PRESERVING LUNG VOLUME AT EXTUBATION. A MULTICENTER PROSPECTIVE, RANDOMIZED CONTROLLED CLINICAL TRIAL (RCT)

Version 2. August 26th 2022.

SUMMARY:

Introduction: At present, the best spontaneous breathing test (SBT) during weaning from mechanical ventilation is a 30-min test with pressure support 8 cmH2O without PEEP. There is a debate about the possible collapse of some alveolar units during such SBT and during extubation with continuous suctioning. A few experiences show extubation without suctioning as feasible and safe.

Hypothesis: Techniques aimed at preserving lung volume during SBT and extubation can yield higher rates of successful extubation.

Primary objective: To define the rates of successful extubation in two extubation approaches aiming at different levels of lung volume preservation: standard SBT (30-min PSV8 without PEEP followed by extubation with continuous suctioning) versus experimental SBT (PSV8+ PEEP5 followed by extubation without suctioning).

Secondary objectives: Reintubation rate, ICU and hospital stays, and mortality in each group.

Design: Prospective, multicenter, randomized study. Two opposing extubation strategies are compared in randomly assigned patients.

INTRODUCTION

Weaning refers to the entire process of liberating the patient from mechanical ventilation (MV) and removing the endotracheal tube (ETT).

In the last 20 years, different strategies and ventilatory modalities of weaning have been described (1-4). According to the literature, pressure support ventilation (PSV) and T-tube are the most used strategies in weaning (5-7). Protocols are recommended since their use has been shown to increase extubation success.

The final phase of weaning is known as a spontaneous breathing test (SBT). According to current scientific evidence, there seems to be no difference in the success of extubation and need for reintubation between T-tube and low PSV for two hours (3). Additionally, success rates of extubation are similar for SBTs done with T-tubes for 30 minutes vs. for 2 hours (2), and between those done with low PSV for 30 minutes vs. for 2 hours (4).

Recently, our group demonstrate that a less demanding SBT (low PSV for 30-min) was better tolerated and allow higher rate of extubation success than a more demanding SBT (T-tube for 2-h) (8).

Simultaneously, including a 1-h rest period with MV after SBT and before extubation was able to improve extubation success in another RCT (9). The authors claimed for respiratory muscle rest as the main factor for such unsupported successful breathing, but recruitment of lung volume after SBT may also occur.

There is a debate about the possible collapse of some alveolar units during such SBT and during extubation with continuous suctioning. A few experiences show extubation without suctioning as feasible and safe (10).

Moreover, patients who fail extubation frequently develop hypoxemia that suggests variable degrees of lung collapse. Then, techniques aimed at preserving lung volume in the peri-extubation period may offer additional advantages.

HYPOTHESIS

Techniques aimed at preserving lung volume during SBT and extubation can yield higher rates of successful extubation.

OBJECTIVES:

Primary: To determine the rate of successful extubation in two opposite weaning strategies.

Secondary: To determine the ICU stay, hospital stay, hospital survival, and 90-day survival in the two groups. To identify the causes of extubation failure.

METHODS

Study design and protocol (informed consent in Appendix 1):

Prospective multicenter, controlled, randomized study.

Inclusion criteria: Patients> 18 years who meet weaning criteria (see below) after at least 24 hours of MV, and with informed consent signed by them or their next of kind.

Exclusion criteria: tracheostomy, do-not-reintubate orders, decision of the responsible physician (e.g., due to a preference for a particular weaning technique according to the underlying pathology), absence of informed consent, mental incapacity without legal representation.

Weaning criteria:

- Suitable cough (Ability to raise secretions to the endotracheal tube) (or PiMax> -15 cmH2O).
- Absence of excessive secretions (<3 aspirations in the last 8 hours).
- Resolution or improvement of the pathology that led to intubation.
- Clinical stability (HR <140 bpm, SBP 90-160, without vasopressors or at minimum doses).
- Adequate oxygenation (SatO2> 90% with FiO2 <0.4).
- Adequate ventilatory mechanics (RR <35 rpm, MIP <-20 cmH2O, Vt> 5 ml / kg, VC> 10 ml/ kg, RR / VT <100 rpm/l).
- Confident awareness level (Glasgow Coma Scale> 13).

Prior to the SBT, attending physicians will state whether they intend to apply prophylactic post-extubation high flow nasal cannula or non-invasive mechanical ventilation. Patients will be in Fowler position (seated at 45º angle), the tracheal secretions will be suctioned before SBT, and FiO2 will remain at the same level than when receiving MV. A cuff-leak test will be performed by deflating the cuff and looking at the difference between inspired and expired volumes.

Patients will be randomized to two weaning strategies (see statistical analysis for more information):

- Standard: PSV 8 cmH2O, PEEP 0 cmH2O for 30 minutes and, when successful, followed by extubation with continuous suctioning.
- Lung volume preservation: PSV 8 cmH2O, PEEP 5 cmH2O for 30 minutes and, when successful, followed by direct extubation without suctioning.

Other components of standard treatment of patients (physiotherapy, nutrition, hydration…) will remain at the discretion of attending physicians and local protocols.

During the SBT, if the patient meets any of the criteria for failure (see below), MV will be reconnected with the same parameters as prior to the SBT.

Failure of SBT will be defined as:

- Subjective indexes:
  - Neurological causes: Agitation or anxiety. Low level of consciousness (Glasgow Coma Scale <13).
  - Increased respiratory work: use of accessory muscles, facial expression suggesting stress, severe dyspnea.
- Objective indexes:
  - Hypoxemia: PaO2 <60 mmHg or SatO2 <90% with FiO2 ≥0.5
  - Tachypnea: RR> 35 rpm
  - Hemodynamic instability: HR> 140 bpm or >20% from baseline; SBP >180 mmHg or >20% from baseline; SBT <90 mmHg; Cardiac arrhythmias.

Patients who fail the SBT will not be randomized in later SBT tests. The day and time of extubation will be recorded in the CRF.

If the patient successfully passes the SBT, an arterial blood gas analysis may be performed at the end of the test.

It is recommended, but not mandatory, to reconnect the patient to MV to rest for 1 hour and, then, proceed to extubation with or without suctioning as randomized.

Extubation failure at 72 hours (regardless of whether reintubation is required) is defined as:

- Respiratory acidosis, pH <7.32, PaCO2> 45 mmHg.
- SatO2 <90% or PaO2 <60 mmHg with FiO2 ≥50%.
- Tachypnea > 35 rpm.

• Deterioration of the level of consciousness, Glasgow Coma Scale <13.

• Uncontrollable agitation.

• Clinical signs of muscle fatigue.

In extubation failure patients, the attending physician will decide on the treatment, either support with non-invasive ventilation or with high flow nasal cannula, or reintubation as Standard of Care at the discretion of the attending physician..

Patients who present extubation failure will not be randomized in later SBTs.

During the SBT, interventions that the physician considers necessary to monitor the success of the test, such as echocardiography or thoracic ultrasound, may be performed. In the event that the physician considers that the findings of these tests do not guarantee successful extubation despite fulfillment of extubation criteria according to the study protocol, the attending physician's decision will prevail over the study protocol. In these cases, it will be recorded in the CRF as extubation failure due to "other causes of weaning failure".

Variables (CRF in Appendix 2):

Demographic variables: Age, sex, weight, height. Comorbidities: heart disease, neurological disease, COPD, diabetes, cancer, chronic renal insufficiency, liver disease. Variables at admission and during SBT: Diagnosis at admission to the ICU, reason for intubation, APACHE II on admission and on the day of extubation, hospital admission date, and date of admission to the ICU.

At the beginning and at the end of the SBT: FiO2, respiratory rate, SaO2, tidal volume during the SBT. If blood gas analysis is performed prior to extubation: PaO2, PaCO2, pH, bicarbonate and base excess.

Outcome variables: Respiratory failure at 72 hours post-extubation and criteria. If blood gas analysis is performed after failure: PaO2, PaCO2, pH, bicarbonate and base excess.

In cases with respiratory failure and rescue NIV, maximum FiO2, IPAP, and maximum EPAP, as well as the hours of application, will be recorded.

If post-extubation high-flow nasal cannula is used, maximum FiO2 and flow will be recorded.

If the patient is reintubated within 72 hours, the time and cause of reintubation will be recorded.

The CRF will be recorded in the RedCap® platform.

RISKS AND BENEFITS OF THE STUDY

We consider that randomizing patients to one or another strategy should not pose any additional risk.

Likewise, the patients participating in the study will not obtain a direct benefit. However, if we determine that one of the weaning strategies results in a higher rate of successful extubation, we could adapt this strategy in our daily clinical practice for benefit of future patients.

Given the characteristics and the absence of clinical risk, the need for additional insurance has not been considered.

STATISTICAL ANALYSIS AND CALCULATION OF SAMPLE SIZE

Considering a basal extubation success of 82%, estimating an increase in absolute extubation success rate of 5%, with an alpha error of 0.05 and a power of 80%, requires a sample size of 822 patients in each group. With the participating hospitals, this sample will be obtained in 12 to 18 months, according to the recruitment rates. Recruitment will begin in October 2022 and will end in May 2024.

The randomization will be carried out with the built -in tool of the REDCAP® platform with computerized random numbers tables and patient N blocks for each hospital (researchers will be blinded on this data). Each participating center will have two different Redcap® profiles. The "recruiter" will have access only to the randomization tool and will not have access to data entry (only one recruiter per center). Another profile will be the "researcher" that will have access to randomization and data entry (as many profiles as researchers for each center). Researchers will have access to the data of their centers, but cannot access the data of other centers. Only trial coordinators will have access to data from all centers.

Before analyzing the results and managing the database, we will check the database to detect errors such as variables or repeated patients, or the lack of values in the

variables through the statistical computer program SPSS version 22® and R-Studio version 3.0®.

When half of the sample has been recruited, a preliminary analysis will be conducted to identify the trend of the results in the primary outcome. If significant ($p< 0.005$) results have been obtained in one of the two randomization groups at that point, the inclusion of patients will be stopped. This analysis will be blinded to investigators.

In the descriptive analysis, quantitative variables will be expressed as means and standard deviations (if normally distributed) and as medians and interquartile ranges (if non-normally distributed). Qualitative variables will be expressed as frequencies and percentages.

Quantitative variables will be compared by Student's t-tests and qualitative variables by chi-square or Fisher's test.

Survival analyses for respiratory failure at 72 hours, reintubation at 72 hours, and mortality at 3 months will be performed with Kaplan-Meier curves with logarithmic rank test for comparison between both groups.

To identify causes of extubation failure, multivariate by logistic regression will be performed, adjusting for confusion factors such as type of pathology, blood gas analysis variables, and center.

The results will be analyzed in three ways:

1. Patients who failed the SBT.
2. Patients who passed the SBT:
    a. Successful extubation
    b. Reintubation within 72 hours.

ETHICAL CONSIDERATIONS

The study has the approval of the Scientific Research Committee (CEIm) of the Fundació Unió Catalana d'Hospitals (See Appendix 3).

During the study, the international ethical standards for human research established in the principles defined in the Declaration of Helsinki and subsequent revisions (Fortaleza, Brazil, October 2013), the Code of Clinical Practices and national recommendations of in accordance with current legislation established in Law 14/2007 on Biomedical Research.

This study will be carried out in accordance with the principles established in the CIOMS International Guidelines. This study will guarantee respect for people through the universal ethical principles of beneficence, non-malfeasance, and justice.

The protocol will be explained to the patient and information provided at all times; patients will be asked whether they want to be included, although this does not necessarily imply that patients themselves must sign the consent form. When patients are unable to sign, a family member or legal representative will be asked to sign. In this way, respect for the principle of autonomy is guaranteed. When the patient or the representative requests their withdrawal from the database despite having signed the consent, it will be withdrawn and the data will be deleted.

This study will be under the Spanish and European legislation: The Organic Law03/2018, of December 5th on Protection of Personal Data and Guarantee of Digital Rights and Regulation (EU) 2016/679 of the European Parliament and of the Council, of April 27th, 2016, on the protection of natural persons in relation to the processing of personal data and the free circulation of these data ("General Data Protection Regulation" or "RGPD"), fully applicable as of May 25th, 2018.

REFERENCES

1. Brochard L, Rauss A, Lemaire F et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Resp Crit Care Med 1994; 150: 896-903.

2. Esteban A, Alía I, Tobin M, Torres A et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Am J Resp Crit Care Med, 1999; 159: 512-518.

3. Esteban A, Alía I, Gordo F, Fernandez R et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. Am J Resp Crit Care Med 1997; 156: 459-465.

4. Perren A, Domenighetti G, Mauri S, Vizzardi N et al. Protocol-directed weaning from mechanical ventilation: clinical outcome in patients randomized for 30-min or 120-min trial with pressure support ventilation. Intensive Care Med 2002; 28: 1058-1063.

5. Esteban A, Anzueto A, Frutos F, et al. Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002; 287: 345-355.

6. Brochard L. Pressure support is the preferred weaning method. As presented at the 5th International Consensus Conference in Intensive Care Medicine: Weaning from Mechanical Ventilation. Hosted by ERS, ATS ESICM, SCCM and SRLF; Budapest, April 28-29, 2005.

7. Esteban A, Anzueto A, Alia I, et al. How is mechanical ventilation employed in the intensive care unit? An international utilization review. Am J Resp Crit Care Med 2000; 161: 1450-1458.

8. Subirà C, Hernández G, Vázquez A, 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(22): 2175-2182.

9. Fernandez MM, González-Castro A, Magret M, et al. Reconnection to mechanical ventilation for 1 h after a successful spontaneous breathing trial reduces reintubation in critically ill patients: a multicenter randomized controlled trial. Intensive Care Med. 2017; 43 (11): 1660-1667.

10. Andreu M, Bertozzi M, Bezzi M, et al. Comparison of Two Extubation Techniques in Critically Ill Adult Subjects: The ExtubAR Randomized Clinical Trial. Respir Care. 2021; 67(1): 76-86.

NESTED SUB-STUDY: LUNG AND DIAPHRAGMATIC ULTARSOUND IN A LUNG VOLUME PRESERVATION STRATEGY DURING EXTUBATION.

Version 2. March 2023.

SUMMARY

Introduction: At present, the standard spontaneous breathing test (SBT) during weaning from mechanical ventilation is a 30-min test with pressure support 8 cmH_2O without PEEP. There is a debate about the possible alveolar collapse during SBT and extubation. Our research group coordinates a RCT to compare standard strategy to a lung volume preservation strategy using PEEP and avoiding aspiration. Ultrasound is a non-invasive diagnostic and monitoring tool that allows assessment of lung aeration.

Hypothesis: A lung volume preservation strategy with 30-minutes SBT with PS 8cm H_2O and 5cmH_2O PEEP followed by extubation without suctioning correlates with a better ultrasound pattern of lung aeration.

Primary objective: Determine the difference in ultrasound lung aeration in two opposing weaning strategies (standard versus lung volume preservation strategy).

Secondary objectives: describe effect of PEEP, aspiration, diaphragm and intercostal musculature during SBT in each arm and in success or failure of SBT or extubation. Assess differences in derecruitment, and specifically in the postero-basal regions and its influence in extubation succeed, ICU stay, hospital stay and mortality.

Design: Nested substudy in the blinded randomized controlled prospective multicenter clinical trial: "Preserving lung volume at extubation. A prospective, randomized controlled multicenter trial" (NCT05526053) (CEI 22/67). The effect in the lung aeration pattern in a volume preservation strategy at extubation is compared to the standard strategy trough a lung ultrasound score.

INTRODUCTION

Mechanical ventilation is the main reason for Intensive Care Unit (ICU) admission. Spontaneous or Self Breathing Test (SBT) is the most effective form in order to evaluate extubation. The latest guidelines ([i]) recommend using pressure support ventilation (PSV) and the latest Randomized Clinical Trial (RCT) ([ii]) shows that SBT of 30 minutes with 8cm H_2O PSV yield higher rates of successful extubation compared to T-tube for 2 hours, mainly due to better test tolerance. However no differences in re-intubation, length of stay or mortality are observed in a 2020 systematic review (iii).

The causes currently related to extubation failure are multifactorial ([iv], [v], [vi]): airway or pulmonary dysfunction, increased resistance, decreased compliance, gas exchange alteration, central nervous system dysfunction and delirium, cardiac dysfunction, respiratory muscle function (mainly the diaphragm), weakness and fatigue, and endocrine dysfunction.

FACTORS INFLUENCING DURING SBT AND EXTUBATION MANEUVER ON LOSS OF PULMONARY AERATION

- Diaphragm weakness

The diaphragm is the muscle that contributes the most to unassisted ventilation, but the mechanisms why diaphragmatic dysfunction is related to SBT failure remain unclear. They probably involve a combination of a decrease in diaphragm force and an increase in impedance that leads to a loss of lung aeration, alveolar collapse and athelectasis ([vii]).

- Decreased positive pressure

The decrease in inspiratory positive pressure favours collapse during inspiration, like PEEP withdrawal does during expiration and this increases the work of breathing for alveolar opening. An ongoing RCT (NCT 04939285) compares two strategies with PEEP and no PEEP.

- Secretions aspiration:

Aspiration favours collapse, while the maintenance of PEEP during cuff-deflation and endotracheal tube (ETT) removal according to an RCT ([viii]) allows the passage of air flow between the ETT and the larynx to improve the discharge of secretions.

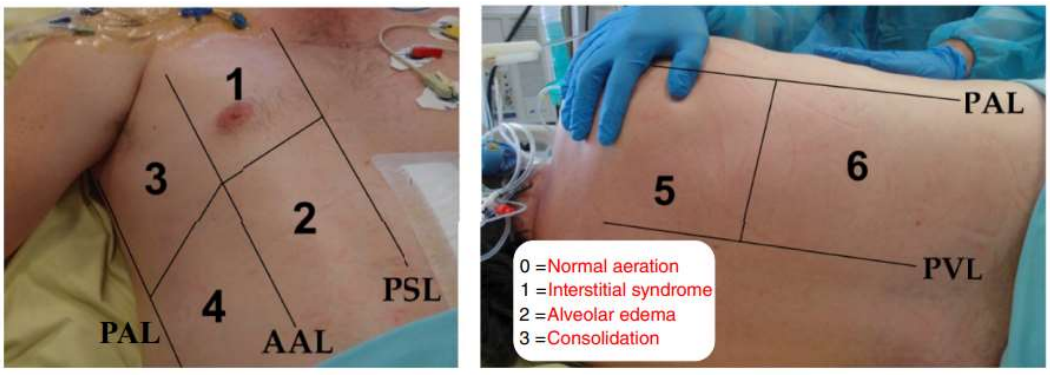
ASSESSEMENT OF THE PULMONARY AERATION DEGREE

- LUNG AND DIAPHRAGMATIC ULTRASOUND

The association between diaphragmatic dysfunction with appearance of pulmonary edema and a pattern of less aeration has been described. A meta-analysis ([ix]) describes some of the most outstanding parameters:

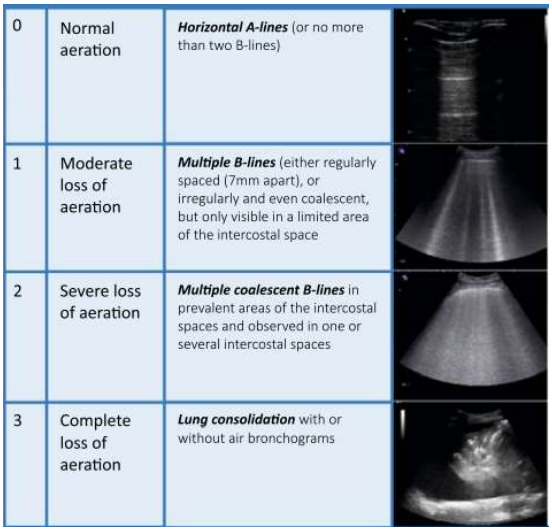
· Lung aeration level by *Lung Ultrasound Score* (LUS score). The latest international guidelines of 2022 ([x]) recommend exploring the maximum possible lung areas, but adapted to the clinical condition. This index recommends the exploration of 12 areas, 6 in each hemithorax (anterior, lateral and posterior subdivided into superior and inferior) [figure 1], giving a score of 0 to 3 points for each depending on the degree of regional aeration [figure 2]: N (normal aeration): presence of pleural sliding with A lines and less than 2 isolated B lines → 0 points; B1 (moderate loss of aeration): more than 2 well-defined B lines → 1 point; B2 (severe loss of aeration): multiple coalescing B lines → 2 points; C (consolidation): pattern of consolidation → 3 points. Ranging from 0 to 36 points, a score of <13 points at the end of a successful SBT is predictive of successful extubation ([xi]).

Figure 1. Lung Ultrasound Score scan areas.



Rouby, *Am J Respir Crit Care Med*, 2018.

Figure 2. Lung Ultrasound Score according to ultrasound pattern.



0	Normal aeration	***Horizontal A-lines*** (or no more than two B-lines)	
1	Moderate loss of aeration	***Multiple B-lines*** (either regularly spaced (7mm apart), or irregularly and even coalescent, but only visible in a limited area of the intercostal space	
2	Severe loss of aeration	***Multiple coalescent B-lines*** in prevalent areas of the intercostal spaces and observed in one or several intercostal spaces	
3	Complete loss of aeration	***Lung consolidation*** with or without air bronchograms	

Tuinman, *Intensive Care Med*, 2020 ([xii])

Simplified indices, such as the modified Lung Ultrasound Score (LUSm) ([xiii]) with exploration of 4 areas in critically patients have been used to avoid mobilization and consequent complications in ICU. LUSm has shown a relationship with the success or failure of extubation and good correlation between different observers. In this case, 4 areas are analysed: antero-superior, antero-inferior, lateral, and postero-basal [figures 3 and 4]. According what has been described in literature reviews, this last area is the place where most pathology is found in critical ill patients ([xiv]). The score range is between 0 and 24 points with risk of extubation failure described for values >7.

Figure 3. LUSm scan areas: 1-antero-superior, 2-antero-inferior, 3-lateral.

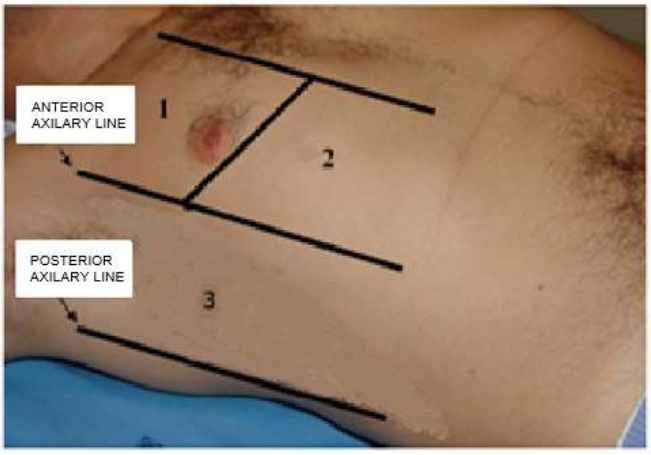
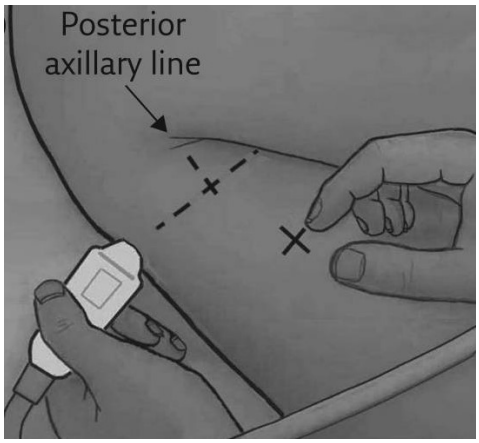


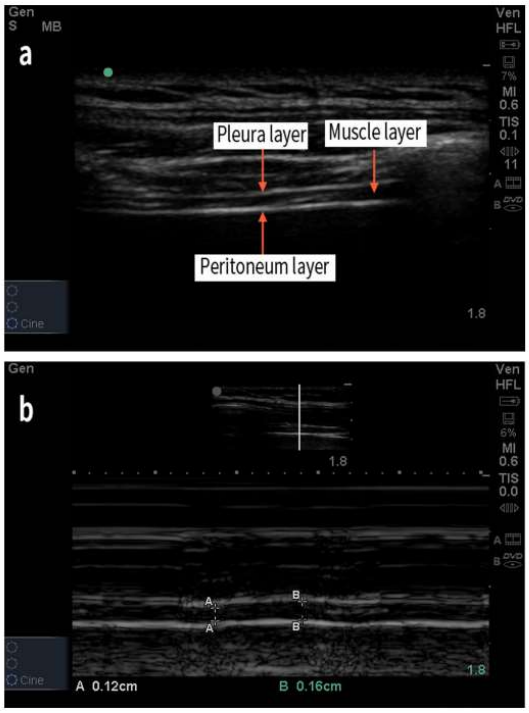
Figure 4. Postero-basal exploration area.



Lichtenstein, *Breathe. 2017*.

· Ultrasound assessment of the respiratory muscles ([xv]). Different measurements of the main muscle implied in breathing have been suggested such as the diaphragmatic thickening fraction (DTF) [figure 5], diaphragmatic excursion (DE) during the respiratory cycle that have been linked to successful extubation both as its own measure and related to the Rapid Shallow Breathing Index (RSBI) ([xvi]) or even loss of diaphragmatic thickness between the first 24-48 hours of mechanical ventilation and SBT ([xvii],[xviii]).

Figure 5. Diaphragmatic thickening measurement.

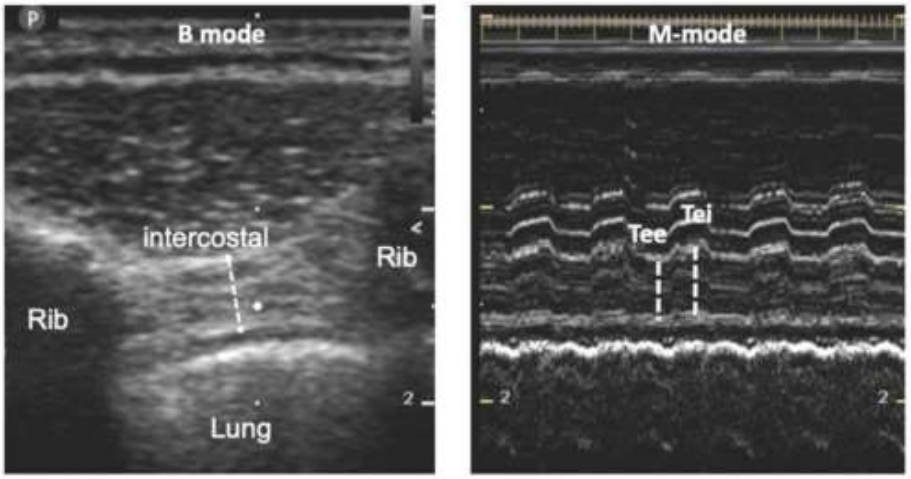


Song, *BMC Pulmonary Medicine*, 2022.

A relationship between diaphragmatic atrophy and the influence on the inspiratory effort has also been described ([xix]).

In the evaluation of accessory muscles, its active use indicates high work of breathing and low diaphragmatic capacity. For this, the thickening of the intercostal musculature (Parasternal Intercostal Muscle Ultrasound) and its thickening fraction (TFic or InterCostal Thickening Fraction) as a measurement of respiratory effort has also been described. [figure 6].

Figure 6. Intercostal thickening measurement.



Dres, *Critical Care Medicine*, 2020.

In summary, part of the causes of extubation failure related to SBT and the ETT withdrawal manoeuvre are related to lung derecruitment or lung collapse, understood as the loss of aerated alveolar surface, partly caused by positive pressure withdrawal, secondary retraction and the lack of ability of the patients to preserve those correctly expanded areas.

Given the multiple factors involved in extubation failure, among the factors discussed, the importance of the recruitment status prior to SBT, the degree of loss during the test, peri-extubation, or the measures for the maintenance of post-extubation recruitment such as prophylactic non-invasive mechanical ventilation (NIV), high-flow nasal cannula therapy (HFNC) or the role of physiotherapy are unknown.

Lung ultrasound is a non-invasive diagnostic and monitoring tool that allows an assessment of the respiratory muscles and the degree of aeration that can be performed at different times in the SBT and extubation process.

Our research group leads and coordinates the RCT "Preserving Lung Volume at Extubation. A Prospective, Multicenter Clinical Trial" (NCT05526053) to compare two opposing extubation strategies: 1) on the one hand a standard 30-minute SBT with pressure support (PSV) modality of 8cmH_2O without end-expiratory pressure (PEEP) followed by extubation with suction, versus 2) a lung volume preservation strategy with 30-min SBT with PSV 8cmH_2O and PEEP 5cmH_2O followed by extubation without

suction. This study was approved by the Ethics Committee of the *Fundació Unió Catalana d'Hospitals* (CEI 22/67) in August 2022.

The present substudy proposes the assessment of the respiratory muscles and the ultrasound pattern of lung aeration using LUSm at different times in the two opposite strategies in the process of SBT and extubation to assess their impact on derecruitment.

HYPOTHESIS

The lung volume preservation strategy with 30-minutes SBT with PS 8cm H_2O and 5cmH_2O PEEP followed by extubation without suctioning correlates with a better ultrasound pattern of lung aeration.

OUTCOMES

PRIMARY OUTCOME:

Determine the difference in ultrasound lung aeration in two opposing weaning strategies (standard versus lung volume preservation strategy).

SECUNDARY OUTCOMES:

- Describe the effect of PEEP during SBT on the ultrasound lung aeration pattern.
- Describe the effect of aspiration during extubation on the ultrasound lung aeration pattern.
- Describe the effect of the diaphragm (thickness, thickening fraction, and thickness evolution between admission and SBT) on the ultrasound lung aeration pattern.
- Describe the effect of the activity of the respiratory accessory muscles (parasternal thickness and thickening) on the pattern of lung aeration.
- Describe the pattern of ultrasound aeration, diaphragmatic thickness and accessory muscles in patients who fail extubation (1. Does not tolerate SBT and 2. Tolerates SBT and reintubation <72 hours).
- Describe the related variables to ultrasound lung aeration loss.

- Describe influence on aeration pattern of prophylactic HFNC or NIV and physiotherapy.
- Describe the ultrasound variables (lung aeration, diaphragm and accessory muscles) related to extubation failure. (1. Does not tolerate SBT and 2. Tolerates SBT and reintubation <72 hours.
- Describe and assess significant differences in the degree of ultrasound derecruitment (recruitment or ΔRCT) in each strategy (standard and preservation of pulmonary volume)
- Describe and assess significant differences in ultrasound derecruitment (ΔRCT) in patients who pass and those who do not pass SBT.
- Assess ultrasound de-recruitment (ΔRCT) and correlate to ICU stay, hospital stay, extubation failure and mortality.

EXPLORATORY OUTCOMES:

- Specifically assess changes in lung aeration in posterobasal regions.
- Describe the relationship between Maximal Inspiratory Pressure, P0.1 and Pocc and diaphragmatic thickness.

METHODS

STUDY DESIGN AND PROTOCOL

Nested substudy in the blinded randomized controlled prospective multicenter clinical trial: "Preserving lung volume at extubation. A prospective, randomized controlled multicenter trial" (NCT05526053) (CEI 22/67)

INCLUSION CRITERIA FOR PARTICIPATING CENTERS

Before starting the study, a technical and competence evaluation of the centres participating in the ultrasound substudy will be carried out (at least 15 have shown interest) within the 34 participating centres in the RCT *Preserving lung volume at Extubation*. At least one collaborator will be designated in charge of the centre with accredited experience in lung ultrasound according to the recommendations of the APECHO study ([xx]) through a course endorsed by the scientific society of intensive care or ultrasound, or at least 25 complete examinations supervised by an expert, who will supervise the personnel of their competent unit for the acquisition of the quality ultrasound images.

Availability of suitable convex and linear probes with the ability to record 3 to 10 seconds video clips.

Ability to download ultrasound images in DICOM format.

Passing the trial period of sending at least 5 scans (all LUSm windows, diaphragmatic and intercostal thickening of 5 different patients) to test that meet the described requirements and can be technically correctly interpreted by an independent observer.

PATIENT INCLUSION CRITERIA

Patients over 18 years with at least 24h of mechanical ventilation and criteria for performing a SBT (Table 1) who participate in the study "Preserving lung volume at extubation. A multicenter prospective, randomized controlled clinical trial (RCT)" (NCT05526053) and agree to participate and sign the specific informed consent (IC) for this study.

Table 1. SBT criteria.

- Effective cough: ability to mobilize secretions up to the endotracheal tube.
- Absence of excessive secretions: <3 aspirations in the last 8 hours.
- Hemodynamic stability: HR<140, SBP 90-160mmHg, no vasopressors or low doses.
- Resolution or improvement of the cause of intubation.
- Adequate oxygenation: SpO_2>90% with FiO_2<0,4.
- Correct ventilatory mechanics: RR<35rpm, MIP < -20cmH_2O, TV >5 and <10ml/kg, RR/TV index <100 bpm/L.
- Adequate level of consciousness: GCS>13

EXCLUSION CRITERIA

Tracheostomy, absence of ultrasound window, pulmonary emphysema, pulmonary bullae or pneumothorax that make ultrasound assessment impossible, previous neuromuscular disease or evidence of paralysis or paradoxical diaphragmatic movement during admission, suboptimal image assessment by the operator, absence of personnel specifically endorsed for the acquisition of ultrasound images in the extubation process.

SAMPLE SIZE

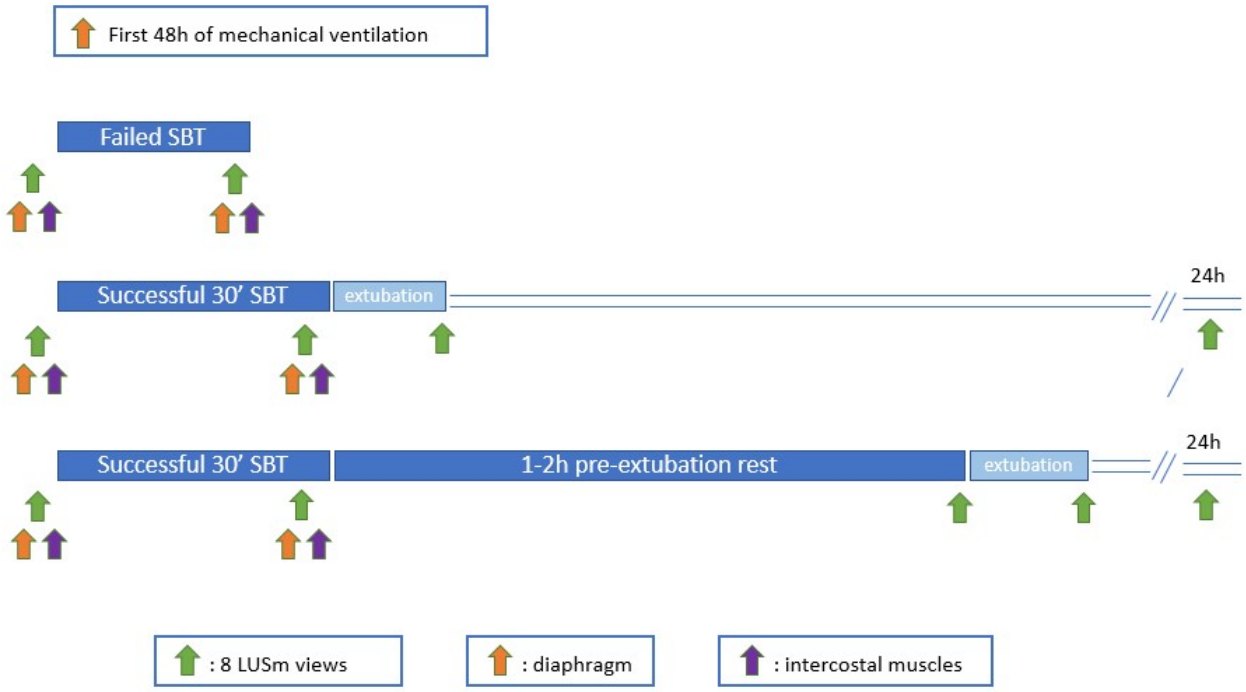
Considering significant a minimum difference of 1 point (SD 2,96) in the LUSm described by Tenza ([13]) (from 0 to 24 points) with an alpha error of 5 % and a power of 80 % 186 patients, 93 in each study group are required.

STUDY PROCEDURE

IMAGE ACQUISITION MOMENTS

Images of the LUSm, diaphragm and intercostal musculature windows will be acquired following the scheme [figure 7], regardless of the standard or volume preservation arm.

Figure 7. Scheme of scan moments.



Essential scans:

1: pre-SBT LUSm

2: according to:

- If SBT fail: LUSm as early as possible, whether it can be before reconnection to ventilation or immediately after reconnection (to be specified).

- If SBT success: immediate post-extubation LUSm.

In case of failed SBT or failed extubation, patients do not re-enter the study.

It is recorded if rest has been performed after SBT, prophylactic high-flow oxygen therapy or non-invasive ventilation and respiratory physiotherapy have been indicated.

IMAGE ACQUISITION FOR LUSm

With the patient at 45º, a 2-4MHz convex probe with a depth between 7 and 12 cm (to be modified according to the clinician's assessment in particular cases) will be used to explore the areas described for LUSm in the following order:

1) Right antero-superior
2) Left antero-superior
3) Right antero-inferior
4) Left antero-inferior
5) Right lateral
6) Left lateral
7) Right postero-basal
8) Left postero-basal

All areas must be explored with the same depth and chosen gain and these characteristics will be fulfilled at different exploration moments.

The postero-basal areas should partially include the diaphragm in the image for the visualization of the costophrenic sinus.

IMAGING ACQUISITION FOR DIAPHRAGM AND INTERCOSTAL THICKNESS AND THICKENING

Measurements will be carried out using a linear probe between 4-15Mhz.

- DIAPHRAGM:

The exploration will begin with the probe in a perpendicular position to the costal arch, between the 9th and 10th right intercostal space and between the anterior and mid-axillary lines. To locate the diaphragm, the probe can be moved cephalic or caudally to the following intercostal spaces to identify the muscle. Once the muscle is located and

without the interference of the lung, the transversal visualization in M mode will be done. The acquisition of at least three breaths in each acquisition and three acquisitions per patient will be recommended. In the subsequent interpretation, if the patient is assisting the ventilator, the thickness in inspiration and expiration will be registered.

The diaphragmatic thickness of patients will be registered within the first 48 hours of mechanical ventilation, since the diaphragmatic development of ventilation-induced diaphragmatic dysfunction ([xxi]) begins early after 24 hours of mechanic ventilation. If the image is not obtained during the first 48 hours, we will only have a diaphragmatic ultrasound measurement on the day of the SBT.

Diaphragmatic thickness measurement will be repeated for enrolled patients prior to initiating SBT, in conjunction with imaging for LUSm. In case that the patient does not enter to study during the extubation process, the image of the first measurement will be deleted.

Therefore, video clips will be obtained at 3 different moments and the images will be labelled with the following numbers:

1) basal diaphragm (<48h de MV): 3 videos of 3 breaths.
2) pre-SBT diaphragm: 3 videos of 3 breaths.
3) Pre-SBT diaphragm during MIP manoeuvre (maximal inspiratory effort): 3 videos of one breath with maximal inspiratory effort.
4) diaphragm at the end of SBT: 3 videos of 3 breaths.

- INTERCOSTAL MUSCULATURE:

The probe will be placed longitudinally in the second intercostal space, about 6 to 8 cm right parasternal. The intercostal muscle will be visualized as a three-layered biconcave structure: two linear hyperechoic membranes extending respectively from the anterior and posterior aspects of the adjacent ribs, and a medial portion with muscular echogenicity. Using the M mode, the acquisition of a least three breaths and three acquisitions per patient will again be recommended. In the subsequent interpretation, if the patient is assisting the ventilator, the thickness in inspiration and expiration will be recorded.

M-mode video clips will be obtained in two different moments with the following labels:

1) pre-SBT intercostal: 3 videos of 3 breaths.

2) intercostal at the end of SBT: 3 videos of 3 breaths.

DOWNLOADING, SENDING AND STORING OF IMAGES

The collaborating manager of the centre will be responsible for downloading the images without any measurements in DICOM format and later sending them to the main research team with the participant's identification number of the study *Preserving lung volume at extubation. A prospective, randomized controlled multicenter trial*.

The images will be sent and stored at the Althaia – Xarxa Assistencial Universitària Manresa through the FileCloud file system, complying with data protection requirements.

IMAGE INTERPRETATION

The interpretation of the images will be done with a DICOM file viewer software by an independent observer blinded to the extubation strategy and time of exploration.

LUSm as already explained will be scored including the partial value of the postero-basal zones, and measurements of diaphragmatic and intercostal thickness and thickening will be performed.

The thickness is measured at the end of expiration and at the peak of inspiration, and the thickening fraction, both diaphragmatic and intercostal, are calculated using the following formula:

$$\text{Thickening fraction} = \frac{thickness\ at\ inspiratory\ peak - thickness\ at\ end\ espiration}{thickness\ at\ end\ espiration}$$

A cut-off for the analysis for feasibility will be done during the recruitment phase.

VARIABLES COLLECTED IN THE CASE REPORT FORM (CRF) (Annex 1)

They will be registered in the RedCap® platform, and will be linked to the identifier assigned to the patient in the main project (See protocol in annex 2).

Demographic variables, related to the SBT and outcome, will already be registered in the CRF of the main project.

Variables at admission and during the SBT: day of hospital admission and in the ICU, admission diagnosis, reason and day of intubation, APACHE II at admission and in the SBT), also already registered in the CRF of the main project.

Ultrasound variables: feasible ultrasound (yes/no and reason). If SBT failure: check ultrasound performed in SBT mode or once reconnected to ventilation.

Clinical variables at the beginning and end of SBT: RR, TV, FiO2, SpO2, blood gases if performed. Respiratory modality in case of pre-SBT diaphragm assessment, fluid balance on the day of the SBT, cumulative fluid balance, pre-SBT measures of Maximal Inspiratory Pressure (MIP), airway occlusion pressure at 100ms (P0.1) and occluded inspiratory airway pressure (Pocc) if possible.

Result variables: success of SBT (yes/no and reason), if decision not to extubate, specify the reason, success or failure of extubation (if failure, reason and blood gases if performed), reintubation (yes/no).

Follow-up variables: record whether prophylactic NIV or high flow has been performed, date of discharge from the ICU, date of hospital discharge, 90-day survival.

RISKS AND BENEFITS OF THE STUDY

Diaphragmatic exploration and LUSm do not suppose any invasive exploration or any risk to the patient. The estimated duration of the LUSm scan ranges from 3 to 14 minutes, although repeat scans on the same patient without probe changes would take approximately 1 to 4 minutes.

Multi-organ ultrasound during the extubation process is part of the clinical evaluation and consequently this study does not imply an overload for the staff, although it is true that time is required to record, download and send images, at all times respecting the protection of personal data.

A complete ultrasound evaluation in the extubation process includes more evaluations (for example, echocardiography) from a multi-organ view, but it is not the subject of this study. It can be done freely at the discretion of the responsible doctor.

The present study focuses exclusively on the degree of lung aeration in order to be able to collect data at a multicenter level and relate them to the strategy of preservation of lung volume.

The sending of ultrasound images is carried out in compliance with the standards of ethics and data protection.

It is intended to associate the ultrasound image with the hypothesis of better lung aeration through a volume preservation strategy, which may be useful in the future to personalise, monitor and decide the most appropriate strategy for each patient in the extubation process.

ETHICAL CONSIDERATIONS

During the conduct of the study, the international ethical standards for human research established in the principles of the Declaration of Helsinki and subsequent revisions (Fortalesa, Brazil, October 2013), the Code of Clinical Practices and national recommendations will be followed in accordance with the current legislation established in Law 14/2007 on Biomedical Research.

Before the start of the study, authorization will be requested from the CEIm of the Fundació Unió Catalana d'Hospitals, as CEIm of reference for the Fundació Althaia Xarxa Assistencial de Manresa. Any modification of the protocol other than administrative changes will require a modification of the protocol that must be approved by the same committee. It will be required the approval of the ethics committees of the collaborating centers.

Data confidentiality:

The promoter and researchers of the study must guarantee the confidentiality of patient data and ensure that it complies at all times with what is established by the current data protection regulations.

Any data that can be related to an identified or identifiable natural person is personal data and therefore falls within the scope of Organic Law 03/2018, of December 5 and Regulation (EU) 2016/ 679 of the European Parliament and of the Council, of April 27, 2016, relating to the protection of natural persons in relation to the processing of personal data and the free movement of such data (General Data Protection Regulation or RGPD), in full application from May 25, 2018.

In accordance with the rights conferred by the current regulations on the Protection of personal data, the patient may exercise the rights of access, rectification, limitation of

treatment, deletion, portability and opposition, directing his request to the researcher principal of the study or the Data Protection Delegate. From the Legal Unit of the Althaia Foundation, Manresa University Assistance Network we will resolve all doubts, complaints, clarifications, suggestions and attend to the exercise of rights via email dpd@althaia.cat, or by post to: Doctor Joan Soler, 1-3, 08243 Manresa, Barcelona. We remind the patient that the data cannot be deleted even if they stop participating in the study to ensure the validity of the research. Participants also have the right to contact the Data Protection Agency if they are not satisfied.

In accordance with current legislation, participants have the right to be informed of data relevant to their health that are obtained in the course of the study. This information will be communicated if they wish; in the event that they prefer not to be informed, the decision will be respected.

Participation in the study is completely voluntary, and if the decision is not to participate, all the medical care needed to receive and the relationship with the medical team that cares for the patient will not be affected.

The principal investigator and the Promoter of the study as owners of the data will be responsible for its custody. The information regarding the identity of the patients will be considered confidential in general. Patient data collected for the study will be identified by a code (001 # onwards), so that no information that could identify the patient is included.

Information sheet and informed consent:

The researcher must explain to each patient the nature of the study, its purposes, procedures, estimated duration, the potential risks and benefits related to participation in the study, as well as any inconvenience that this may entail. Each of the participants must be warned that their participation in the study is voluntary and that they can leave the study at any time, without this affecting their subsequent medical treatment, nor the relationship with the doctor treating them.

The patient must have sufficient time to understand the researcher's explanations contained in the information sheet (see annex 3a) before signing the informed consent

(annex 3b). No patient can be included in the study without first giving written consent that will be recorded in the patient's medical record.

This study has been submitted for approval by the Research Ethics Committee of the *Fundació Unió Catalana d''Hospitals* in February 2022 and requires the approval of the ethics committees of the collaborating centres.

REFERENCES

[i] Schmidt GA, Girard TD, Kress JP, et al. Liberation from mechanical ventilation in critically ill adults: executive summary of an official American College of Chest Physicians/American Thoracic Society clinical practice guideline. Chest. 2017;151(1): 160-165.

[ii] Subirà C, Hernández G, Vázquez A, Rodríguez-García R, González-Castro A, García C, Rubio O, Ventura L, 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 Jun 11;321(22):2175-2182.

[iii] Li Y, Li H, Zhang D. Comparison of T-piece and pressure support ventilation as spontaneous breathing trials in critically ill patients: a systematic review and meta-analysis. Crit Care. 2020 Feb 26;24(1):67.

[iv] Heunks LM, van der Hoeven JG. Clinical review: the ABC of weaning failure--a structured approach. Crit Care. 2010;14(6):245. doi: 10.1186/cc9296.

[v] Baptistella AR, Sarmento FJ, da Silva KR, Baptistella SF, Taglietti M, Zuquello RÁ, Nunes Filho JR. Predictive factors of weaning from mechanical ventilation and extubation outcome: A systematic review. J Crit Care. 2018 Dec;48:56-62.

[vi] Thille AW, Richard JC, Brochard L. The decision to extubate in the intensive care unit. Am J Respir Crit Care Med. 2013;187(12):1294-1302.

[vii] Blumhof S, Wheeler D, Thomas K, McCool FD, Mora J. Change in Diaphragmatic Thickness During the Respiratory Cycle Predicts Extubation Success at Various Levels of Pressure Support Ventilation. Lung. 2016 Aug;194(4):519-25.

[viii] Andreu MF, Dotta ME, Bezzi MG, Borello S, Cardoso GP, Dib PC et al. Safety of Positive Pressure Extubation Technique. Respir Care. 2019 Aug;64(8):899-907.

[ix] Llamas-Álvarez AM, Tenza-Lozano EM, Latour-Pérez J. Diaphragm and Lung Ultrasound to Predict Weaning Outcome: Systematic Review and Meta-Analysis. Chest. 2017 Dec;152(6):1140-1150.

[x] Demi L, Wolfram F, Klersy C, De Silvestri A, Ferretti VV, Muller M, Miller et al. New International Guidelines and Consensus on the Use of Lung Ultrasound. J Ultrasound Med. 2022 Aug 22.

[xi] Soummer A, Perbet S, Brisson H, Arbelot C, Constantin JM, Lu Q, et al.; Lung Ultrasound Study Group. Ultrasound assessment of lung aeration loss during a successful weaning trial predicts postextubation distress. Crit Care Med 2012;40:2064–2072.

[xii] Tuinman PR, Jonkman AH, Dres M, Shi ZH, Goligher EC, Goffi A, de Korte C, Demoule A, Heunks L. Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients-a narrative review. Intensive Care Med. 2020 Apr;46(4):594-605.

[xiii] Tenza-Lozano E, Llamas-Alvarez A, Jaimez-Navarro E, Fernández-Sánchez J. Lung and diaphragm ultrasound as predictors of success in weaning from mechanical ventilation. Crit Ultrasound J. 2018 Jun 18;10(1):12.

[xiv] Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest. 2008 Jul;134(1):117-25.

[xv] Tuinman PR, Jonkman AH, Dres M, et al. Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients-a narrative review. Intensive Care Med. 2020;46(4):594-605.

[xvi] Song J, Qian Z, Zhang H, et al. Diaphragmatic ultrasonography-based rapid shallow breathing index for predicting weaning outcome during a pressure support ventilation spontaneous breathing trial. BMC Pulm Med. 2022;22(1):337.

[xvii] Demoule A, Jung B, Prodanovic H, et al. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact-a prospective study. Am J Respir Crit Care Med. 2013;188(2):213-219.

[xviii] Dres M, Dubé BP, Mayaux J, et al. Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. Am J Respir Crit Care Med. 2017;195(1):57-66.

[xix] Goligher EC, Fan E, Herridge MS, et al. Evolution of Diaphragm Thickness during Mechanical Ventilation. Impact of Inspiratory Effort. Am J Respir Crit Care Med. 2015;192(9):1080-1088.

[xx] Rouby JJ, Arbelot C, Gao Y, Zhang M, Lv J, An Y et al; APECHO Study Group. Training for Lung Ultrasound Score Measurement in Critically Ill Patients. Am J Respir Crit Care Med. 2018 Aug 1;198(3):398-401.

[xxi] Spiesshoefer J, Kersten A, Enriquez Geppert J, et al. State-of-the-Art Opinion Article on Ventilator-Induced Diaphragm Dysfunction: Update on Diagnosis, Clinical Course, and Future Treatment Options. Respiration.