), although not statistically significant (Hernández et al. 2024). In contrast, a multicenter trial in high-risk adults found HFNC to be non-inferior to NIV, with fewer adverse effects and shorter ICU stays (Hernández et al. 2016). These findings suggest that the choice of modality may depend on patient risk stratification.

Other weaning-focused trials investigated structured protocols. Fan et al. (2015) showed that protocol-directed weaning in neurological patients significantly shortened weaning times and reduced duration of mechanical ventilation, particularly in conscious patients. Girard et al. (2008) demonstrated that pairing spontaneous awakening trials (SATs) with spontaneous breathing trials (SBTs) increased ventilator-free days, reduced ICU and hospital length of stay, and improved 1-year survival compared to standard practice.

Similarly, Jansen et al. (2010) reported that lactate-guided resuscitation in ICU patients with hyperlactatemia reduced adjusted hospital mortality and facilitated earlier liberation from mechanical ventilation.

One crossover trial in extremely preterm infants identified cardiorespiratory variability measures—particularly heart rate variability and respiratory variability—as predictors of extubation success, with moderate predictive accuracy (AUC 0.75–0.80) (Latremouille et al. 2022). These findings highlight the potential role of physiologic biomarkers in guiding extubation decisions in neonates. The narrative review by De Jong et al. (2020) provided important context for obese patients, describing pathophysiological challenges, higher risk of atelectasis and airway closure, and the need for higher positive end-expiratory pressure (PEEP) during mechanical ventilation. The authors recommended prophylactic NIV post-extubation to reduce complications, reinforcing trial evidence from Hernández et al. (2022, 2024).

The BLISS study protocol (Daniels et al. 2015) addressed infant nutrition and feeding practices, hypothesizing long-term benefits on growth, energy regulation, and obesity risk. Although not an ICU-focused study, it adds indirect insight into pediatric outcomes that may influence susceptibility to critical illness later in life. Across the included studies, consistent evidence supports the use of structured protocols (SAT/SBT, protocolized weaning, lactate-guided therapy) to improve liberation from mechanical ventilation and reduce mortality. NIV appears superior to HFNC in select high-risk or obese subgroups, while HFNC provides a well-tolerated alternative in broader ICU populations. In neonates, physiological monitoring shortly after extubation may aid prediction of outcomes. The narrative review highlighted the unique challenges of ventilation in obese patients, reinforcing the need for individualized ventilatory strategies.

**Table 1: summary of studies**

Citation	Study Design	Sample Size	Population Characteristics	Methodology	Study Aim
Hernández et al. 2024	Randomized controlled trial	144 patients	Adults with obesity (BMI >30) at intermediate risk for reintubation	Compared NIV with active humidification vs HFNC for 48h post-extubation	To assess whether NIV reduces reintubation compared with HFNC in obese patients
Jansen et al. 2010	Multicenter randomized controlled trial	348 patients	ICU patients with lactate $\geq 3.0$ mmol/L on admission	Randomized to lactate-guided resuscitation vs control group without lactate guidance	To determine whether lactate-guided therapy reduces hospital mortality
Latremouille et al. 2022	Randomized crossover trial	23 extremely preterm infants	Infants $\leq 1250$ g BW undergoing first extubation	Measured HRV, diaphragmatic activity, and RV during different non-invasive supports	To assess predictive value of cardiorespiratory measures for extubation success

Fan et al. 2015	Randomized controlled trial	144 patients	Neurological ICU patients requiring MV >24h	Compared protocol-directed vs physician-directed ventilator weaning	To evaluate impact of protocol-directed weaning on MV duration and outcomes
Girard et al. 2008	Randomized controlled trial	336 patients	Mechanically ventilated adult ICU patients	Compared daily SAT+SBT vs standard sedation plus daily SBT	To test whether paired SAT and SBT improves outcomes in MV patients
De Jong et al. 2020	Narrative review	Not applicable	Obese ICU patients	Literature review of ventilation management in obese patients	To summarize evidence and strategies for ventilation of obese patients in ICU
Hernández et al. 2022	Randomized controlled trial	182 patients	Adults with ≥4 risk factors (very high risk for extubation failure)	Randomized to NIV with humidification vs HFNC for 48h post-extubation	To determine if NIV is superior to HFNC in preventing reintubation
Daniels et al. 2015	Randomized controlled trial (protocol)	200 families	Infants from Dunedin, NZ, starting complementary feeding	Compared BLISS (baby-led feeding) vs standard feeding with 12-month intervention	To evaluate efficacy and safety of baby-led introduction to solids
Hernández et al. 2016	Multicenter randomized clinical trial	604 patients	ICU patients with ≥1 high-risk factor for reintubation	Randomized to NIV vs high-flow oxygen for 24h post-extubation	To test noninferiority of HFNC compared to NIV for preventing reintubation

**Table 2: demographics, main findings, and outcomes**

Citation	Demographic Data	Main Findings	Outcomes
Hernández et al. 2024	Median age 61 yrs; 45% male; obese (BMI >30)	NIV group had lower reintubation rate (23.6%) vs HFNC (33.3%), but difference not statistically significant	Reintubation within 7 days; Bayesian analysis suggested high probability of benefit with NIV
Jansen et al. 2010	348 ICU patients with hyperlactatemia (≥3.0 mmol/L)	Lactate-guided therapy reduced adjusted hospital mortality; improved SOFA scores and earlier weaning	Hospital mortality 33.9% vs 43.5%; earlier ICU discharge in lactate group
Latremouille et al. 2022	23 preterm infants, GA ~26 wks, BW ~760 g	Cardiorespiratory variability (HRV, RV) parameters predicted extubation success	Moderate predictive accuracy (AUC 0.75–0.80) for extubation success
Fan et al. 2015	144 neurological ICU patients; both conscious and unconscious subgroups	Protocol-directed weaning reduced weaning time significantly vs physician-directed	Shorter MV duration and lower NCU stay/cost in intervention group; greater effect in conscious patients

Girard et al. 2008	336 mechanically ventilated adult ICU patients	SAT+SBT protocol increased ventilator-free days and reduced ICU/hospital stay	Lower 1-year mortality (HR 0.68); NNT = 7.4 to save one life
De Jong et al. 2020	Review—no direct patient cohort	Obesity increases risk of complications; NIV preferred for ARF; higher PEEP required in invasive ventilation	Optimized strategies reduce complications; obesity paradox in ICU mortality noted
Hernández et al. 2022	182 very high-risk patients; mean age 60 yrs; 64% male	NIV significantly reduced reintubation (23.3%) vs HFNC (38.8%)	Shorter hospital stays (20 vs 26.5 days); no major difference in mortality or complications
Daniels et al. 2015	200 families in Dunedin, New Zealand	BLISS baby-led weaning acceptable; addresses concerns about iron, choking, growth	Primary outcome: BMI at 12 months; also diet quality, iron/zinc status, choking incidence
Hernández et al. 2016	604 high-risk ICU patients; mean age 65 yrs; 64% male	HFNC noninferior to NIV for reintubation; fewer adverse effects with HFNC	Reintubation ~22.8% HFNC vs 19.1% NIV; lower ICU stay with HFNC; fewer therapy withdrawals

## DISCUSSION

This systematic review synthesized evidence from six studies that examined weaning and extubation strategies, predictive parameters, and underlying pathophysiological mechanisms affecting ventilated patients. Collectively, the findings highlight the multifactorial nature of liberation from mechanical ventilation and the importance of individualized approaches.

Burns et al. (2024) emphasized structured liberation protocols, early transition to noninvasive ventilation in patients with chronic obstructive pulmonary disease (COPD), and the prophylactic use of noninvasive support strategies after extubation. Their review reinforces the growing consensus that systematic weaning processes improve extubation outcomes and reduce the risk of reintubation. Similarly, Baptistella et al. (2018) identified more than 50 predictive parameters for successful weaning and extubation. Among these, the Rapid Shallow Breathing Index (RSBI) remains the most frequently studied and clinically applied tool, though reliance on a single measure was cautioned against, highlighting the need for multidimensional evaluation.

The heterogeneity of predictive measures across studies underscores the complexity of extubation readiness. In addition to RSBI, Baptistella et al. (2018) reported age, maximum inspiratory pressure, and other physiologic markers as contributing to outcome prediction. This aligns with Saguil and Fargo (2020), who demonstrated that patients recovering from acute respiratory distress syndrome (ARDS) should undergo spontaneous breathing trials once the underlying pathology improves, further illustrating the importance of integrating disease-specific considerations into extubation protocols. Underlying pathophysiology plays a pivotal role in determining liberation outcomes.

Sagui and Fargo (2020) outlined how ARDS induces inflammatory injury and pulmonary edema, prolonging the need for ventilatory support. Optimal ventilatory strategies in these patients, such as low tidal volume and high positive end-expiratory pressure, were shown to improve outcomes and facilitate eventual weaning. Complementing this, Dres et al. (2017) described diaphragm weakness as a major barrier to successful liberation, often developing during ICU stay due to sepsis and prolonged ventilation. They emphasized that respiratory muscle dysfunction is strongly associated with increased mortality and prolonged mechanical ventilation.

Further insight into muscle physiology was provided by experimental evidence (D5, D6). Animal and translational studies demonstrated that prolonged mechanical ventilation induces rapid diaphragmatic atrophy and contractile dysfunction, often termed ventilator-induced diaphragm dysfunction (VIDD).

These findings provide biological plausibility for clinical observations of difficult weaning and highlight the need for preventive strategies, such as early mobilization, inspiratory muscle training, or pharmacological interventions. Together, these mechanistic insights bridge the gap between clinical outcomes and underlying pathophysiological mechanisms.

The evidence converges on the importance of early recognition of readiness to wean, comprehensive evaluation beyond a single index, and incorporation of disease-specific and physiological markers. Protocolized weaning and prophylactic use of noninvasive support appear beneficial in reducing complications and improving extubation success. Moreover, recognizing diaphragm weakness and targeting preventive strategies may improve liberation rates and long-term outcomes. Future research should focus on refining predictive models, validating composite indices, and evaluating interventions that mitigate respiratory muscle dysfunction.

## CONCLUSION

This systematic review highlights that successful liberation from mechanical ventilation depends on structured weaning protocols, individualized extubation strategies, and accurate physiological predictors. Evidence supports the use of spontaneous awakening and breathing trials, lactate-guided therapy, and protocol-directed weaning to reduce mortality and shorten ventilation duration.

Noninvasive ventilation is particularly beneficial in high-risk and obese patients, while high-flow nasal cannula remains a safe, well-tolerated alternative in broader ICU populations. In neonates, cardiorespiratory variability measures may assist in predicting extubation success.

Preventing ventilator-induced diaphragm dysfunction and tailoring approaches to patient-specific risks are critical to improving outcomes. Future research should focus on validating composite predictive tools and developing interventions that preserve respiratory muscle function, ultimately enhancing survival and quality of care in critically ill patients.

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