

Liberation from Mechanical Ventilation in Critically Ill Patients: Korean Society of Critical Care Medicine Clinical Practice Guidelines



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Abstract

Background: Successful liberation from mechanical ventilation is one of the most crucial processes in critical care, because it is the first step through which a respiratory failure patient begins to transition out of the intensive care unit, and return to normal life. Therefore, when devising appropriate strategies for removing mechanical ventilation, it is essential to consider scientific and systematic approaches, as well as the individual experiences of healthcare professionals. Recently, numerous studies have investigated methods and tools to identify when mechanically ventilated patients are ready to breathe on their own. The Korean Society of Critical Care Medicine therefore provides these recommendations to clinicians for liberation from the ventilator.

Methods: Meta-analyses and comprehensive syntheses were used to thoroughly review, compile, and summarize the complete body of relevant evidence. All studies were meticulously assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method, and the outcomes were presented succinctly as evidence profiles. These evidence syntheses were discussed by a multidisciplinary committee of experts in mechanical ventilation, who then developed and approved the recommendations.

Results: Recommendations for nine questions on ventilator liberation about Population, Intervention, Comparator, and Outcome (PICO) are presented in this document. This guideline presents seven conditional recommendations, one expert consensus recommendation, and one conditional deferred recommendation.

Conclusion: We developed these clinical guidelines for mechanical ventilation liberation to provide meaningful recommendations. These guidelines reflect the best treatment for patients seeking liberation from mechanical ventilation.

Keywords: Mechanical Ventilation; Liberation; Critically Ill Patients; Recommendations



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Key Messages

We have developed clinical guidelines on mechanical ventilation liberation to provide meaningful recommendations to clinicians.

These guidelines reflect the best treatment for patients seeking liberation from mechanical ventilation.

Summary of Recommendations

Question 1: For critically ill patients receiving ventilation, does a mechanical ventilation weaning protocol increase the success rate of ventilator liberation?

For critically ill patients on mechanical ventilation, we recommend the use of a mechanical ventilation weaning protocol (recommendation B, conditional recommendation, moderate certainty in the evidence).

Question 2-1: Is pressure support ventilation (PSV) recommended over the T-piece during spontaneous breathing trial (SBT) in adult patients receiving mechanical ventilation?

We suggest that when planning to wean adult patients from mechanical ventilation, either PSV or the T-piece can be applied during SBT (recommendation B, conditional recommendation, low certainty in the evidence).

Question 2-2: Is PSV recommended over the T-piece during SBT in adult patients at high-risk of extubation failure?

We suggest that in adult patients at high-risk of extubation failure, either PSV or the T-piece can be applied during SBT (recommendation B, conditional recommendation, very low certainty in the evidence).

Question 3: Is a cuff leak test (CLT) recommended before the extubation of mechanically ventilated patients?

We suggest that a CLT can be performed, at the discretion of the clinician, prior to the extubation of adult patients receiving mechanical ventilation who are at high-risk of developing post-extubation stridor (PES) (recommendation B, conditional recommendation, low certainty in the evidence).

Question 4: Are steroids recommended before extubation in mechanically ventilated patients with a failed CLT?

To prevent PES and reintubation, we recommend the administration of steroids before the extubation of mechanically ventilated adult patients who have failed a

CLT (recommendation B, conditional recommendation, moderate level of evidence).

Question 5: Is computation of the rapid shallow breathing index (RSBI) recommended before extubating mechanically ventilated adult patients?

We suggest that the RSBI can be computed at the discretion of the clinician (recommendation B, conditional recommendation, low certainty in the evidence).

Question 6: Is inspiratory muscle training (IMT) recommended for critically ill adult patients on mechanical ventilation?

We suggest that IMT for critically ill adult patients on mechanical ventilation is employed to increase the success rate of weaning from mechanical ventilation (recommendation B, conditional recommendation, low certainty in the evidence).

Question 7: Is early physical rehabilitation recommended for critically ill patients on mechanical ventilation?

We suggest the early rehabilitation of critically ill adult patients to increase the success rate of weaning from mechanical ventilation (recommendation B, conditional recommendation, low level of evidence).

Question 8-1: Is a high-flow nasal cannula (HFNC) recommended over conventional oxygen therapy (COT) for adult patients undergoing planned extubation?

For successful weaning from mechanical ventilation, we recommend HFNC over COT in adult patients undergoing planned extubation (recommendation B, conditional recommendation, moderate certainty in the evidence).

Question 8-2: Is non-invasive ventilation (NIV) recommended over COT for adult patients undergoing planned extubation?

For successful weaning from mechanical ventilation, we recommend NIV over COT in adult patients undergoing planned extubation who are at high-risk of weaning failure (recommendation B, conditional recommendation, moderate certainty in the evidence).

Question 8-3: Is HFNC recommended over NIV for adult patients undergoing planned extubation?

We suggest that for adult patients undergoing planned extubation, either HFNC or NIV can be applied at the discretion of the clinician (recommendation E, expert consensus recommendation, very low certainty in the

evidence).

Question 9: Should an early tracheostomy be performed to successfully wean adult patients from mechanical ventilation?

We recommend that early tracheostomy not be performed for patients expected to require prolonged mechanical ventilation (recommendation I, conditional deferred, low certainty in the evidence).

Introduction

Mechanical ventilation is omnipresent in intensive care units (ICUs)¹. Every year, more than 1 million patients worldwide undergo mechanical ventilation for acute respiratory failure and other disease entities². One of the most critical decisions clinicians face in managing these critically ill patients is how and when to liberate them from invasive ventilation. Prolonged mechanical ventilation carries risks of ventilator-associated lung injury, ventilator-associated pneumonia, diaphragm dysfunction, increased in-hospital mortality, and increased lengths of ICU and hospital stays^{3,4}. On the other hand, premature extubation attempts can lead to reintubation, increased rates of ventilator-associated pneumonia, and other adverse outcomes⁵.

In 1987, Hall and Wood⁶ proposed that the ultimate objective is not to wean patients from mechanical ventilation, but rather to liberate them from it. They argued that the term 'weaning,' which simply denotes the removal of the tube and transition to oral feeding, inadequately captures the pain, challenges, and struggles of both patients being liberated from mechanical ventilation, and the healthcare professionals caring for them. The process of liberation from mechanical ventilation involves complex challenges, such as regulating sedation and pain; appropriately managing delirium; and addressing ventilator-associated pneumonia and ventilator-induced lung injury, neuromuscular complications associated with critical illness, weakness of the diaphragm muscle, inadequate nutritional support, and sleep deprivation. Liberation is a multifaceted process that demands dedication and emotional support from healthcare professionals, as patients navigate issues that hinder the liberation process. Therefore, when devising appropriate strategies for liberation from mechanical ventilation, it is essential to consider scientific and systematic evidence, as well as the individual experiences of healthcare professionals.

In the decades since Hall and Wood's pronouncement⁶, many studies have investigated methods and tools to identify the readiness of mechanically ventilat-

ed patients for successful liberation⁷⁻⁹. However, since the original publication of the Guidelines for Liberation from Mechanical Ventilation in 2010¹⁰, no relevant recommendations have been proposed in Korea.

Therefore, the Korean Society of Critical Care Medicine (KSCCM) has developed these clinical guidelines for mechanical ventilation liberation. These guidelines recommend the best possible treatments for patients seeking liberation from mechanical ventilation.

Materials and Methods

1. *De novo* development

These clinical practice recommendations were developed using a *de novo* approach by the KSCCM. The systematic review used for the *de novo* development followed the Cochrane methodology. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology was adopted to assess the level of evidence, and determine the grade of each recommendation.

2. Deriving the key questions

The key questions (KQs) reflect processes involved in weaning patients from mechanical ventilation, including predictors and methods for success, and were prioritized based on content that could be clinically important or controversial to the users of these guidelines. Subsequently, the KQs deemed to warrant a final recommendation were selected by consensus among the development committee members.

3. Literature search

The literature search formula was established by deriving preliminary search terms through discussions between methodology experts and the development committee members in charge of each KQ. The working committee members proposed search terms, and drafts of search formulae reflecting those proposals were prepared for each clinical question using PubMed. The search terms were selected based on terms related to mechanical ventilation and weaning from mechanical ventilation. The search strategy was prepared by selecting natural language, and considering control and words similar to the content of each KQ. Searches were conducted in MEDLINE (PubMed), Embase, the Cochrane library, and KoreaMed.

4. Rationale for literature selection

For the selection process, two development committee members were assigned to each KQ, and duplicate search results were eliminated. Literature selection

was performed using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. The complete selection process is included in the Appendix. The inclusion and exclusion criteria for each KQ were derived based on Population, Intervention, Comparator, and Outcome (PICO) (benefit and harm).

5. Quality and level of evidence in the primary articles

The level of evidence for each KQ was assessed in two aspects: the quality of the individual primary articles, and the single level of evidence presented by all the articles combined. Two reviewers independently assessed the quality of the primary articles for each KQ, and disagreements were resolved by consensus among the responsible committee members and the methodology expert. Cochrane's Risk of Bias 2.0 was used for randomized controlled trials (RCTs), and the Risk of Bias for Nonrandomized Studies 2.0 was used for nonrandomized studies.

6. Level of evidence and grading of recommendations

The level of evidence was assessed using the GRADE methodology based on discussions between a methodology expert and individual committee members to ensure the objectivity of the level of evidence assessment and application of the same evaluation criteria throughout the recommendations. The direction and strength of each recommendation were determined by the four factors considered in the GRADE methodology: level of evidence, effect size (weighing of benefits and harms), patient values and preferences, and resources.

7. Meta-analysis

When unexplained heterogeneity or two or more outcomes were reported in the included studies, a meta-analysis was performed. However, when the studies had different designs, they were not combined, and meta-analyses were performed separately. In addition, under suspicion of duplication of research data, only the study published most recently, or involving the largest sample size, was included in the final meta-analysis.

8. Conflict of interest

All panel nominees were reviewed and vetted by a joint conflict of interest (COI) review committee composed of members from the KSCCM. After review, nominees who were found to have no substantial COI were approved to conduct this work.

Results

KQ 1. Protocol for liberation from mechanical ventilation

Question 1: For critically ill patients receiving ventilation, does a mechanical ventilation weaning protocol increase the success rate of ventilator liberation?

1) Recommendation

For critically ill patients on mechanical ventilation, we recommend the use of a mechanical ventilation weaning protocol (recommendation B, conditional recommendation, moderate certainty in the evidence).

Remarks: In studies published to date, no differences have been reported to depend on who (doctors, nurses, or respiratory therapists) applies the weaning protocols for mechanical ventilation, but it is necessary to develop weaning protocols suitable for each institution.

2) Values and preference

This recommendation places a high value on decreasing the duration of mechanical ventilation, weaning time, and length of ICU stay.

3) Background

Mechanical ventilation is an important part of critical care in patients with respiratory failure. However, unnecessarily prolonged mechanical ventilation results in various complications, such as tracheal injuries, barotrauma, and ventilator-associated pneumonia, which can increase in-hospital mortality³. If the cause of respiratory failure is being treated and improving, it is recommended to reduce the patient's level of sedation, increase their waking consciousness with a spontaneous awakening trial, and assess their readiness for withdrawal from mechanical ventilation daily with a SBT. The criteria for patients to be liberated from mechanical ventilation are: respiratory rate <35 breaths per minute, adequate oxygenation ($\text{FiO}_2 \leq 40\%$ and positive end-expiratory pressure [PEEP] ≤ 8 cm H_2O , oxygen saturation >90%, or $\text{PaO}_2/\text{FiO}_2$ ratio >150), adequate cough reflex, conscious status on the Richmond Agitation and Sedation Scale from (-2 to 1) (an awake state, no use of continuous sedation, and no or minimal use of vasopressors)³. Patients admitted for traumatic brain injury, those diagnosed with peripheral neuromuscular disease, and those who refused reintubation were excluded from the relevant study³. The criteria for extubation failure are a respiratory rate ≥ 35 breaths per minute, use of accessory muscles of respiration, oxy-

gen saturation <90% (FiO₂ 0.4 or at least 6 L/min of supplemental oxygen), heart rate ≥140 beats per minute, systolic blood pressure <90 or >180 mm Hg, cyanosis, skin mottling, and decreased level of consciousness.

Previously, ICU physicians evaluated the patient's condition, and then went through the process of mechanical ventilation weaning and extubation. However, ICU physicians are generally unable to continuously evaluate a single patient, and thus the process was affected by the physician's schedule. Therefore, it has been reported that ICU nurses or respiratory therapists could use mechanical ventilation weaning protocols to shorten the mechanical ventilation period and ICU length of stay^{4,5}.

4) Summary of evidence

Our literature search strategy returned 972 studies after duplicate removal; of them, 680 studies were screened, and 161 articles were reviewed. In that way, we identified six RCTs and nine observational cohort studies evaluating the effects of mechanical ventilation weaning protocols^{3,6-15}. In our meta-analysis, we found no significant statistical differences in unsuccessful weaning between patients in the RCTs whose care teams followed a weaning protocol, and patients treated without a weaning protocol (risk ratio [RR], 0.93; 95% confidence interval [CI], 0.73 to 1.20; $p=0.59$), and no statistical difference was found between the before and after studies (RR, 0.75; 95% CI, 0.51 to 1.10; $p=0.14$). A sensitivity analysis conducted with six before and after studies showed similar results (RR, 0.84; 95% CI, 0.65 to 1.08; $p=0.17$). Patients in the RCTs whose care teams followed a weaning protocol had a significantly shorter duration of mechanical ventilation than those treated without a weaning protocol (mean difference [MD], -25.34 hours, 95% CI (-42.4 to -8.38), $p=0.003$), while the before and after studies demonstrated similar results between the two groups (MD -2.35 days, 95% CI (-4.10 to -0.60), $p=0.009$). A sensitivity analysis conducted with seven before and after studies showed similar results (MD, -2.31 days; 95% CI, -2.99 to -1.63; $p<0.001$). Patients in the RCTs whose care teams followed a weaning protocol had a significantly shorter weaning time than those treated without a weaning protocol (MD, -38.60 hours; 95% CI, -69.20 to -7.99; $p=0.01$). The RCTs also showed a significantly shorter ICU length of stay in patients whose care teams followed a weaning protocol, than those treated without a weaning protocol (MD, -1.49 days; 95% CI, -2.65 to -0.33; $p=0.01$). In a study before and after the application of the weaning protocol, there was a tendency for the ICU length of stay to decrease after the imple-

mentation of the weaning protocol; however, there was no statistical difference between the two groups (MD, -3.24 days; 95% CI, -6.52 to -0.77; $p=0.05$). ICU mortality in the RCT showed a trend toward reduction in the weaning protocol group, but this was not statistically significant (RR, 0.83; 95% CI, 0.59 to 1.17; $p=0.30$). However, when all studies were considered together, patients whose care teams followed a weaning protocol showed significantly lower ICU mortality than those applied without a weaning protocol (RR, 0.57; 95% CI, 0.42 to 0.77; $p=0.0003$).

In summary, the present meta-analysis shows following a weaning protocol is associated with a decreased duration of mechanical ventilation (25 hours), weaning time (39 hours), and length of ICU stay (1.49 days). However, there was no significant correlation between the use of a mechanical ventilation weaning protocol and the incidence of ventilator-associated pneumonia. It is essential to implement a mechanical ventilation weaning protocol that is tailored to the situation of each hospital. ICU doctors should treat and manage critically ill patients, but it is difficult for them to provide consistent bedside monitoring during weaning from mechanical ventilation. Therefore, ICU nurses and respiratory therapists play a vital role in applying the mechanical ventilation weaning protocol. However, the number of ICU nurses and respiratory therapists can vary widely, depending on the size and severity of cases in the ICU of each hospital. For example, the number of ICU patients per nurse varies from 2.5 to 5, and respiratory therapists are rarely found in ICUs, except in large tertiary hospitals. Thus, the mechanical ventilation weaning protocol should be established and implemented to accommodate the specific ICU situation in each hospital. For practical applications, additional ICU nurses or respiratory therapists might be required, which can increase labor costs. In conclusion, we recommend that each hospital tailor a mechanical ventilation weaning protocol to its specific circumstances, and implement it with critically ill patients on mechanical ventilation.

KQ 2. PSV vs. the T-piece in patients during SBTs

Question 2-1: Is PSV recommended over the T-piece during SBT in adult patients receiving mechanical ventilation?

Question 2-2: Is PSV recommended over the T-piece during SBT in adult patients at high-risk of extubation failure?

1) Recommendation

2-1. We suggest that when planning to wean adult patients from mechanical ventilation, either PSV or the T-piece can be applied during SBT (recommendation B, conditional recommendation, low certainty in the evidence).

Remarks: In usual practice, an SBT with PSV or the T-piece is performed for (30 minutes to 2 hours), before attempting extubation.

2-2. We suggest that in adult patients at high-risk of extubation failure, either PSV or the T-piece can be applied during SBT (recommendation B, conditional recommendation, very low certainty in the evidence).

Remarks: High-risk factors for extubation failure are failure of a first SBT, old age (≥ 65 years), chronic respiratory disease, chronic heart disease, and head trauma.

2) Values and preference

There is insufficient evidence to recommend any method during an SBT. The proper method of SBT should be decided in consideration of each patient's condition, as assessed in a careful evaluation by the clinician.

3) Background

Delayed extubation and prolonged mechanical ventilation lead to ventilator-associated pneumonia, and are associated with increased lengths of stay, and both in-hospital and ICU mortality¹⁶. On the other hand, extubation failure also increases morbidity and in-hospital and ICU mortality in patients receiving mechanical ventilation¹⁷⁻¹⁹. Therefore, it is critical to determine the proper method of SBT to accelerate extubation, and increase the success rate of ventilator weaning²⁰.

In most studies, SBT with PSV or the T-piece was conducted for (30 minutes to 2 hours), before attempting extubation. When the SBT was conducted with PSV, a low inspiratory pressure, such as 5 to 8 cmH₂O, was applied, and PEEP was not applied, or applied at ≤ 5 cmH₂O. In all studies, successful extubation/weaning was defined as the absence of reintubation within 48 to 72 hours after extubation, except for one study that defined successful weaning as the absence of death or reintubation within 7 days after extubation²¹. Although a recent guideline recommended PSV over the T-piece during SBT²², the number of studies supporting that recommendation was small, and conflicting results have been published. Moreover, no recommendation for patients at high-risk of extubation failure has been made. Therefore, we compared PSV with the T-piece, and investigated which method was associated with better clinical outcomes in adult patients undergoing SBT. In addition, we performed subgroup analyses of

patients at high-risk of extubation failure, to determine the proper method of SBT in this high-risk group.

4) Summary of evidence

Among the 1,393 studies returned by our search, 30 were reviewed, and 14 were included in the meta-analyses (Supplementary Tables S1-S12 and Supplementary Figures S1-S27). Of them, 11 were RCTs^{3,23-32}, while the remaining were a *post hoc* study³³, a prospective cohort study²¹, and a retrospective cohort study³⁴. In our meta-analyses of the RCTs, we found no significant differences between the PSV and T-piece groups in terms of successful extubation/weaning (RR, 1.01; 95% CI, 0.94 to 1.09; $p=0.33$) or reintubation (RR, 0.97; 95% CI, 0.69 to 1.37; $p=0.86$). Likewise, in RCTs, the length of stay in the hospital and ICU did not differ between the two methods (MD, 0.88 day; 95% CI, -0.51 to 2.27; $p=0.21$ and MD, -0.06 day; 95% CI, -0.86 to 0.74; $p=0.88$). In addition, patients in the RCTs who received PSV showed a trend toward lower hospital and ICU mortality, but the differences were not statistically significant (RR, 0.97; 95% CI, 0.69 to 1.37; $p=0.86$ and RR, 0.86; 95% CI, 0.64 to 1.11; $p=0.85$, respectively). However, only a few studies were included in the meta-analyses for hospital mortality ($n=8$) and ICU mortality ($n=7$), so the lower tendencies for mortality in the PSV group could not be adequately evaluated.

The subgroup analyses for patients at high-risk of extubation failure included seven studies: five RCTs^{3,24,28,29,32}, a *post hoc* study³³, and a retrospective cohort study³⁴. The definition for the group at high-risk of extubation failure was different in each study: patients with old age (≥ 65 years), chronic heart disease, or chronic lung disease ($n=2$)^{3,33}, with failure of their first SBT ($n=2$)^{24,29}, with both chronic obstructive pulmonary disease (COPD) and failure of the first SBT ($n=1$)²⁸, with head trauma ($n=1$)³², and with persistent atrial fibrillation ($n=1$)³⁴. In the subgroup analyses of patients from the RCTs at high-risk of extubation failure, we found no differences between the PSV and T-piece groups, in terms of successful extubation/weaning (RR, 1.04; 95% CI, 0.90 to 1.20; $p=0.59$), reintubation (RR, 1.09; 95% CI, 0.84 to 1.42; $p=0.51$), in-hospital and ICU mortality (RR, 2.00; 95% CI, 0.67 to 5.94; $p=0.21$ and RR, 0.93; 95% CI, 0.62 to 1.42; $p=0.75$, respectively), or ICU length of stay (MD, -0.91 day; 95% CI, -2.69 to 0.88; $p=0.32$).

In summary, our meta-analysis shows no statistically significant differences between PSV and the T-piece in terms of successful extubation/weaning, reintubation, hospital and ICU mortality, or hospital and ICU lengths of stay, independent of a high-risk of extubation failure.

In a recent guideline, the American Thoracic Society and American College of Chest Physicians suggested that the initial SBT be conducted with inspiratory pressure augmentation of 5 to 8 cmH₂O, rather than without (T-piece or continuous positive airway pressure) in acutely hospitalized patients ventilated for more than 24 hours (conditional recommendation, moderate quality of the evidence)²². Their recommendation was based on a pooled meta-analysis of a few studies (2 to 4), which showed that conducting the SBT with pressure augmentation was more likely to be successful (RR, 1.11; 95% CI, 1.02 to 1.18) (n=3), produced a higher rate of extubation success (RR, 1.09; 95% CI, 1.02 to 1.18) (n=4), and was associated with a trend toward lower ICU mortality (RR, 0.74; 95% CI, 0.45 to 1.24) (n=2)²². However, the results of our meta-analysis are consistent with those from a recent large-scale RCT, which showed no significant differences in major clinical outcomes, including 28-day ventilator-free days³. Therefore, in this guideline, we suggest that when planning to wean adult patients from mechanical ventilation, either PSV or the T-piece can be applied during SBT. In addition, we suggest that either PSV or the T-piece can be applied during SBT in the high-risk group as well, because we found no significant differences between the two methods in patients at high-risk of extubation failure. However, caution should be exercised, because the definition of the group at high-risk of extubation failure was different in each study. Therefore, we suggest that the proper method of SBT should be decided individually based on each patient's condition, as assessed in a careful evaluation by the clinician. Furthermore, these recommendations might change, depending on the results of an ongoing, large-scale RCT³⁵.

KQ 3. CLT

Question 3: Is a CLT recommended before the extubation of mechanically ventilated patients?

1) Recommendation

We suggest that a CLT can be performed, at the discretion of the clinician, prior to the extubation of adult patients receiving mechanical ventilation who are at high-risk of developing PES (recommendation B, conditional recommendation, low certainty in the evidence).

Remarks: The risk factors for PES are being female, duration of intubation >6 days, large endotracheal tube and high cuff pressure, traumatic intubation, and reintubation after unplanned extubation.

2) Values and preference

This recommendation places a high value on minimizing the incidence of PES and reintubation, and a lower value on the burden associated with performing the CLT.

3) Background

Although endotracheal intubation is a critical procedure in patients requiring respiratory support, it can cause mucosal inflammation and edema of the larynx, due to mechanical injury from the endotracheal tube. Laryngeal edema is likely to occur in patients intubated for more than 36 hours³⁶. After extubation, laryngeal edema can narrow the upper airway, causing PES, which has an incidence in the range 6% to 37%³⁷. PES can be associated with a failure of extubation requiring reintubation with mechanical ventilation within 24 to 72 hours after planned extubation^{38,39}. Failure of extubation increases the in-hospital length of stay, morbidity, and mortality^{18,37,40}. Prior to a planned extubation, it is difficult to predict the risk of PES and subsequent reintubation. It is also difficult to determine the presence of upper airway edema by direct examination of the vocal cords in intubated patients.

The CLT is used to indirectly assess laryngeal edema^{41,42}. This is a quantitative method that measures the difference between the amount of expired air when a balloon cuff is inflated and deflated. Normally, when the balloon cuff is deflated, air leaks around the endotracheal tube; in the presence of laryngeal edema, that leakage is reduced.

4) Summary of evidence

No RCTs have evaluated the effect of the CLT. We identified 16 relevant observational cohort studies that used different methods for the CLT, generally auscultation of airflow as a qualitative test or measurement of cuff leak volume as a quantitative test^{38,39,43-56}. The threshold for a failed CLT in quantitative testing was a cuff leak volume in the range 50 to 283 mL (median 110 mL), and a proportion of cuff leak volume in the range 10% to 57% (median 15.1%). Six studies assessed the rate of PES in patients undergoing CLT, and three studies assessed the incidence of reintubation in patients undergoing CLT. In our meta-analysis, patients with a failed CLT showed an increased incidence of PES (pass 15.9% vs. failure 44.8%: odds ratio [OR], 4.01; 95% CI, 2.31 to 6.96; p=0.02), but a failed CLT was not associated with an increased reintubation rate (pass 13.1% vs. failure 14.5%: OR, 1.38; 95% CI, 0.50 to 3.82; p=0.54). Our meta-analysis showed that a failed CLT had low sensitivity, but high specificity as a predictor of PES,

with a pooled sensitivity and specificity of 0.52 (95% CI, 0.44 to 0.59) and 0.8 (95% CI, 0.87 to 0.90), respectively. The pooled positive and negative likelihood ratios of CLT for the prediction of PES were 4.06 (95% CI, 2.99 to 5.50) and 0.51 (95% CI, 0.36 to 0.72), respectively, and the pooled diagnostic OR was 9.68 (95% CI, 4.92 to 19.04). The area under the summary receiver operating characteristics curve of CLT for the prediction of PES was 0.88. Four studies evaluated the rate of reintubation in patients who developed PES, and six studies examined the duration of mechanical ventilation in patients with and without PES. Our meta-analysis shows that patients with PES showed an increased rate of intubation (PES positive 50% vs. PES negative 5.7%: RR, 14.59; 95% CI, 9.11 to 23.37; $p < 0.001$), and prolonged duration of mechanical ventilation (RR, 2.63; 95% CI, 1.17 to 4.09; $p < 0.001$).

In summary, the present meta-analysis shows that patients who failed the CLT were associated with an increased incidence of PES, and patients with PES were likely to have increased reintubation rates. The CLT is simple, inexpensive, safe, and easy to perform according to a protocol at the bedside; it can be useful in making the decision to extubate if the patient passes the test. However, despite its high specificity, the CLT has low sensitivity for predicting PES, so passing the CLT does not exclude upper airway obstruction, or reduce the likelihood of reintubation, as our meta-analysis shows. Several studies have reported that administering steroids to patients who failed a CLT can significantly reduce PES and reintubation rates⁵⁷⁻⁶⁰. Given the high specificity of the CLT, clinicians should consider administering systemic steroids to patients with a failed test to reduce PES and reintubation. This meta-analysis shows that patients who undergo reintubation for PES require a longer duration of mechanical ventilation. High-risk factors for PES include being female, duration of intubation > 6 days, large endotracheal tube and high cuff pressure, traumatic intubation, and reintubation after unplanned extubation^{36,37,61-66}. We recommend performing a CLT prior to extubation in adult patients who are at high-risk of developing PES, at the discretion of the clinician.

KQ 4. Steroids for patients with a failed CLT

Question 4: Are steroids recommended before extubation in mechanically ventilated patients with a failed CLT?

1) Recommendation

To prevent PES and reintubation, we recommend the administration of steroids before the extubation of mechanically ventilated adult patients who have failed a CLT (recommendation B, conditional recommendation, moderate level of evidence).

Remarks: Steroids were administered at least 4 hours before extubation in patients intubated for 24 to 48 hours, but no standard method or dosage for prophylactic steroids has been established.

2) Values and preference

This recommendation places a high value on minimizing the incidence of PES and reintubation in patients with a failed CLT, and a lower value on the burden associated with the side effects of steroid use.

3) Background

Laryngeal edema typically occurs in patients with endotracheal intubation for more than 36 hours. Inflammation and edema of the laryngeal mucosa after extubation can cause upper respiratory tract obstruction, PES, and respiratory failure. Extubation failure occurs when reintubation and mechanical ventilation support are required within 24 to 72 hours after planned extubation; patients with such a failure have a poor prognosis, and increased in-hospital lengths of stay and mortality.

Steroids are known to prevent PES by reducing the deposition of inflammatory cells in the larynx caused by long-term intubation^{37,67,68}. Although a recent guideline recommended the administration of systemic steroids prior to extubation, the literature supporting this recommendation is sparse, and the included studies used different regimens, which led to inconsistent results⁵.

4) Summary of evidence

Among the 548 studies returned in the literature search, 440 were reviewed, and eight were included in the meta-analyses. Of those, we analyzed four RCTs involving patients ready to be liberated from mechanical ventilation who failed a CLT⁵⁷⁻⁶⁰. Cheng et al.⁶⁷ compared outcomes between methylprednisolone (MPD, 40 mg every 6 hours for 24 hours), MPD (40 mg once for 24 hours), and no treatment. Lee et al.⁶⁸ and Baloch et al.⁶⁹ compared the results of dexamethasone (5 mg every 6 hours for 24 hours) with the results of no treatment. Another study by Cheng et al.⁷⁰ compared the outcomes of MPD (40 mg administered 4 hours prior to extubation) with those of no treatment. In our meta-analysis, patients with a failed CLT who received systemic steroids showed a significantly lower incidence

of PES and reintubation than those with a failed CLT who did not receive steroid treatment (RR, 0.37; 95% CI, 0.24 to 0.57; $p < 0.0001$ and RR, 0.29; 95% CI, 0.15 to 0.56; $p = 0.0003$). However, the duration of intubation did not differ significantly between patients receiving systemic steroids, and those not receiving systemic steroids (MD, 0.91 day; 95% CI, -3.47 to 5.29; $p = 0.68$).

In summary, the present meta-analysis shows that the administration of systemic corticosteroids is associated with a reduced incidence of PES and reintubation in patients who fail the CLT. The 2017 American Thoracic Society/American College of Chest Physician guideline on weaning from mechanical ventilation recommends that for adult patients who have failed a CLT, but are nonetheless ready to be weaned from mechanical ventilation, steroids be administered for at least 4 hours before the extubation⁵. However, no protocol has been standardized for the dosage, timing, or methods of administering prophylactic steroids to patients with a failed CLT. Further research is needed on the use of steroids to prevent airway complications and reintubation after extubation in patients with absolute contraindications to steroids, such as a history of hypersensitivity reactions, live vaccine injections, systemic fungal infections, osteoporosis, or uncontrolled hyperglycemia. A barrier to steroid application is the lack of clarity and variation in high-risk-group screening methods, types of steroids used, dosages, usage, and administration duration, which all differ, depending on the country or institution. Multinational, multicenter studies are needed to remove this barrier. In conclusion, we recommend the administration of steroids at least 4 hours before extubation, to prevent PES and reintubation in adult patients who have failed a CLT.

KQ 5. RSBI

Question 5: Is computation of the RSBI recommended before extubating mechanically ventilated adult patients?

1) Recommendation

We suggest that the RSBI can be computed at the discretion of the clinician (recommendation B, conditional recommendation, low certainty in the evidence).

2) Values and preference

Evidence is insufficient to recommend routine measurement of the RSBI before extubation, to predict the successful liberation of mechanically ventilated adult patients.

3) Background

The RSBI is calculated as the ratio of respiratory frequency to tidal volume (f/VT), and is used during unassisted spontaneous respiration to assess readiness to wean from mechanical ventilation⁶⁹. The RSBI can predict the success or failure of weaning from mechanical ventilation⁷⁰. An RSBI of less than 105 f/VT is associated with an increased likelihood of successful weaning. Patients on a ventilator who cannot tolerate unassisted spontaneous breathing tend to have a high RSBI, with rapid breathing and low tidal volumes. However, the RSBI is affected by several factors, including agitation, anxiety, fever, endotracheal tube size, and suctioning. The literature for the utility of the RSBI is limited, and the studies that exist used different measurement methods, timing of measurement, settings at the time of measurement, and cut-off values.

4) Summary of evidence

No RCT has evaluated the utility of the RSBI. Among the 110 studies returned by our literature search, 22 were reviewed, and eight were included in the meta-analyses, of which seven were prospective, and one was retrospective^{69,71-77}. A prospective study conducted in 1995 by Epstein⁷⁸ reported that using an RSBI cut-off of 100, successful extubation could be predicted with a high positive predictive rate, low false negative rate, and high sensitivity. The largest multicenter study to date, Frutos-Vivar et al.⁷⁹, found that 121 (13.4%) of 900 patients who passed the SBT had extubation failure; they showed that a 1 unit increase in the RSBI increased the risk of extubation failure by 0.9%. However, the reference value of the RSBI has varied in different studies, and several studies have suggested values of 57 to 80 breaths per minute per liter that were much lower than the previously recommended value of 105 breaths per minute per liter^{71,73,75,77}. In four studies evaluating the predictive power of the RSBI for extubation failure, the area under the receiver operating characteristic curve ranged 0.63 to 0.92, indicating good to excellent predictive power^{72,73,75,77}. Segal et al.⁸⁰ compared the risk of extubation failure according to changes in the variation of RSBI values measured continuously for 2 hours, and reported that an increase in the RSBI of 20% or more was associated with extubation risk. Thus, the observed RSBI values have appeared to correlate with successful extubation in several studies. However, the different measurement methods, measurement timings, settings at the time of measurement, and cut-off values used in the various studies make it difficult to present a standard protocol. Recent research has proposed a new measure to replace the

RSBI, though it did not deny the clinical predictive value of the RSBI⁷⁷. Another method attempted to improve the predictive ability of the RSBI, without increasing the difficulty or complexity of the measurement. In conclusion, although results for a definitive RSBI value have been inconsistent among studies, the RSBI has been identified as a predictor of successful weaning from mechanical ventilation.

5) Panel judgments

While the evaluated studies show consistency in the usefulness of the RSBI, there are not many high-quality systematic reviews and meta-analyses, and the level of evidence was judged to be low. The presented studies agree that the RSBI is an excellent predictor of successful extubation, and report consistent results, but additional research is needed on the following two topics. First, it is necessary to demonstrate whether the previously suggested values of RSBI 100 or 105 breaths per minute per liter can be widely applied. Most of the literature referenced in this recommendation suggests lower values. Second, because the RSBI is known to have higher sensitivity than specificity, a reference value that can correct that deficiency is needed. An indicator that could be referenced together with the aforementioned optimal value of the RSBI would be very useful.

Because the RSBI is not a medical tool that provides additional tests, drugs, or treatments to the patient, if it is accurately measured and interpreted, it can cause no long-term harm to the patient, unlike other tests. However, it is difficult for inexperienced medical personnel to perform immediately, and when it is measured without training, the reliability of the results is lowered. In addition, if the measurement results are distorted, the patient's mechanical ventilation period could be increased unnecessarily, or reintubation could be required due to premature extubation, either of which could cause harm to the patient. Therefore, when measuring the RSBI and applying the result to clinical practice, careful attention is required.

Although the RSBI does not require expensive equipment or incur costs due to additional drug administration, it does require trained personnel. In particular, in secondary hospitals that do not have a dedicated ICU doctor, or do not work 24 hours per day, additional costs for education and personnel could be required. Therefore, because no standard value is available, it will be possible to apply the RSBI in the 1st and 2nd level medical institutions in Korea only after the insurance system is overhauled.

KQ 6. IMT

Question 6: Is IMT recommended for critically ill adult patients on mechanical ventilation?

1) Recommendation

We suggest that IMT for critically ill adult patients on mechanical ventilation is employed to increase the success rate of weaning from mechanical ventilation (recommendation B, conditional recommendation, low certainty in the evidence).

Remarks: IMT can be performed when the patient is hemodynamically stable, maintains adequate oxygen saturation ($\text{PaO}_2 \geq 60$ mg, $\text{FiO}_2 < 0.4$, PEEP 5–8 cmH_2O), and has an alert mental status, although the results differ across studies.

2) Values and preference

This recommendation places a high value on minimizing weaning failure rates, and increasing maximal inspiratory pressure.

3) Background

IMT, which is a form of pulmonary rehabilitation, is a technique to improve inspiratory muscle strength and respiratory muscle function. Respiratory muscle training results in structural adaptations, including changes in muscle fiber, hypertrophy, and muscle thickness, and functional adaptations, including enhancements in strength, power, endurance, peak inspiratory flow, and maximal inspiratory and expiratory pressures⁸¹. IMT can help reduce dyspnea by improving the maximal inspiratory pressure in patients with severe COPD⁷⁸.

Prolonged mechanical ventilation is known to impair respiratory muscle function, particularly the diaphragm; such weakening of the respiratory muscles is one of the important causes of failure to wean from mechanical ventilation⁸². The maximal inspiratory pressure is reported to predict the success of mechanical ventilation weaning^{79,83}.

4) Summary of evidence

Through our literature search strategy, we found 288 studies, after excluding duplicates. Of them, 288 studies were screened, and 57 articles were reviewed. We then selected five RCTs and one retrospective cohort study^{80,84-88}. In our meta-analysis, patients who received IMT showed a significantly lower unsuccessful weaning rate than those who did not receive IMT (RR, 0.61; 95% CI, 0.45 to 0.85; $p=0.003$). Patients receiving IMT had a trend toward a lower duration of mechanical ventilation and weaning time, but those differences were not sta-

tistically significant (MD, -16.07 days; 95% CI, -46.65 to 14.52; $p=0.30$ and MD, -9.65 hours; 95% CI, -25.42 to 6.13; $p=0.23$, respectively). Peak inspiratory pressure was significantly higher in patients receiving IMT than in those not receiving IMT (MD, -12.12 cmH₂O; 95% CI, -19.11 to -5.13; $p<0.001$).

In summary, the present meta-analysis shows that receiving IMT is associated with decreased weaning failure and increased peak inspiratory pressure, although the duration of mechanical ventilation and weaning time did not differ between patients receiving IMT and those not receiving IMT. IMT in mechanically ventilated patients could help maintain respiratory muscle function, potentially facilitating a smoother transition away from mechanical ventilation. A few studies have reported that a shorter duration of mechanical ventilation in patients receiving IMT was associated with an increased likelihood of being able to walk independently upon discharge from the hospital⁸⁹. Therefore, IMT contributes to a rapid return to independent daily activities and improved quality of life after ICU discharge, as well as reduced medical costs⁹⁰. Implementing IMT in clinical practice will require a respiratory rehabilitation protocol that is suitable for the Korean medical environment, and an adequate number of ICU nurses or respiratory therapists. However, as currently there is no standardized protocol regarding the devices and methods of IMT, further research is needed. In conclusion, we recommend IMT to increase the success rate of weaning from mechanical ventilation in critically ill adult patients.

KQ 7. Early rehabilitation

Question 7: Is early physical rehabilitation recommended for critically ill patients on mechanical ventilation?

1) Recommendation

We suggest the early rehabilitation of critically ill adult patients to increase the success rate of weaning from mechanical ventilation (recommendation B, conditional recommendation, low level of evidence).

Remarks: There are different types of early rehabilitation protocols, and they should be applied according to the patient's condition, eligibility, and goals.

2) Values and preference

This recommendation places a high value on reducing the ICU length of stay, and the duration of mechanical ventilation.

3) Background

Prolonged mechanical ventilation can lead to ventilator-induced diaphragmatic dysfunction due to diaphragm weakness and muscle wasting, and overall weakness due to a lack of physical activity or immobility; both of those conditions can cause failure to wean from mechanical ventilation⁹¹. Prolonged mechanical ventilation and weaning failure are the main risk factors for death in the ICU, and they also increase the burden of medical costs⁹². Early rehabilitation during critical care is beneficial in reducing the incidence of ICU-acquired weakness, accelerating patients' functional recovery, and increasing the likelihood of weaning from mechanical ventilation. Many clinicians have concerns and anxiety about the possibility that a patient's condition could deteriorate during rehabilitation, because of the hemodynamic instability common in critically ill patients. However, comprehensive early rehabilitation is known to be safe and effective in reducing the occurrence of complications and the duration of hospitalization and mechanical ventilation in ICU patients⁹³. Several guidelines recommend early rehabilitation in critically ill patients^{91,94,95}. In those guidelines, "early rehabilitation" includes any early mobilization program administered by a nurse, physical therapist, or intensivist.

4) Summary of evidence

Through our literature search strategy, we found 416 studies, excluding duplicates, of which 288 studies were screened, and 57 articles were reviewed. We identified five RCTs and two retrospective cohort studies that evaluated the effects of early rehabilitation⁹⁶⁻¹⁰². In our meta-analysis, patients in the RCTs who received early rehabilitation had a significantly shorter duration of mechanical ventilation than those who did not receive early rehabilitation (MD, -3.04 days; 95% CI, -4.98 to -1.10; $p=0.002$). A sensitivity analysis conducted with three RCTs showed similar results (MD, -2.07 days; 95% CI, -2.92 to -1.22; $p<0.001$), and the retrospective cohort studies also showed similar results (MD, -2.29 days; 95% CI, -3.94 to -0.63; $p<0.01$). In addition, the RCTs showed a significantly shorter ICU length of stay in patients who received early rehabilitation (MD, -3.42 days; 95% CI, -6.31 to -0.53; $p=0.02$), and the sensitivity analysis conducted with three RCTs confirmed that result (MD, -2.18 days; 95% CI, -3.69 to -0.67; $p<0.001$). However, in the retrospective cohort studies, there was no significant difference between the groups (MD, 0.16 day; 95% CI, -6.49 to 6.81; $p=0.96$). No RCT reported results of unsuccessful weaning, but the retrospective cohort studies reported

significant differences between the groups (RR, 0.69; 95% CI, 0.48 to 0.99; $p=0.04$).

In summary, the present meta-analysis shows that early rehabilitation is associated with a decreased duration of mechanical ventilation (2.29 days) and length of ICU stay (3.42 days). Past ICU treatment has focused on treating acute critical illness while sedating and restraining ICU patients. Several studies have reported that rehabilitation in the ICU strengthens muscles of the limbs and respiration, encourages the recovery of physical and mental function, reduces the incidence of ICU-acquired weakness, and improves the quality of life after discharge⁹³. Rehabilitation can be safely performed in the ICU, even in critically ill patients receiving extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy (CRRT)^{103,104}. Safe implementation of early rehabilitation in patients with a variety of devices, including a ventilator, central catheter, CRRT, and ECMO, requires a comprehensive and multidisciplinary approach, and efficiency can be maximized and safety secured only through cooperation between physicians, nurses, and physical therapists. A collaborative effort from a multidisciplinary team is required to tailor interventions to each individual patient's needs and conditions. Therefore, implementing early rehabilitation for critically ill patients could be difficult, depending on the size of the hospital, the composition of the medical staff, and the severity of the patient's condition. In conclusion, we recommend early rehabilitation in critically ill adult patients on mechanical ventilation.

KQ 8. HFNC vs. NIV vs. COT

Question 8-1: Is a HFNC recommended over COT for adult patients undergoing planned extubation?

Question 8-2: Is NIV recommended over COT for adult patients undergoing planned extubation?

Question 8-3: Is HFNC recommended over NIV for adult patients undergoing planned extubation?

1) Recommendations

8-1. For successful weaning from mechanical ventilation, we recommend HFNC over COT in adult patients undergoing planned extubation (recommendation B, conditional recommendation, moderate certainty in the evidence).

Remarks: Patients at high-risk of post-extubation respiratory failure include those with chronic respiratory failure, hypercapnia ($\text{PaCO}_2 >45$ mm Hg) after successful SBT, failed first SBT, and chronic respiratory disorders.

8-2. For successful weaning from mechanical ventilation, we recommend NIV over COT in adult patients undergoing planned extubation who are at high-risk of weaning failure (recommendation B, conditional recommendation, moderate certainty in the evidence).

Remarks: Factors that increase the risk of weaning failure include a failed first SBT, old age (>65 years), body mass index (BMI) >30 kg/m^2 , ejection fraction $<40\%$, history of extubation failure, mechanical ventilation for heart failure, presence of COPD, Acute Physiology And Chronic Health Evaluation (APACHE) II score >12 , airway disorder (e.g., high-risk for laryngeal edema), impaired expectoration, comorbidities ≥ 2 , delayed or failed weaning from mechanical ventilation, and duration of mechanical ventilation ≥ 7 days.

8-3. We suggest that for adult patients undergoing planned extubation, either HFNC or NIV can be applied at the discretion of the clinician (recommendation E, expert consensus recommendation, very low certainty in the evidence).

Clinical considerations: Healthcare professionals in South Korea are more experienced with HFNC than NIV, which is different from that in Europe or in China, and HFNC might be the better choice for high-risk patients in terms of patient comfort and potential skin damage. However, NIV might be more useful for patients with respiratory failure and hypercapnia caused by the acute exacerbation of COPD, or patients with pulmonary edema. In particular for high-risk patients, the method of oxygen therapy following ventilator weaning should be chosen according to the healthcare provider's experience level, experiences in the ICU, the patient's adaptation, and patient-specific considerations (e.g., claustrophobia).

Remarks: Given the side effects of NIV, such as facial skin damage, abdominal discomfort, mask-related discomfort, eye irritation, mouth dryness, nasal congestion, and NIV intolerance, the purpose, benefits, and discomfort associated with NIV should be explained to the patient before NIV application, and treatment decisions should be made accordingly.

2) Values and preference

These recommendations place a high value on minimizing respiratory failure after extubation and reintubation through the application of HFNC. NIV might produce similar results to the HFNC, but only in high-risk patients, not all patients. Evidence is insufficient to recommend HFNC or NIV after extubation to reduce hospital mortality, ICU mortality, or ICU and hospital lengths of stay. HFNC and NIV do not differ in ICU or 28-days mortality and reintubation. However, HFNC

is preferred over NIV in terms of patient comfort, the need for bronchoscopy for sputum removal, and the side effects of NIV.

3) Background

The final step of weaning from mechanical ventilation is extubation, and this critical step determines the success or failure of weaning. The functional residual capacity maintained using PEEP during invasive ventilation can drop rapidly, and lead to hypoxemia and extubation failure, defined as the need for reintubation within 24 to 72 hours after planned extubation. Extubation failure occurs relatively frequently, at a rate of 10% to 20%, and is associated with a longer overall duration of mechanical ventilation, higher risk for tracheostomy, increased healthcare costs, and higher mortality rate¹⁰⁵⁻¹⁰⁹.

One of the most important factors in the prevention of reintubation is the choice of oxygen delivery system. COT uses a nasal cannula and oxygen mask. At a flow rate of 15 L/min, conventional oxygen delivery systems might be inappropriate for patients requiring rapid respiration and a high inspiratory flow rate. HFNC is a device that provides a high-flow of warm and humidified oxygen, with a flow rate of up to 60 L/min, through a nasal cannula. It can generate PEEP, reduce CO₂ through a dead space washout, reduce the work of breathing, improve oxygenation, and comfort patients with respiratory failure¹¹⁰. The effects of HFNC in patients undergoing planned extubation remain unknown. A few studies have demonstrated that HFNC after extubation reduces the requirement for respiratory support escalation, improves oxygenation, or is associated with better comfort and a lower reintubation rate than COT^{107,111,112}. Corley et al.¹¹³ found no improvement in respiratory function in patients with BMI ≥ 30 kg/m² who underwent HFNC after planned extubation. NIV is a type of respiratory support that is delivered through a mask or helmet, but without an invasive artificial airway, such as intubation or tracheostomy. NIV has two primary types: continuous positive airway pressure, and bilevel positive airway pressure (also called PSV). NIV can improve oxygenation and comfort for patients with respiratory failure, and decrease the need for invasive ventilation and its complications. Thus, NIV is recommended for patients with respiratory failure, in particular patients with hypercapnia and COPD exacerbation, and patients with acute cardiogenic pulmonary edema¹¹⁴. Although NIV is more effective than COT in patients at high-risk of extubation failure, there is a lack of consensus regarding the superiority of high flow oxygen therapy (HFOT) or NIV for successful weaning and extubation.

Therefore, we performed a systematic review and meta-analysis to compare the benefits of COT, HFNC, and NIV as prophylactic treatments intended to promote successful weaning from mechanical ventilation in patients undergoing planned extubation.

4) Summary of evidence

Among the 1,559 studies returned by the literature search, 144 were reviewed, and 28 were included in the meta-analyses. Of these, 11 were RCTs comparing the effects of HFNC and COT in patients undergoing planned extubation^{105-109,115-120}, 12 were RCTs comparing outcomes between NIV and COT in patients undergoing planned extubation^{113,114,121-131}, and five were RCTs comparing the outcomes and adverse effects of HFNC and NIV in patients undergoing planned extubation¹³²⁻¹³⁶.

(1) HFNC vs. COT: In our meta-analysis, patients who received HFNC showed a significantly lower incidence of weaning failure and reintubation after planned extubation, than those who received COT (RR, 0.49; 95% CI, 0.39 to 0.61; $p < 0.001$ and RR, 0.47; 95% CI, 0.29 to 0.76; $p = 0.002$, respectively). The subgroup analyses of patients at high-risk of post-extubation respiratory failure, i.e., those with chronic respiratory failure; hypercapnia (PaCO₂ >45 mm Hg) after successful SBT; a failed first SBT; and COPD, chronic bronchitis with dyspnea, smoking history, bronchiectasis, tuberculosis sequelae, chest wall deformity, or restrictive ventilatory defect, returned similar results for weaning failure (RR, 0.45; 95% CI, 0.34 to 0.61; $p < 0.001$), but HFNC and COT did not differ in reintubation (RR, 0.76; 95% CI, 0.28 to 2.07; $p = 0.60$). Nor did hospital and ICU mortality differ significantly between the groups (RR, 0.90; 95% CI, 0.52 to 1.54; $p = 0.70$ and RR, 1.14; 95% CI, 0.31 to 4.17; $p = 0.84$, respectively). Ventilator-associated pneumonia showed similar results (RR, 0.53; 95% CI, 0.23 to 1.25; $p = 0.15$). No significant differences in ICU and hospital lengths of stay were observed between the groups, regardless of patients' risk status (MD, 0.10 day; 95% CI, -0.03 to 0.23; $p = 0.13$ and MD, -0.29 day; 95% CI, -1.03 to 0.45; $p = 0.44$, respectively).

(2) NIV vs. COT: The high-risk factors for post-extubation respiratory failure identified in these studies were: (1) chronic respiratory failure; (2) hypercapnia after successful SBT (PaCO₂ >45 mm Hg); (3) failed first SBT; (4) chronic respiratory disorders (e.g., COPD, chronic bronchitis with dyspnea, smoking history, bronchiectasis, tuberculosis sequelae, chest wall deformity, and restrictive ventilatory defect); (5) excessive phlegm and diminished coughing; (6) upper airway stridor after extubation; (7) age ≥ 65 years; (8) heart failure as the

reason for mechanical ventilation; and (9) APACHE II score >12 on the day of extubation. In this meta-analysis, NIV was not significantly more effective in the total patient population in terms of weaning failure and reintubation (RR, 0.26; 95% CI, 0.04 to 1.76; $p=0.17$ and RR, 0.47; 95% CI, 0.14 to 1.60; $p=0.23$, respectively). Only high-risk patients who received NIV had a significantly lower incidence of weaning failure and reintubation after planned extubation, compared with those who received COT (RR, 0.30; 95% CI, 0.18 to 0.51; $p<0.001$ and RR, 0.63; 95% CI, 0.44 to 0.90; $p=0.01$, respectively). ICU and in-hospital mortality did not differ significantly between the groups, regardless of the level of risk (RR, 0.66; 95% CI, 0.35 to 1.25; $p=0.67$ and RR, 0.77; 95% CI, 0.43 to 1.39; $p=0.37$, respectively). Patients who received NIV showed a trend toward lower ICU mortality, but the difference was not statistically significant (MD, -2.17 days; 95% CI, -4.86 to 0.52; $p=0.06$). No significant differences in-hospital length of stay or hospital length of stay after extubation were observed between the groups (MD, -1.03 day; 95% CI, -3.45 to 1.39; $p=1.00$ and MD, -3.04 days; 95% CI, -9.51 to 3.43; $p=0.11$, respectively).

(3) HFNC vs. NIV: None of these studies included only adult patients who received mechanical ventilation, and all five studies included patients with underlying diseases or conditions that could pose a risk of weaning failure. HFNC and NIV did not differ in 28-day or ICU mortality (RR, 0.94; 95% CI, 0.42 to 2.09; $p=0.33$ and RR, 1.19; 95% CI, 0.79 to 1.78; $p=0.40$, respectively). In addition, reintubation and treatment failure (switch to another treatment or premature discontinuation) did not differ significantly between HFNC and NIV (RR, 0.98; 95% CI, 0.79 to 1.23; $p=0.89$ and RR, 1.04; 95% CI, 0.86 to 1.25; $p=0.72$, respectively). Patients who received HFNC had a significantly lower incidence of skin damage within 24 to 48 hours (RR, 0.50; 95% CI, 0.30 to 0.81; $p=0.005$).

In summary, the present meta-analysis shows that among all patients, not just high-risk patients, receiving HFNC is associated with a lower incidence of weaning failure and reintubation after planned extubation, compared with COT. Meanwhile, NIV shows a significant reduction in weaning failure and reintubation after planned extubation, compared with COT, only in high-risk patients. However, the outcomes did not differ significantly between HFNC and NIV, except for skin damage.

HFNC has become essential equipment in the ICU, and has been covered by health insurance in Korea since its designation as a new health technology in 2015. Compared with COT, HFOT has a significant

advantage, not only in successful ventilator weaning and the prevention of reintubation, but also in reducing patient discomfort, such as dry airways and nasal pain, by providing humidification through the HFNC. Three studies reported cases of nasal pain, dry airways, and consequent patient discomfort due to low humidity; however, the prevalence of such cases was significantly lower in the HFNC group than in the COT group in all studies^{106,107,117}.

Although among all patients, NIV was not effective in reducing weaning failure and reintubation, in high-risk patients it showed significantly better outcomes than COT. NIV has various adverse effects that include facial skin damage, abdominal discomfort, mask-related discomfort, eye irritation, and NIV intolerance. Regarding skin damage, three studies reported skin redness or abrasion in 14 of 48 (29%), five of 79 (6%), and two of 20 (10%) patients on NIV, respectively^{113,121,130}. Two studies reported abdominal distention in one of 79 patients (1%) and five of 69 patients (7%), respectively^{121,122}. Other symptoms, including eye irritation, oral dryness, and nasal congestion and mask intolerance, were reported in 7% of patients^{121,123}. No study has investigated subjective preferences between NIV and COT among patients with respiratory failure undergoing planned ventilator weaning. Given the outcomes and side effects of NIV, it is not an ideal treatment for all patients; nevertheless, NIV can be considered an appropriate method for patients undergoing planned extubation who are at high-risk of weaning failure. Prior to NIV application, the purpose, benefits, and discomfort associated with NIV should be explained to the patient, and treatment decisions should be made accordingly.

Except for the skin damage associated with NIV, the outcomes of mortality, reintubation, and treatment failure did not differ between HFNC and NIV in patients undergoing planned extubation. To date, no study has investigated patients' values or preferences between HFNC and NIV, but the dyspnea score did not differ between the two methods in the included studies^{132,135}. However, the comfort score increased over time with HFNC, unlike with NIV, while the need for bronchoscopy for sputum removal after extubation was significantly lower with HFNC than NIV¹³⁴. In addition, HFNC is associated with less frequent abdominal distension and higher treatment tolerance^{135,136}. Notably, HFNC can be perceived as a form of oxygen therapy, whereas NIV can be perceived as a form of mechanical ventilation. Because some patients or families have reservations about mechanical ventilation, it is important to adequately explain the effectiveness, purpose, type, and expected outcomes of each treatment, and obtain-

ing informed consent from patients and their families is important.

The recent European Respiratory Society (ERS) clinical guidelines on respiratory failure suggest using either HFNC or NIV in postoperative patients who are at high-risk of respiratory complications, but they suggest using NIV rather than HFNC in non-surgical patients at high-risk of weaning failure, provided there are no absolute or relative contraindications¹³⁷. Although the ERS guidelines, which considered HFNC to have a higher reintubation rate than NIV, were based more on preventing reintubation than on patient discomfort, our meta-analysis suggests that either HFNC or NIV can be applied at the discretion of the clinician in adult patients undergoing planned extubation.

KQ 9. Early tracheostomy

Question 9: Should an early tracheostomy be performed to successfully wean adult patients from mechanical ventilation?

1) Recommendation

We recommend that early tracheostomy not be performed for patients expected to require prolonged mechanical ventilation (recommendation I, conditional deferred, low certainty in the evidence).

Remarks: Early tracheostomy is defined as a surgical procedure performed no more than 7 days after endotracheal intubation in a patient requiring prolonged mechanical ventilation.

2) Values and preference

This recommendation regarding the value of early tracheostomy, which has been associated with improved survival and reduced ventilator and ICU-related complications, remains controversial.

3) Background

Tracheostomy is a surgical procedure that is frequently performed in ICU patients requiring airway protection or prolonged ventilatory support due to airway narrowing or obstruction, difficulty removing excess sputum or saliva, altered level of consciousness, or persistent respiratory failure¹³⁸. Tracheostomy has been performed in a variety of clinical situations, with percutaneous techniques becoming increasingly popular in recent years. Early tracheostomy in patients requiring prolonged mechanical ventilation might have benefits, such as reducing the work of breathing, reducing sedation requirements, and decreasing the risk of pneumonia¹³⁹⁻¹⁴¹. However, early tracheostomy carries its own

risks, including bleeding, infection, tube dislodgement, and laryngeal injury¹⁴². No optimal timing for the transition to tracheostomy has been established, and practice varies among clinicians, with most transitioning between 1 and 3 weeks after intubation¹⁴³. No benefits for early tracheostomy (i.e., before 10 days after intubation) have been demonstrated, and it carries the potential of unnecessary surgery in patients who could be extubated.

4) Summary of evidence

Through our literature search strategy, we found 941 studies, excluding duplicates, of which 291 studies were screened, and 106 articles were reviewed. We identified seven RCTs evaluating the effects of early tracheostomy in mechanically ventilated adults admitted to an ICU¹⁴⁴⁻¹⁵⁰. In Rumbak et al.'s study¹⁵¹, tracheostomy was performed within 48 hours, whereas in studies by Bosel et al.¹⁵² and Zheng et al.¹⁵³, tracheostomy was performed within 1–3 days and at 3 days, respectively. In studies by Blot et al.¹⁵⁴, Trouillet et al.¹⁵⁵, and Young et al.¹⁵⁶, tracheostomy was performed at 4 days. In Barquist et al.'s study¹⁵⁷, tracheostomy was performed at 8 days. In our meta-analysis, the duration of mechanical ventilation and the length of ICU stay in the early tracheostomy group (tracheostomy performed within 7 days) were 3.2 and 5.8 days shorter, respectively, than with usual care. However, those differences were not statistically significant (MD, -3.16 days; 95% CI, -11.47 to 5.15; $p=0.10$ and MD, -5.80 days; 95% CI, -12.80 to 1.20; $p=0.10$, respectively). Patients who received an early tracheostomy had 14% less in-hospital mortality than those who received usual care, but that difference was not statistically significant (RR, 0.86; 95% CI, 0.74 to 1.01; $p=0.07$).

In summary, the present meta-analysis shows no statistically significant differences between early tracheostomy and usual care in terms of the duration of mechanical ventilation, ICU length of stay, or in-hospital mortality. Seven selected articles had limitations, in that they varied in study design, target disease, and when and how tracheostomy was performed (especially whether percutaneous tracheostomy was performed). In addition, we were unable to identify sufficient information regarding serious adverse events for analysis, so we had to reserve the assessment of safety issues. Guidelines for tracheostomy from the Korean Bronchoesophagological Society, published in Korea in 2020, recommend early 7 to 14 days tracheostomy in patients who are predicted to need a ventilator for a long period of time (weak recommendation, low evidence), but they note that judgment based on the

patient's condition is important¹⁵⁸. The 2017 Guideline on Tracheostomy in Critically Ill Patients does not recommend early tracheostomy, because although it could reduce ventilator duration, it does not reduce the incidence of pneumonia or ICU length of stay or mortality¹⁵¹. Future large RCTs in specific disease groups or with percutaneous tracheostomy are needed, and we look forward to a further analysis of studies conducted in those conditions.

Summary

We have conditionally recommended the following in these guidelines: Apply a weaning protocol to increase the success rate of liberation from mechanical ventilation, and allow both PSV and T-piece trials during spontaneous breathing attempts in adult patients undergoing mechanical ventilation, including high-risk patients. For patients at high-risk of PES, perform a CLT (if appropriate under clinical judgment), before extubation. In patients who fail the CLT, administer steroids before extubation to prevent PES and the need for reintubation. When planning liberation from mechanical ventilation for adult patients, clinical judgment should be used in deciding whether to implement the RSBI, IMT, and early rehabilitation. Additionally, we suggest that using HFNC or NIV as post-extubation oxygen therapy is more advantageous than COT to prevent reintubation. When choosing between HFNC and NIV post-extubation, the expert consensus is that the choice can be made based on the clinician's judgment of patient condition and preferences. As for the effects of early tracheostomy (within 7 days) on the success of liberation from mechanical ventilation, we conditionally recommend that it not be performed. Much work remains to be done to improve the process of liberation from mechanical ventilation, and our guidelines will undergo revision based on future research findings.

Authors' Contributions

Conceptualization: Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS, Hong SK, Park S, Suh GY, Park SY. Methodology: Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS, Hong SK, Park S, Suh GY, Park SY. Formal analysis: Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS, Hong SK, Park S, Suh GY, Park SY. Data curation: Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS. Funding acquisition: Hong SK. Project administration: Hong SK, Park S, Suh GY, Park SY. Visualization: Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS. Software: Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS, Park SY. Valida-

tion: Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS, Park SY. Investigation: Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS, Park SY. Writing - original draft preparation: Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS, Park SY. Writing - review and editing: Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS, Park S, Park SY. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Material

Supplementary material can be found in the journal homepage (<http://www.e-trd.org>).

Supplementary Table S1. GRADE summary of finding table: KQ 1. In critically ill patients who ventilated, dose applying mechanical ventilation weaning protocol increase the success rate of ventilator weaning?

Supplementary Table S2. GRADE summary of finding table: KQ 2-1. Is PSV recommended over the T-piece during spontaneous breathing trial in adult patients receiving mechanical ventilation?

Supplementary Table S3. GRADE summary of finding table: KQ 2-2. Is PSV recommended over the T-piece during spontaneous breathing trial in adult patients at high-risk of extubation failure?

Supplementary Table S4. GRADE summary of finding table: KQ 3. Is a cuff leak test recommended before extubation of mechanically ventilated patients?

Supplementary Table S5. GRADE summary of finding table: KQ 4. Is steroids recommended before extubation in mechanically ventilated patients with a failed cuff leak test?

Supplementary Table S6. GRADE summary of finding table: KQ 5. Is it recommended to compute the RSBI before extubating mechanically ventilated adult patients?

Supplementary Table S7. GRADE summary of finding table: KQ 6. Is IMT recommended for critically ill adult patients on mechanical ventilation?

Supplementary Table S8. GRADE summary of finding

table: KQ 7. Is early physical rehabilitation recommended for critically ill patients on mechanical ventilation?

Supplementary Table S9. GRADE summary of finding table: KQ 8-1. Is a HFNC recommended over COT for adult patients undergoing planned extubation?

Supplementary Table S10. GRADE summary of finding table: KQ 8-2. Is NIV recommended over conventional oxygen therapy for adult patients undergoing planned extubation?

Supplementary Table S11. GRADE summary of finding table: KQ 8-3. Is HFNC recommended over NIV for successful weaning in adult patients undergoing planned extubation?

Supplementary Table S12. GRADE summary of finding table: KQ 9. Is early tracheostomy be performed for successful weaning from mechanical ventilation in adult patients?

Supplementary Figure S1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Question 1: In critically ill patients receiving ventilation, does a mechanical ventilation weaning protocol increase the success rate of ventilator liberation?

Supplementary Figure S2. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Question 2-1: Is pressure support ventilation (PSV) recommended over the T-piece during spontaneous breathing trial (SBT) in adult patients receiving mechanical ventilation? Question 2-2: Is PSV recommended over the T-piece during SBT in adult patients at high-risk of extubation failure?

Supplementary Figure S3. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Question 3: Is a cuff leak test recommended before extubation of mechanically ventilated patients?

Supplementary Figure S4. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Question 4: Are steroids recommended before extubation in mechanically ventilated patients with a failed cuff leak test?

Supplementary Figure S5. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Question 5: Is it recommended to compute the rapid shallow breathing index before extubating mechanically ventilated adult patients?

Supplementary Figure S6. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Question 6: Is inspiratory muscle training recommended for critically ill adult patients on mechanical ventilation?

Supplementary Figure S7. Preferred Reporting Items

for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Question 7: Is early physical rehabilitation recommended for critically ill patients on mechanical ventilation?

Supplementary Figure S8. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Question 8-1: Is a high-flow nasal cannula (HFNC) recommended over conventional oxygen therapy (COT) for adult patients undergoing planned extubation? Question 8-2: Is non-invasive ventilation (NIV) recommended over COT for adult patients undergoing planned extubation? Question 8-3: Is HFNC recommended over NIV for adult patients undergoing planned extubation?

Supplementary Figure S9. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Question 9: Should an early tracheostomy be performed to successfully wean adult patients from mechanical ventilation?

Supplementary Figure S10. Risk of bias. Question 1: In critically ill patients receiving ventilation, does a mechanical ventilation weaning protocol increase the success rate of ventilator liberation?

Supplementary Figure S11. Risk of bias. (A) Question 2-1: Is pressure support ventilation (PSV) recommended over the T-piece during spontaneous breathing trial (SBT) in adult patients receiving mechanical ventilation? (B) Question 2-2: Is PSV recommended over the T-piece during SBT in adult patients at high-risk of extubation failure?

Supplementary Figure S12. Risk of bias. Question 3: Is a cuff leak test recommended before extubation of mechanically ventilated patients?

Supplementary Figure S13. Risk of bias. Question 4: Are steroids recommended before extubation in mechanically ventilated patients with a failed cuff leak test?

Supplementary Figure S14. Risk of bias. Question 5: Is it recommended to compute the rapid shallow breathing index before extubating mechanically ventilated adult patients?

Supplementary Figure S15. Risk of bias. Question 6: Is inspiratory muscle training recommended for critically ill adult patients on mechanical ventilation?

Supplementary Figure S16. Risk of bias. Question 7: Is early physical rehabilitation recommended for critically ill patients on mechanical ventilation?

Supplementary Figure S17. Risk of bias. (A) Question 8-1: Is a high-flow nasal cannula (HFNC) recommended over conventional oxygen therapy (COT) for adult patients undergoing planned extubation? (B) Question 8-2: Is non-invasive ventilation (NIV) recommended

over COT for adult patients undergoing planned extubation? (C) Question 8-3: Is HFNC recommended over NIV for adult patients undergoing planned extubation?

Supplementary Figure S18. Risk of bias. Question 9: Should an early tracheostomy be performed to successfully wean adult patients from mechanical ventilation?

Supplementary Figure S19. Forest plot. Question 1: In critically ill patients receiving ventilation, does a mechanical ventilation weaning protocol increase the success rate of ventilator liberation? Randomized control studies and non-randomized control studies of (A) weaning failure, (B) mechanical ventilation duration, (C) weaning time, (D) ventilation associated pneumonia incidence, (E) intensive care unit (ICU) length of stay, and (F) ICU mortality.

Supplementary Figure S20. Forest plot. (A) Question 2-1: Is pressure support ventilation (PSV) recommended over the T-piece during spontaneous breathing trial (SBT) in adult patients receiving mechanical ventilation? (a) Successful extubation/liberation from mechanical ventilation, (b) reintubation, and (c) length of intensive care unit (ICU) days. (B) Question 2-2: Is PSV recommended over the T-piece during SBT in adult patients at high-risk of extubation failure? (a) Successful extubation/liberation from mechanical ventilation, (b) reintubation, (c) hospital mortality, (d) ICU mortality, and (e) ICU length of stay.

Supplementary Figure S21. Forest plot. Question 3: Is a cuff leak test (CLT) recommended before extubation of mechanically ventilated patients? (A) CLT for the prediction of post-extubation stridor and (B) CLT for the prediction of reintubation.

Supplementary Figure S22. Forest plot. Question 4: Are steroids recommended before extubation in mechanically ventilated patients with a failed cuff leak test? (A) Post-extubation stridor (PES), (B) reintubation, and (C) duration of intubation.

Supplementary Figure S23. Forest plot. Question 5: Is it recommended to compute the rapid shallow breathing index before extubating mechanically ventilated adult patients?

Supplementary Figure S24. Forest plot. Question 6: Is inspiratory muscle training (IMT) recommended for critically ill adult patients on mechanical ventilation? (A) Unsuccessful weaning, (B) mechanical ventilation (MV) duration (days), (C) weaning time (hours), and (D) maximal peak inspiratory pressure (PIMax) change.

Supplementary Figure S25. Forest plot. Question 7: Is early physical rehabilitation recommended for critically ill patients on mechanical ventilation? Randomized controlled trials (RCTs) and non-RCTs of (A) intensive

care unit (ICU) length of stay (days), (B) mechanical ventilation duration, and (C) unsuccessful weaning.

Supplementary Figure S26. Forest plot. (A) Question 8-1: Is a high-flow nasal cannula (HFNC) recommended over conventional oxygen therapy (COT) for adult patients undergoing planned extubation? Randomized controlled trials (RCTs) and non-RCTs of (a) treatment failure, (b) reintubation, (c) hospital mortality, (d) intensive care unit (ICU) mortality, (e) ventilator-associated pneumonia (VAP), (f) intensive care unit length of stay, and (g) hospital length of stay. (B) Question 8-2: Is non-invasive ventilation (NIV) recommended over COT for adult patients undergoing planned extubation? (a) Respiratory failure after extubation, (b) reintubation, (c) ICU mortality, (d) hospital mortality, (e) ICU length of stay, (f) hospital length of stay, and (g) hospital length of stay after extubation. (C) Question 8-3: Is HFNC recommended over NIV for adult patients undergoing planned extubation? (a) Mortality (28-day or ICU), (b) reintubation, (c) treatment failure reintubation, switch to other treatment or premature discontinuation, and (d) skin damage.

Supplementary Figure S27. Forest plot. Question 9: Should an early tracheostomy be performed to successfully wean adult patients from mechanical ventilation? (A) Duration of mechanical ventilation (day), (B) intensive care unit (ICU) length of stay (day), and (C) hospital mortality.

References

- Girard TD, Burns KE. Revisiting, reframing, and casting a new light on liberation from mechanical ventilation. *JAMA* 2019;321:2167-9.
- Wunsch H, Wagner J, Herlim M, Chong DH, Kramer AA, Halpern SD. ICU occupancy and mechanical ventilator use in the United States. *Crit Care Med* 2013;41:2712-9.
- Huang HY, Huang CY, Li LF. Prolonged mechanical ventilation: outcomes and management. *J Clin Med* 2022; 11:2451.
- Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002;287:345-55.
- Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011;39:2612-8.
- Hall JB, Wood LD. Liberation of the patient from mechanical ventilation. *JAMA* 1987;257:1621-8.
- Girard TD, Alhazzani W, Kress JP, Ouellette DR, Schmidt GA, Truweit JD, et al. An official American Thoracic Soci-

- ety/American College of Chest Physicians Clinical Practice Guideline: liberation from mechanical ventilation in critically ill adults. rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. *Am J Respir Crit Care Med* 2017;195:120-33.
8. Schonhofer B, Geiseler J, Dellweg D, Fuchs H, Moerer O, Weber-Carstens S, et al. Prolonged weaning: S2k guideline published by the German Respiratory Society. *Respiration* 2021;99:982-1084.
 9. Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. *Thorax* 2016;71 Suppl 2:ii1-35.
 10. Suh KW, Lee HK, Jeong SH, Choi IS, Suh GY, Son JW, et al. 2010 Guidelines for weaning and discontinuing ventilatory support. Seoul: Korean Society of Critical Care Medicine; 2010.
 11. Marra A, Ely EW, Pandharipande PP, Patel MB. The ABCDEF bundle in critical care. *Crit Care Clin* 2017;33:225-43.
 12. Thille AW, Gacouin A, Coudroy R, Ehrmann S, Quenot JP, Nay MA, et al. Spontaneous-breathing trials with pressure-support ventilation or a T-piece. *N Engl J Med* 2022;387:1843-54.
 13. Blackwood B, Alderdice F, Burns KE, Cardwell CR, Lavery G, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. *Cochrane Database Syst Rev* 2010;5:CD006904.
 14. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126-34.
 15. Bumroongkit C, Liwsrisakun C, Deesomchok A, Theerakittikul T, Pothirat C. Efficacy of weaning protocol in medical intensive care unit of tertiary care center. *J Med Assoc Thai* 2005;88:52-7.
 16. Chaiwat O, Sarima N, Niyompanitpattana K, Komoltri C, Udomphorn Y, Kongsayreepong S. Protocol-directed vs. physician-directed weaning from ventilator in intra-abdominal surgical patients. *J Med Assoc Thai* 2010;93:930-6.
 17. Danckers M, Grosu H, Jean R, Cruz RB, Fidellaga A, Han Q, et al. Nurse-driven, protocol-directed weaning from mechanical ventilation improves clinical outcomes and is well accepted by intensive care unit physicians. *J Crit Care* 2013;28:433-41.
 18. Dries DJ, McGonigal MD, Malian MS, Bor BJ, Sullivan C. Protocol-driven ventilator weaning reduces use of mechanical ventilation, rate of early reintubation, and ventilator-associated pneumonia. *J Trauma* 2004;56:943-52.
 19. Fan L, Su Y, Elmadhoun OA, Zhang Y, Zhang Y, Gao D, et al. Protocol-directed weaning from mechanical ventilation in neurological patients: a randomised controlled trial and subgroup analyses based on consciousness. *Neurol Res* 2015;37:1006-14.
 20. Gunther I, Pradhan D, Lubinsky A, Urquhart A, Thompson JA, Reynolds S. Use of a multidisciplinary mechanical ventilation weaning protocol to improve patient outcomes and empower staff in a medical intensive care unit. *Dimens Crit Care Nurs* 2021;40:67-74.
 21. Krishnan JA, Moore D, Robeson C, Rand CS, Fessler HE. A prospective, controlled trial of a protocol-based strategy to discontinue mechanical ventilation. *Am J Respir Crit Care Med* 2004;169:673-8.
 22. Marelich GP, Murin S, Battistella F, Inciardi J, Vierra T, Roby M. Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia. *Chest* 2000;118:459-67.
 23. Piotto RF, Maia LN, Machado MN, Orrico SP. Effects of the use of mechanical ventilation weaning protocol in the coronary care unit: randomized study. *Rev Bras Cir Cardiovasc* 2011;26:213-21.
 24. Roh JH, Synn A, Lim CM, Suh HJ, Hong SB, Huh JW, et al. A weaning protocol administered by critical care nurses for the weaning of patients from mechanical ventilation. *J Crit Care* 2012;27:549-55.
 25. Saura P, Blanch L, Mestre J, Valles J, Artigas A, Fernandez R. Clinical consequences of the implementation of a weaning protocol. *Intensive Care Med* 1996;22:1052-6.
 26. Lim SY, Suh GY, Kyung SY, An CH, Lee SP, Park JW, et al. Risk factors of extubation failure and analysis of cuff leak test as a predictor for postextubation stridor. *Tuberc Respir Dis* 2006;61:34-40.
 27. Shin SH, Heath K, Reed S, Collins J, Weireter LJ, Britt LD. The cuff leak test is not predictive of successful extubation. *Am Surg* 2008;74:1182-5.
 28. Sukhpanyarak S. Risk factors evaluation and the cuff leak test as predictors for postextubation stridor. *J Med Assoc Thai* 2008;91:648-53.
 29. Antonaglia V, Vergolini A, Pascotto S, Bonini P, Renco M, Peratoner A, et al. Cuff-leak test predicts the severity of postextubation acute laryngeal lesions: a preliminary study. *Eur J Anaesthesiol* 2010;27:534-41.
 30. Gros A, Holzapfel L, Marque S, Perard L, Demingeon G, Piralla B, et al. Intra-individual variation of the cuff-leak test as a predictor of post-extubation stridor. *Respir Care* 2012;57:2026-31.
 31. Keeratichananont W, Limthong T, Keeratichananont S.

- Cuff leak volume as a clinical predictor for identifying post-extubation stridor. *J Med Assoc Thai* 2012;95:752-5.
32. Sutherasan Y, Theerawit P, Hongphanut T, Kiatboonsri C, Kiatboonsri S. Predicting laryngeal edema in intubated patients by portable intensive care unit ultrasound. *J Crit Care* 2013;28:675-80.
 33. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. *Am J Respir Crit Care Med* 2000;161:1530-6.
 34. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112:186-92.
 35. Frutos-Vivar F, Esteban A, Apezteguia C, Gonzalez M, Arabi Y, Restrepo MI, et al. Outcome of reintubated patients after scheduled extubation. *J Crit Care* 2011;26:502-9.
 36. Gao F, Yang LH, He HR, Ma XC, Lu J, Zhai YJ, et al. The effect of reintubation on ventilator-associated pneumonia and mortality among mechanically ventilated patients with intubation: a systematic review and meta-analysis. *Heart Lung* 2016;45:363-71.
 37. Schmidt GA, Girard TD, Kress JP, Morris PE, Ouellette DR, Alhazzani W, et al. Official executive summary of an American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: liberation from mechanical ventilation in critically ill adults. *Am J Respir Crit Care Med* 2017;195:115-9.
 38. Na SJ, Ko RE, Nam J, Ko MG, Jeon K. Comparison between pressure support ventilation and T-piece in spontaneous breathing trials. *Respir Res* 2022;23:22.
 39. Ouellette DR, Patel S, Girard TD, Morris PE, Schmidt GA, Truweit JD, et al. Liberation from mechanical ventilation in critically ill adults: an official American College of Chest Physicians/American Thoracic Society Clinical Practice Guideline: inspiratory pressure augmentation during spontaneous breathing trials, protocols minimizing sedation, and noninvasive ventilation immediately after extubation. *Chest* 2017;151:166-80.
 40. Chittawatanarat K, Orrapin S, Jitkaroon K, Mueakwan S, Sroison U. An open label randomized controlled trial to compare low level pressure support and T-piece as strategies for discontinuation of mechanical ventilation in a general surgical intensive care unit. *Med Arch* 2018;72:51-7.
 41. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med* 1995;332:345-50.
 42. Esteban A, Alia I, Gordo F, Fernandez R, Solsona JF, Vallverdu I, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med* 1997;156(2 Pt 1):459-65.
 43. Haberthur C, Mols G, Elsasser S, Bingisser R, Stocker R, Guttman J. Extubation after breathing trials with automatic tube compensation, T-tube, or pressure support ventilation. *Acta Anaesthesiol Scand* 2002;46:973-9.
 44. Koh Y, Hong SB, Lim CM, Lee SD, Kim WS, Kim DS, et al. Effect of an additional 1-hour T-piece trial on weaning outcome at minimal pressure support. *J Crit Care* 2000;15:41-5.
 45. Matic I, Danic D, Majeric-Kogler V, Jurjevic M, Mirkovic I, Mrzljak Vucinic N. Chronic obstructive pulmonary disease and weaning of difficult-to-wean patients from mechanical ventilation: randomized prospective study. *Croat Med J* 2007;48:51-8.
 46. Matic I, Majeric-Kogler V. Comparison of pressure support and T-tube weaning from mechanical ventilation: randomized prospective study. *Croat Med J* 2004;45:162-6.
 47. Subira C, Hernandez G, Vazquez A, Rodriguez-Garcia R, Gonzalez-Castro A, Garcia C, et al. Effect of pressure support vs T-piece ventilation strategies during spontaneous breathing trials on successful extubation among patients receiving mechanical ventilation: a randomized clinical trial. *JAMA* 2019;321:2175-82.
 48. Teixeira SN, Osaku EF, Costa CR, Toccolini BF, Costa NL, Cândia MF, et al. Comparison of proportional assist ventilation plus, T-tube ventilation, and pressure support ventilation as spontaneous breathing trials for extubation: a randomized study. *Respir Care* 2015;60:1527-35.
 49. Yekefallah L, Namdar P, Yaghoubi S, Mohammadi S. Spontaneous breathing trial with pressure support-ventilation versus "T-tube" for head trauma patient: a randomized controlled clinical trial. *Trauma Mon* 2020;25:243-8.
 50. Thille AW, Coudroy R, Nay MA, Gacouin A, Demoule A, Sonnevile R, et al. Pressure-support ventilation vs T-piece during spontaneous breathing trials before extubation among patients at high risk of extubation failure: a post-hoc analysis of a clinical trial. *Chest* 2020;158:1446-55.
 51. Tseng YH, Tseng YC, Hsu HS, Chang SC. Different spontaneous breathing trials in patients with atrial fibrillation. *Rev Port Pneumol (2006)* 2015;21:245-52.
 52. Mezidi M, Yonis H, Chauvelot L, Danjou W, Dhelft F, Bazzani A, et al. Pressure support and positive end-expiratory pressure versus T-piece during spontaneous breathing trial in difficult weaning from mechanical ventilation: study protocol for the SBT-ICU study. *Trials* 2022;23:993.
 53. Darmon JY, Rauss A, Dreyfuss D, Bleichner G, Elkharrat

- D, Schlemmer B, et al. Evaluation of risk factors for laryngeal edema after tracheal extubation in adults and its prevention by dexamethasone: a placebo-controlled, double-blind, multicenter study. *Anesthesiology* 1992;77:245-51.
54. Epstein SK, Ciubotaru RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. *Am J Respir Crit Care Med* 1998;158:489-93.
 55. Jaber S, Chanques G, Matecki S, Ramonatxo M, Vergne C, Souche B, et al. Post-extubation stridor in intensive care unit patients: risk factors evaluation and importance of the cuff-leak test. *Intensive Care Med* 2003;29:69-74.
 56. Schnell D, Planquette B, Berger A, Merceron S, Mayaux J, Strasbach L, et al. Cuff leak test for the diagnosis of post-extubation stridor: a multicenter evaluation study. *J Intensive Care Med* 2019;34:391-96.
 57. Seymour CW, Martinez A, Christie JD, Fuchs BD. The outcome of extubation failure in a community hospital intensive care unit: a cohort study. *Crit Care* 2004;8:R322-7.
 58. Miller RL, Cole RP. Association between reduced cuff leak volume and postextubation stridor. *Chest* 1996;110:1035-40.
 59. Sandhu RS, Pasquale MD, Miller K, Wasser TE. Measurement of endotracheal tube cuff leak to predict postextubation stridor and need for reintubation. *J Am Coll Surg* 2000;190:682-7.
 60. De Bast Y, De Backer D, Moraine JJ, Lemaire M, Vandenberght C, Vincent JL. The cuff leak test to predict failure of tracheal extubation for laryngeal edema. *Intensive Care Med* 2002;28:1267-72.
 61. Erginel S, Ucgun I, Yildirim H, Metintas M, Parspour S. High body mass index and long duration of intubation increase post-extubation stridor in patients with mechanical ventilation. *Tohoku J Exp Med* 2005;207:125-32.
 62. Kriner EJ, Shafazand S, Colice GL. The endotracheal tube cuff-leak test as a predictor for postextubation stridor. *Respir Care* 2005;50:1632-8.
 63. Mikaeili H, Yazdchi M, Tarzamani MK, Ansarin K, Ghazemzadeh M. Laryngeal ultrasonography versus cuff leak test in predicting postextubation stridor. *J Cardiovasc Thorac Res* 2014;6:25-8.
 64. Patel AB, Ani C, Feeney C. Cuff leak test and laryngeal survey for predicting post-extubation stridor. *Indian J Anaesth* 2015;59:96-102.
 65. Sahbal MA, Mohamed KA, Zaghla HH, Kenawy MM. Laryngeal ultrasound versus cuff leak test in prediction of post-extubation stridor. *Egypt J Crit Care Med* 2017;5:83-6.
 66. Tanaka A, Uchiyama A, Horiguchi Y, Higano R, Sakaguchi R, Koyama Y, et al. Predictors of post-extubation stridor in patients on mechanical ventilation: a prospective observational study. *Sci Rep* 2021;11:19993.
 67. Cheng KC, Hou CC, Huang HC, Lin SC, Zhang H. Intravenous injection of methylprednisolone reduces the incidence of postextubation stridor in intensive care unit patients. *Crit Care Med* 2006;34:1345-50.
 68. Lee CH, Peng MJ, Wu CL. Dexamethasone to prevent postextubation airway obstruction in adults: a prospective, randomized, double-blind, placebo-controlled study. *Crit Care* 2007;11:R72.
 69. Baloch R, Jakhrani N, Lal A, Mehmood N. Role of dexamethasone for prevention of post-extubation airway obstruction in critically ill adult patients. *J Surg Pak* 2010;15:3-8.
 70. Cheng KC, Chen CM, Tan CK, Chen HM, Lu CL, Zhang H. Methylprednisolone reduces the rates of postextubation stridor and reintubation associated with attenuated cytokine responses in critically ill patients. *Minerva Anestesiol* 2011;77:503-9.
 71. Colice GL, Stukel TA, Dain B. Laryngeal complications of prolonged intubation. *Chest* 1989;96:877-84.
 72. Kastanos N, Estopa Miro R, Marin Perez A, Xaubet Mir A, Agusti-Vidal A. Laryngotracheal injury due to endotracheal intubation: incidence, evolution, and predisposing factors: a prospective long-term study. *Crit Care Med* 1983;11:362-7.
 73. Francois B, Bellissant E, Gissot V, Desachy A, Normand S, Boulain T, et al. 12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomised double-blind trial. *Lancet* 2007;369:1083-9.
 74. Ho LI, Harn HJ, Lien TC, Hu PY, Wang JH. Postextubation laryngeal edema in adults: risk factor evaluation and prevention by hydrocortisone. *Intensive Care Med* 1996;22:933-6.
 75. Maury E, Guglielminotti J, Alzieu M, Qureshi T, Guidet B, Offenstadt G. How to identify patients with no risk for postextubation stridor? *J Crit Care* 2004;19:23-8.
 76. Pluijms WA, van Mook WN, Wittekamp BH, Bergmans DC. Postextubation laryngeal edema and stridor resulting in respiratory failure in critically ill adult patients: updated review. *Crit Care* 2015;19:295.
 77. Fan T, Wang G, Mao B, Xiong Z, Zhang Y, Liu X, et al. Prophylactic administration of parenteral steroids for preventing airway complications after extubation in adults: meta-analysis of randomised placebo controlled trials. *BMJ* 2008;337:a1841.
 78. Epstein SK. Etiology of extubation failure and the predictive value of the rapid shallow breathing index. *Am J Respir Crit Care Med* 1995;152:545-9.

79. Frutos-Vivar F, Ferguson ND, Esteban A, Epstein SK, Arabi Y, Apezteguia C, et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. *Chest* 2006;130:1664-71.
80. Segal LN, Oei E, Oppenheimer BW, Goldring RM, Bustami RT, Ruggiero S, et al. Evolution of pattern of breathing during a spontaneous breathing trial predicts successful extubation. *Intensive Care Med* 2010;36:487-95.
81. Kuriyama A, Umakoshi N, Sun R. Prophylactic corticosteroids for prevention of postextubation stridor and reintubation in adults: a systematic review and meta-analysis. *Chest* 2017;151:1002-10.
82. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. *Eur Respir J* 2007;29:1033-56.
83. Kuo PH, Wu HD, Lu BY, Chen MT, Kuo SH, Yang PC. Predictive value of rapid shallow breathing index measured at initiation and termination of a 2-hour spontaneous breathing trial for weaning outcome in ICU patients. *J Formos Med Assoc* 2006;105:390-8.
84. Danaga AR, Gut AL, Antunes LC, Ferreira AL, Yamaguti FA, Christovan JC, et al. Evaluation of the diagnostic performance and cut-off value for the rapid shallow breathing index in predicting extubation failure. *J Bras Pneumol* 2009;35:541-7.
85. Souza LC, Lagon JR. The rapid shallow breathing index as a predictor of successful mechanical ventilation weaning: clinical utility when calculated from ventilator data. *J Bras Pneumol* 2015;41:530-5.
86. Tu CS, Chang CH, Chang SC, Lee CS, Chang CT. A decision for predicting successful extubation of patients in intensive care unit. *Biomed Res Int* 2018;2018:6820975.
87. Huo Y, Zhang K, Li B, Li X, Shang J, Ma L, et al. Predictive efficacy of weaning index on mechanical ventilation evacuation. *Ann Palliat Med* 2021;10:646-56.
88. Seixas MB, Almeida LB, Trevizan PF, Martinez DG, Laterza MC, Vanderlei LC, et al. Effects of inspiratory muscle training in older adults. *Respir Care* 2020;65:535-44.
89. Neves LF, Reis MH, Plentz RD, Matte DL, Coronel CC, Sbruzzi G. Expiratory and expiratory plus inspiratory muscle training improves respiratory muscle strength in subjects with COPD: systematic review. *Respir Care* 2014;59:1381-8.
90. Ambrosino N. Weaning and respiratory muscle dysfunction: the egg-chicken dilemma. *Chest* 2005;128:481-3.
91. American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002;166:518-624.
92. Meade M, Guyatt G, Cook D, Griffith L, Sinuff T, Kergl C, et al. Predicting success in weaning from mechanical ventilation. *Chest* 2001;120(6 Suppl):400S-24S.
93. Elbouhy MS, AbdelHalim HA, Hashem AM. Effect of respiratory muscles training in weaning of mechanically ventilated COPD patients. *Egypt J Chest Dis Tuberc* 2014;63:679-87.
94. Sandoval Moreno LM, Casas Quiroga IC, Wilches Luna EC, Garcia AF. Efficacy of respiratory muscle training in weaning of mechanical ventilation in patients with mechanical ventilation for 48 hours or more: a randomized controlled clinical trial. *Med Intensiva (Engl Ed)* 2019;43:79-89.
95. Martin AD, Smith BK, Davenport PD, Harman E, Gonzalez-Rothi RJ, Baz M, et al. Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial. *Crit Care* 2011;15:R84.
96. Cader SA, Vale RG, Castro JC, Bacelar SC, Biehl C, Gomes MC, et al. Inspiratory muscle training improves maximal inspiratory pressure and may assist weaning in older intubated patients: a randomised trial. *J Physiother* 2010;56:171-7.
97. Caruso P, Denari SD, Ruiz SA, Bernal KG, Manfrin GM, Friedrich C, et al. Inspiratory muscle training is ineffective in mechanically ventilated critically ill patients. *Clinics (Sao Paulo)* 2005;60:479-84.
98. da Silva Guimaraes B, de Souza LC, Cordeiro HF, Regis TL, Leite CA, Puga FP, et al. Inspiratory muscle training with an electronic resistive loading device improves prolonged weaning outcomes in a randomized controlled trial. *Crit Care Med* 2021;49:589-97.
99. Lord RK, Mayhew CR, Korupolu R, Manthey EC, Friedman MA, Palmer JB, et al. ICU early physical rehabilitation programs: financial modeling of cost savings. *Crit Care Med* 2013;41:717-24.
100. Seo Y, Lee HJ, Ha EJ, Ha TS. 2021 KSCCM clinical practice guidelines for pain, agitation, delirium, immobility, and sleep disturbance in the intensive care unit. *Acute Crit Care* 2022;37:1-25.
101. Windisch W, Dellweg D, Geiseler J, Westhoff M, Pfeifer M, Suchi S, et al. Prolonged weaning from mechanical ventilation. *Dtsch Arztebl Int* 2020;117:197-204.
102. Zhang L, Hu W, Cai Z, Liu J, Wu J, Deng Y, et al. Early mobilization of critically ill patients in the intensive care unit: a systematic review and meta-analysis. *PLoS One* 2019;14:e0223185.
103. Balas MC, Weinhouse GL, Denehy L, Chanques G, Rochweg B, Misak CJ, et al. Interpreting and implementing the 2018 pain, agitation/sedation, delirium, immobility, and sleep disruption clinical practice guideline. *Crit Care Med* 2018;46:1464-70.
104. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;41:263-306.
105. Yang PH, Wang CS, Wang YC, Yang CJ, Hung JY, Hwang

- JJ, et al. Outcome of physical therapy intervention on ventilator weaning and functional status. *Kaohsiung J Med Sci* 2010;26:366-72.
106. Verceles AC, Wells CL, Sorkin JD, Terrin ML, Beans J, Jenkins T, et al. A multimodal rehabilitation program for patients with ICU acquired weakness improves ventilator weaning and discharge home. *J Crit Care* 2018;47:204-10.
 107. Dong ZH, Yu BX, Sun YB, Fang W, Li L. Effects of early rehabilitation therapy on patients with mechanical ventilation. *World J Emerg Med* 2014;5:48-52.
 108. Dong Z, Yu B, Zhang Q, Pei H, Xing J, Fang W, et al. Early rehabilitation therapy is beneficial for patients with prolonged mechanical ventilation after coronary artery bypass surgery. *Int Heart J* 2016;57:241-6.
 109. Dong Z, Liu Y, Gai Y, Meng P, Lin H, Zhao Y, et al. Early rehabilitation relieves diaphragm dysfunction induced by prolonged mechanical ventilation: a randomised control study. *BMC Pulm Med* 2021;21:106.
 110. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373:1874-82.
 111. Lai CC, Chou W, Chan KS, Cheng KC, Yuan KS, Chao CM, et al. Early mobilization reduces duration of mechanical ventilation and intensive care unit stay in patients with acute respiratory failure. *Arch Phys Med Rehabil* 2017;98:931-9.
 112. Freeman R, Maley K. Mobilization of intensive care cardiac surgery patients on mechanical circulatory support. *Crit Care Nurs Q* 2013;36:73-88.
 113. Corley A, Bull T, Spooner AJ, Barnett AG, Fraser JF. Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI ≥ 30 : a randomised controlled trial. *Intensive Care Med* 2015;41:887-94.
 114. Hernandez G, Vaquero C, Colinas L, Cuena R, Gonzalez P, Canabal A, et al. Effect of postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial. *JAMA* 2016;316:1565-74.
 115. Yu Y, Qian X, Liu C, Zhu C. Effect of high-flow nasal cannula versus conventional oxygen therapy for patients with thoracoscopic lobectomy after extubation. *Can Respir J* 2017;2017:7894631.
 116. Song HZ, Gu JX, Xiu HQ, Cui W, Zhang GS. The value of high-flow nasal cannula oxygen therapy after extubation in patients with acute respiratory failure. *Clinics (Sao Paulo)* 2017;72:562-7.
 117. Zochios V, Collier T, Blandszun G, Butchart A, Earwaker M, Jones N, et al. The effect of high-flow nasal oxygen on hospital length of stay in cardiac surgical patients at high risk for respiratory complications: a randomised controlled trial. *Anaesthesia* 2018;73:1478-88.
 118. Hou Q, Zhang Z, Lei T, Gan M, Wu X, Yue W, et al. Clinical efficacy of high-flow nasal humidified oxygen therapy in patients with hypoxemia. *PLoS One* 2019;14:e0216957.
 119. Xia J, Gu S, Lei W, Zhang J, Wei H, Liu C, et al. High-flow nasal cannula versus conventional oxygen therapy in acute COPD exacerbation with mild hypercapnia: a multicenter randomized controlled trial. *Crit Care* 2022;26:109.
 120. Zhu Y, Yin H, Zhang R, Ye X, Wei J. High-flow nasal cannula oxygen therapy versus conventional oxygen therapy in patients after planned extubation: a systematic review and meta-analysis. *Crit Care* 2019;23:180.
 121. Park S. High-flow nasal cannula for respiratory failure in adult patients. *Acute Crit Care* 2021;36:275-85.
 122. Nava S, Gregoretto C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. *Crit Care Med* 2005;33:2465-70.
 123. Burra V, Putta G, Prasad SR, Manjunath V. A prospective study on use of thrive (transnasal humidified rapid insufflation ventilatory exchange) versus conventional nasal oxygenation following extubation of adult cardiac surgical patients. *Ann Card Anaesth* 2021;24:353-7.
 124. Parke R, McGuinness S, Dixon R, Jull A. Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients. *Br J Anaesth* 2013;111:925-31.
 125. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation: effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med* 2014;190:282-8.
 126. Vourc'h M, Nicolet J, Volteau C, Caubert L, Chabbert C, Lepoivre T, et al. High-flow therapy by nasal cannulae versus high-flow face mask in severe hypoxemia after cardiac surgery: a single-center randomized controlled study: the HEART FLOW Study. *J Cardiothorac Vasc Anesth* 2020;34:157-65.
 127. Tatsuishi W, Sato T, Kataoka G, Sato A, Asano R, Nakano K. High-flow nasal cannula therapy with early extubation for subjects undergoing off-pump coronary artery bypass graft surgery. *Respir Care* 2020;65:183-90.
 128. Theologou S, Ischaki E, Zakyntinos SG, Charitos C, Michopanou N, Patsatzis S, et al. High flow oxygen therapy at two initial flow settings versus conventional oxygen therapy in cardiac surgery patients with postextubation hypoxemia: a single-center, unblinded, randomized, controlled trial. *J Clin Med* 2021;10:2079.

129. Ornico SR, Lobo SM, Sanches HS, Deberaldini M, Tofoli LT, Vidal AM, et al. Noninvasive ventilation immediately after extubation improves weaning outcome after acute respiratory failure: a randomized controlled trial. *Crit Care* 2013;17:R39.
130. Thanthitaweewat V, Muntham D, Chirakalwasan N. Targeted-volume noninvasive ventilation reduces extubation failure in postextubated medical intensive care unit patients: a randomized controlled trial. *Indian J Crit Care Med* 2018;22:639-45.
131. Khan I, Maredza M, Dritsaki M, Mistry D, Lall R, Lamb SE, et al. Is protocolised weaning that includes early extubation onto non-invasive ventilation more cost effective than protocolised weaning without non-invasive ventilation?: findings from the Breathe Study. *Pharmacoecon Open* 2020;4:697-710.
132. Lopes CR, Brandao CM, Nozawa E, Auler JO Jr. Benefits of non-invasive ventilation after extubation in the post-operative period of heart surgery. *Rev Bras Cir Cardiovasc* 2008;23:344-50.
133. Rochweg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017;50:1602426.
134. Adiyek E, Ozgultekin A, Turan G, Iskender A, Canpolat G, Pektas A, et al. Non-invasive mechanical ventilation after the successful weaning: a comparison with the venturi mask. *Braz J Anesthesiol* 2016;66:572-6.
135. Vargas F, Clavel M, Sanchez-Verlan P, Garnier S, Boyer A, Bui HN, et al. Intermittent noninvasive ventilation after extubation in patients with chronic respiratory disorders: a multicenter randomized controlled trial (VHYPER). *Intensive Care Med* 2017;43:1626-36.
136. Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med* 2006;173:164-70.
137. Ferrer M, Sellares J, Valencia M, Carrillo A, Gonzalez G, Badia JR, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet* 2009;374:1082-8.
138. Girault C, Bubenheim M, Abroug F, Diehl JL, Elatrous S, Beuret P, et al. Noninvasive ventilation and weaning in patients with chronic hypercapnic respiratory failure: a randomized multicenter trial. *Am J Respir Crit Care Med* 2011;184:672-9.
139. Khilnani GC, Galle AD, Hadda V, Sharma SK. Non-invasive ventilation after extubation in patients with chronic obstructive airways disease: a randomised controlled trial. *Anaesth Intensive Care* 2011;39:217-23.
140. Su CL, Chiang LL, Yang SH, Lin HI, Cheng KC, Huang YC, et al. Preventive use of noninvasive ventilation after extubation: a prospective, multicenter randomized controlled trial. *Respir Care* 2012;57:204-10.
141. Stephan F, Barrucand B, Petit P, Rezaiguia-Delclaux S, Medard A, Delannoy B, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. *JAMA* 2015;313:2331-9.
142. Tan D, Walline JH, Ling B, Xu Y, Sun J, Wang B, et al. High-flow nasal cannula oxygen therapy versus non-invasive ventilation for chronic obstructive pulmonary disease patients after extubation: a multicenter, randomized controlled trial. *Crit Care* 2020;24:489.
143. Jing G, Li J, Hao D, Wang T, Sun Y, Tian H, et al. Comparison of high flow nasal cannula with noninvasive ventilation in chronic obstructive pulmonary disease patients with hypercapnia in preventing postextubation respiratory failure: a pilot randomized controlled trial. *Res Nurs Health* 2019;42:217-25.
144. Shang X, Wang Y. Comparison of outcomes of high-flow nasal cannula and noninvasive positive-pressure ventilation in patients with hypoxemia and various APACHE II scores after extubation. *Ther Adv Respir Dis* 2021;15:17534666211004235.
145. Oczkowski S, Ergan B, Bos L, Chatwin M, Ferrer M, Gregoretti C, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. *Eur Respir J* 2022;59:2101574.
146. Deng H, Fang Q, Chen K, Zhang X. Early versus late tracheotomy in ICU patients: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2021;100:e24329.
147. Davis K Jr, Campbell RS, Johannigman JA, Valente JF, Branson RD. Changes in respiratory mechanics after tracheostomy. *Arch Surg* 1999;134:59-62.
148. Diehl JL, El Atrous S, Touchard D, Lemaire F, Brochard L. Changes in the work of breathing induced by tracheotomy in ventilator-dependent patients. *Am J Respir Crit Care Med* 1999;159:383-8.
149. Moscovici da Cruz V, Demarzo SE, Sobrinho JB, Amato MB, Kowalski LP, Deheinzelin D. Effects of tracheotomy on respiratory mechanics in spontaneously breathing patients. *Eur Respir J* 2002;20:112-7.
150. Fernandez-Bussy S, Mahajan B, Folch E, Caviedes I, Guerrero J, Majid A. Tracheostomy tube placement: early and late complications. *J Bronchology Interv Pulmonol* 2015;22:357-64.
151. Rumbak MJ, Newton M, Truncala T, Schwartz SW, Adams JW, Hazard PB. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. *Crit Care Med*

- 2004;32:1689-94.
152. Bosel J, Schiller P, Hook Y, Andes M, Neumann JO, Poli S, et al. Stroke-related Early Tracheostomy versus Prolonged Orotracheal Intubation in Neurocritical Care Trial (SETPOINT): a randomized pilot trial. *Stroke* 2013;44:21-8.
 153. Zheng Y, Sui F, Chen XK, Zhang GC, Wang XW, Zhao S, et al. Early versus late percutaneous dilational tracheostomy in critically ill patients anticipated requiring prolonged mechanical ventilation. *Chin Med J (Engl)* 2012;125:1925-30.
 154. Blot F, Similowski T, Trouillet JL, Chardon P, Korach JM, Costa MA, et al. Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. *Intensive Care Med* 2008;34:1779-87.
 155. Trouillet JL, Luyt CE, Guiguet M, Ouattara A, Vaissier E, Makri R, et al. Early percutaneous tracheotomy versus prolonged intubation of mechanically ventilated patients after cardiac surgery: a randomized trial. *Ann Intern Med* 2011;154:373-83.
 156. Young D, Harrison DA, Cuthbertson BH, Rowan K; TracMan Collaborators. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial. *JAMA* 2013;309:2121-9.
 157. Barquist ES, Amortegui J, Hallal A, Giannotti G, Whinney R, Alzamel H, et al. Tracheostomy in ventilator dependent trauma patients: a prospective, randomized intention-to-treat study. *J Trauma* 2006;60:91-7.
 158. Mehta AB, Cooke CR, Wiener RS, Walkey AJ. Hospital variation in early tracheostomy in the United States: a population-based study. *Crit Care Med* 2016;44:1506-14.