CRITCARE BITES

LIBERATION FROM MECHANICAL VENTILATION

Clare Fong
Alexandra Hospital, National University Hospital

SICM
Society of Intensive Care Medicine
SINGAPORE

MAD FOR MEDICINE

OUTLINE

- Assess if the patient is ready for extubation
- Understand different spontaneous breathing trials methods
- Approaching a difficult-to-wean patient
- Post extubation support (e.g. NIV and HFNC)
- When to trach

An Official American Thoracic Society/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

INTRODUCTION

- 30% of MV patients will experience weaning problems
- Weaning may occupy up to 40-50% of total duration of mechanical ventilation
- 1-5% of all MV patients may fail all attempts and become ventilator dependent
- Mortality increases with the duration of mechanical ventilation
  - VAP, airway trauma

WEANING FAILURE

Simple weaning	Difficult weaning	Prolonged weaning
Patients who proceed from initiation of weaning to successful extubation on the first attempt without difficulty	Patients who fail initial weaning and require **up to 3 SBTs** or **as long as 7 days** from the first SBT to achieve successful weaning	Patients who **fail at least 3 weaning attempts** or require **>7 days of weaning** after the first SBT
~69% of patients	~15% of patients	~15% of patients
ICU mortality ~5%	ICU mortality ~25%	ICU mortality 25%

- In prolonged wean: progressive reduction of ventilator assistance
  - Diminishing PS with an increasing duration off PS mode
- Ventilator dependent: after 3 months of weaning attempts made
  - Unless evidence of irreversible disease such as high spinal cord injury, ALS

BEGIN WITH THE END IN MIND

- Ventilator liberation protocol
  - Shorten duration of mechanical ventilation
  - No increase in rate of re-intubation
- Daily interruption of sedation: daily SAT followed by SBT (ABC, Lancet 2008)
  - More ventilator free days, less time in coma, less time in ICU/ hospital
  - Improved 1-year survival
  - Decreased tracheostomy rates
  - Higher rate of self-extubation but overall rate of re-intubation is the same
- Conservative fluid mx in ARDS (FACTT study)
- Prevent VAP (ventilator associated pneumonia)
- Early PTOT

ALWAYS TRY, PATIENT MAY SURPRISE YOU

- Daily checks for SBT will identify patients not clinically considered ready for weaning
- Many patients passed the 2 hour SBT and were successfully extubated despite not being considered ready by clinicians (Brochard AJRCCM 1994, Esteban NEJM 1995)

Predicting ≠ checking

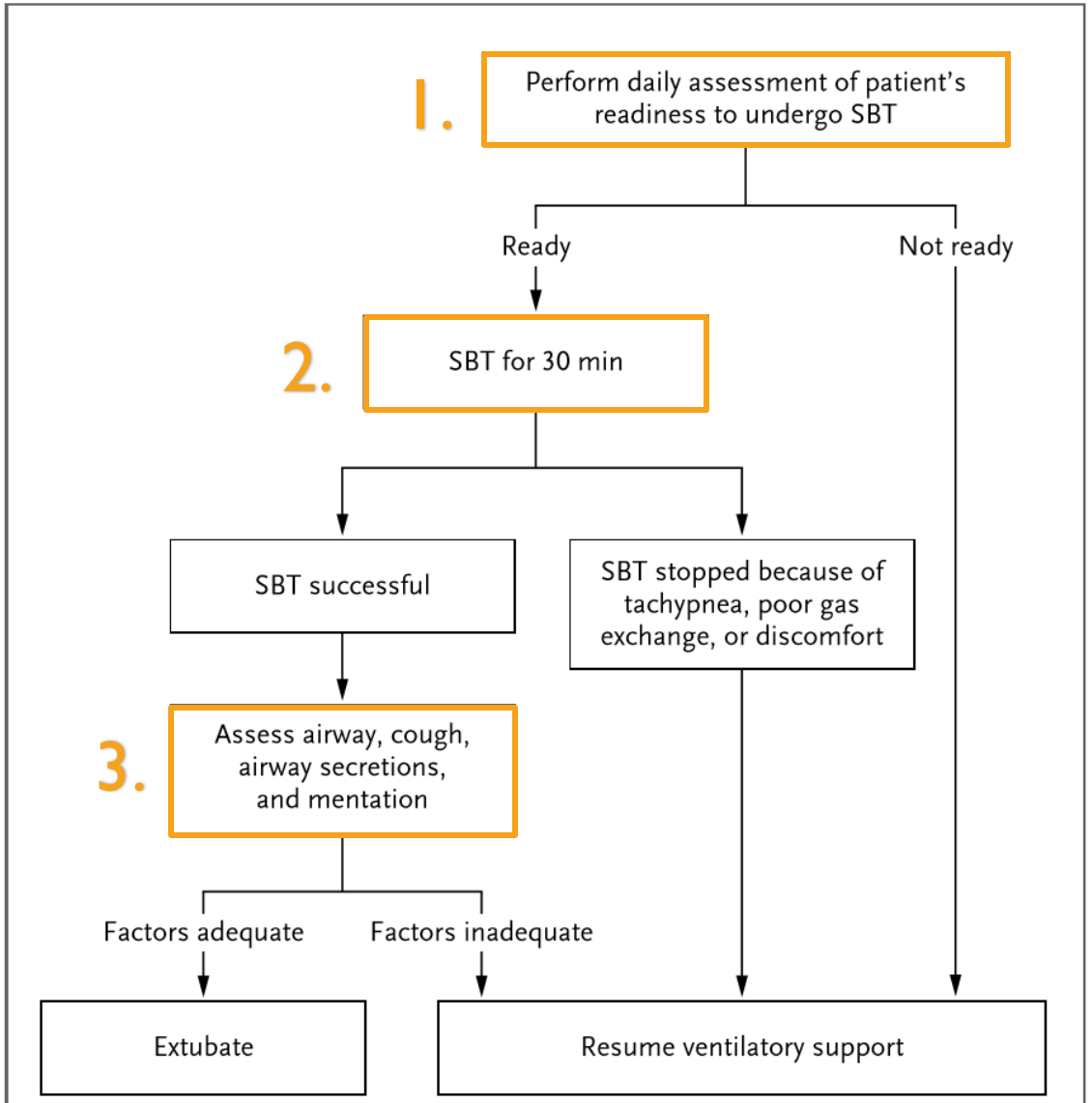


Figure 1. A Common Algorithm for the Transition from Mechanical Ventilation to Spontaneous Breathing.

SBT denotes spontaneous-breathing trial.

3 STEPS

1. Assess readiness to wean
2. Spontaneous breathing trial
3. Ability to protect the airway

N Engl J Med 2012;367:2233-2239

STEP ONE: READINESS TO WEAN

- Resolution of initial reason for intubation
- Adequate oxygenation: $PaO_2 \geq 60mmHg$ or $SpO_2 \geq 90\%$ on $FiO_2 \leq 0.4$, PEEP ≤ 8 cmH_2O, PF ratio ≥ 150
- Adequate ventilation
- Absence of major organ failure
- Hemodynamic instability
  - Minimal or no need for vasopressors (Noradrenaline < 0.1mcg/kg/min)
- Able to initiate spontaneous breaths
- Stable neurological status: arousable, minimal sedation
- Ability to protect the airway: good cough and gag reflex, ≤ moderate amount of secretions with suctioning frequency < 2 hours
- Acid-base status: pH >7.25

WEANING PREDICTORS

- **Rapid Shallow Breathing Index (RSBI)**
- CROP index (Compliance, RR, arterial Oxygenation, Pi_{max})
  - Pi_{max} absolute number >30cmH2O successful weaning
- Minute ventilation
- Work of breathing
- **P0.1 and airway occlusion pressure**
- Gastric mucosal acidosis
- Oxygen cost of breathing
- **Hypercapnia during SBT**
- **BNP**
- Lung ultrasound

RSBI

- **Rapid shallow breathing index = RR/VT (L)**
- Most studied, but has not been shown to improve clinical outcomes
  - Duration of mechanical ventilation, ICU LOS, re-intubation rate similar, but one-day longer to extubate (Tanios, CCM 2006)
- **RSBI >105: weaning failure**
- RSBI <105 (positive): higher probability of successful extubation
- Small increase of weaning success for positive RSBI, but large increase in weaning failure in patients with a negative RSBI (Yang and Tobin, NEJM 2001, Chest 2001 Systematic Review)

$P_{0.1}$ AND AIRWAY OCCLUSION PRESSURE

- $P_{0.1}$ is the pressure developed in the occluded airway 100ms after the onset of inspiration
- Marker of respiratory drive
  - Unexpected occlusion: no reaction to mechanical load
  - Begins from EELV ∴ any drop in airway pressure is independent of the recoil pressure of the lung/ thorax
  - Flow is interrupted, independent of resistance
- Range of values
  - Normal: 0.5-1.5 cmH2O
  - COPD: 2.5-5 cmH2O
- High $P_{0.1}$ associated with failure
  - Generally >4-6 cmH2O
  - Significant overlap occurred between groups (no clear threshold)

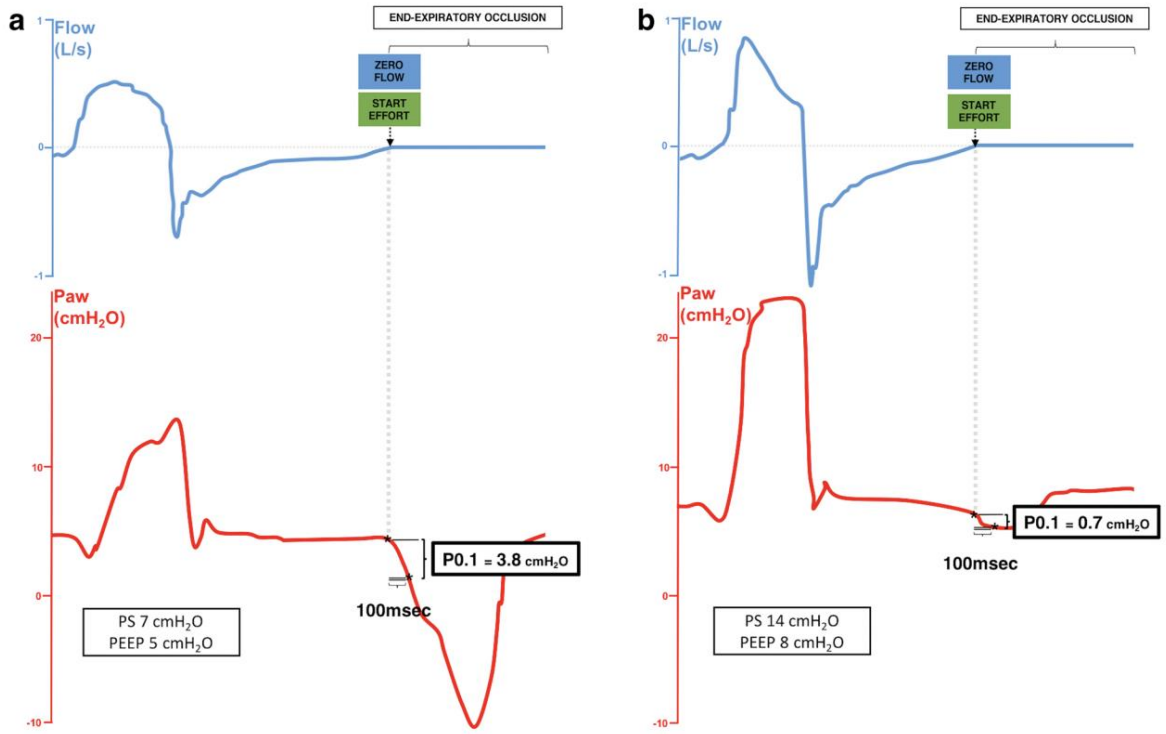
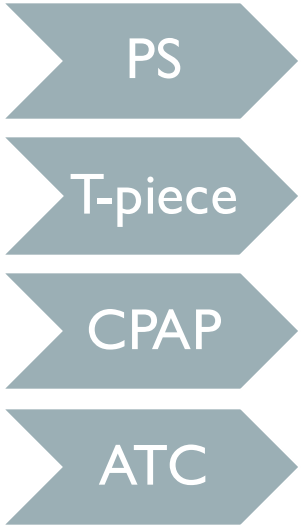


Fig. 1 Measurement of airway occlusion pressure ($P_{0.1}$). Airway pressure (P_{aw} in red) and flow (in blue) during an un-occluded breath and a breath during an end-expiratory occlusion of two different patients under assisted mechanical ventilation with two very different levels of drive. $P_{0.1}$ is measured from the P_{aw} tracing as the drop in airway pressure during the first 100 ms of the breath against an occluded airway. Patient corresponding to tracing (**a**) has a lower ventilatory support and higher respiratory drive than patient corresponding to tracing (**b**). *PS* pressure support, *PEEP* positive end-expiratory pressure level

Intensive Care Med. 2018 Sep;44(9):1532-1535
Intensive Care Med. 2004 Feb;30(2):234-240.

STEP TWO: SPONTANEOUS BREATHING TRIALS

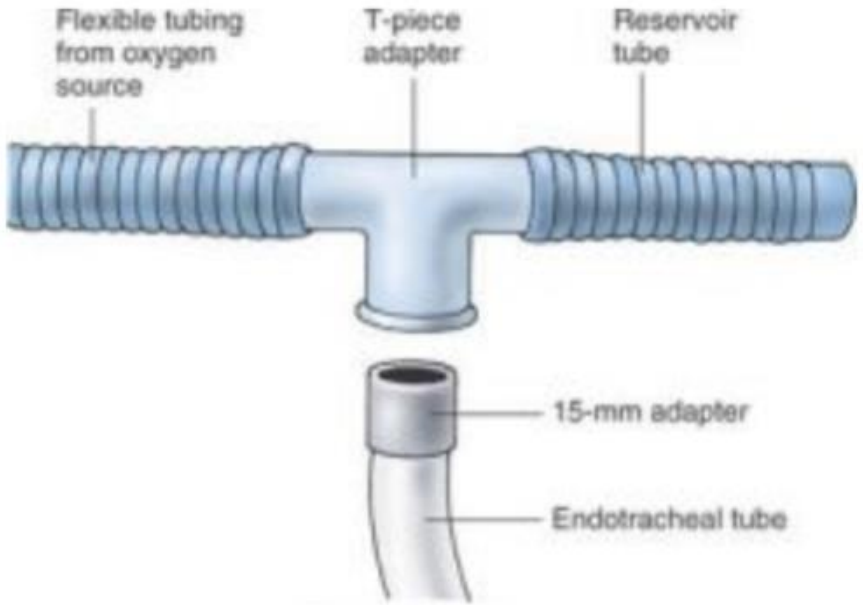
- Trial to demonstrate that an invasively ventilated patient can breathe on minimal or no support



- No added benefit in waiting longer
- Detrimental effects of respiratory muscle overload often occur early in the SBT

T-PIECE

- T-shaped device
- Connects oxygen source to artificial airway (ETT or tracheostomy)
- Flow rate 8-10L/min (FiO2 60-100%)
- Does not provide ventilation



https://pulmcast.com/mind-palace/2019/5/16/getting-patients-off-the-vent

Method of SBT	Settings	Advantages/ Disadvantages
Low level PS	PS 5-8 cmH2O +/- PEEP <5 cmH2O FiO2 <0.4 for 30min	✔ Patient effort lower than T-piece, reduces by 30-40% ✘ Possibly underestimates WOB (upper airway resistance) and extubation failure risk
T-piece	Disconnect from ventilator Oxygen via T-piece for 30min	✔ Accurately replicated WOB after extubation ✘ Higher false failure rate resulting in delayed extubation. More cardiac stress in heart failure patients
CPAP	CPAP 5 cmH2O for 30min	✔ Patient effort lower, reduces by 30-40%. Augment cardiac output in patients with LV failure ✘ Not able to set PEEP differently
ATC	Selected on ventilator, ETT size input	✔ Provides a pressure that compensates for ETT resistance. As effective as PSV, useful in narrow ETTs

- ATS/ ACCP 2017 guidelines: **low level PS (5-8 cmH2O)** instead of T-piece or CPAP in patients ventilated >24h
- Cochrane 2014 Review: low quality evidence, PS superior to T-piece for successful SBT among patients with simple weaning

FAILURE OF SBT

- RR > 35/min
- Saturation < 90%
- HR > 140/min or development of arrhythmias
- Sustained increase n HR > 20%
- Hypertension > 180mmHg or < 90mmHg
- Anxiety / diaphoresis
- Respiratory distress
- Altered mental state

OTHER PARAMETERS DURING SBT

- Reduced breathing variability
- Loss of lung aeration on lung ultrasound
- Diaphragm ultrasound
- BNP
- Hypercapnia
- Airway resistance
- Decrease in mixed venous saturation

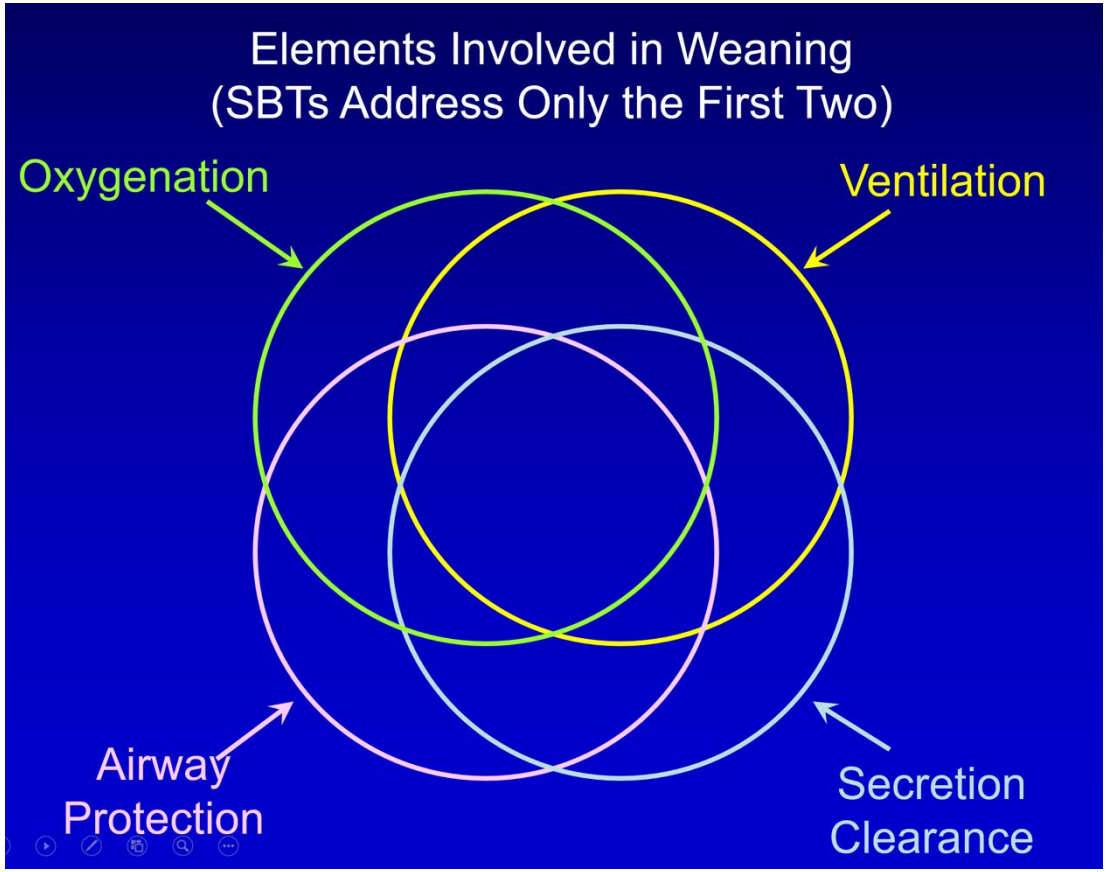
DOES A FAILED SBT PREDICT NEED FOR CONTINUED VENTILATORY SUPPORT?

- No studies have tried extubating patients with failed SBT
- Iatrogenic factors
  - ETT discomfort
  - Dysynchrony
  - Delirium
- In patients who self-extubate before meeting weaning criteria, only 40-60% require re-intubation

FAILURE OF SBT

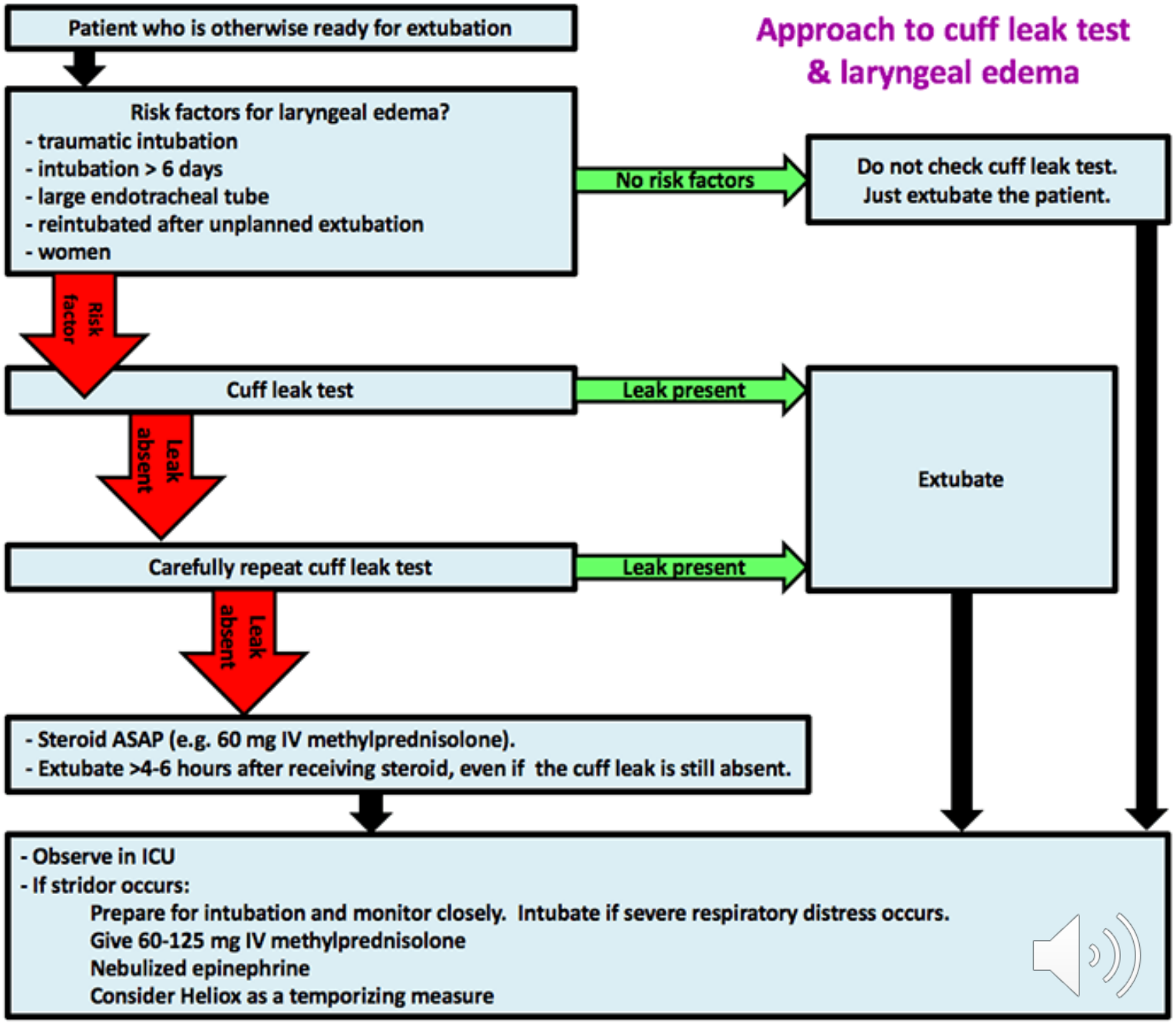
Low VC and MIP	Muscle weakness
Low RSBI, low $P_{0.1}$	Insufficient drive
High RSBI or low minute ventilation	Excessive WOB for patient's capabilities
High minute ventilation, normal PCO2	Excessive CO2 production High dead space

STEP THREE:
ABILITY TO PROTECT THE AIRWAY



CUFF LEAK TEST

- Risk of post extubation upper airway obstruction increases with duration of mechanical ventilation, female gender, traumatic intubation or repeated intubations
- Should only be performed in patients at risk of laryngeal edema
- Steroids reduce re-intubation and post-extubation stridor in high risk patients (as identified by the leak test)



Am J Respir Crit Care Med. 2017 Jan 1;195(1):120-133.

Effect of cuff leak test on probability of reintubation

Pre-test probability of reintubation	Post-test probability, if cuff leak is *absent*	Post-test probability, if cuff leak is *present*
1%	4%	0.5%
3%		%
5%		%
10%	30%	5%
15%	41%	8%
25%	57%	13%
35%	68%	20%

Therefore, cuff leak test should only be performed in high risk patients with at least a 10% pre-test probability of re-intubation

- Absence of a cuff leak increases likelihood of re-intubation (LR +4)
- Presence of a cuff leak reduces likelihood of re-intubation (LR -0.5)
- Ideal extubation failure rate ~15%
- Thus, in patients with low pre-test probability of re-intubation, even if no cuff leak, the risk of re-intubation is still acceptable

https://emcrit.org/pulmcrit/cuff-leak/

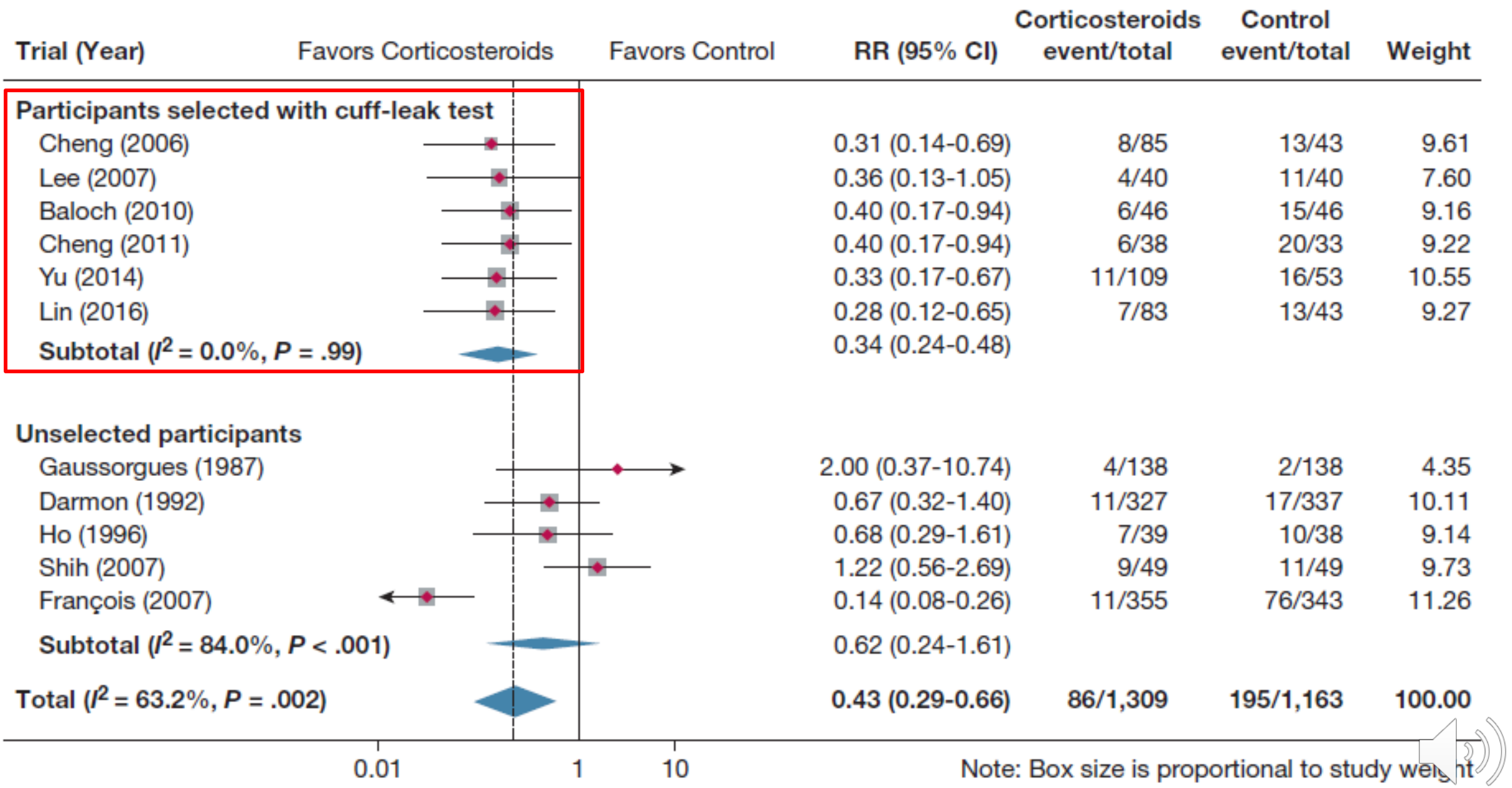
HOW TO PERFORM A CUFF-LEAK TEST?

- Positive leak means the airway is patent
- ACVC
  - Cuff is deflated for 4-6 consecutive breaths
  - Listen for audible leak
  - >110ml or 10% difference between the inspiratory tidal volume (before deflation) and the expiratory tidal volume (after cuff deflation)
  - >110ml: NPV 98% for post-extubation stridor (Millar and Cole, et al)
- Spontaneously breathing patients
  - Cuff deflated and monitored for the first 30 seconds looking for gurgling
  - Tube is then obstructed with the finger while the patient continues to breathe around the tube

CORTICOSTEROIDS

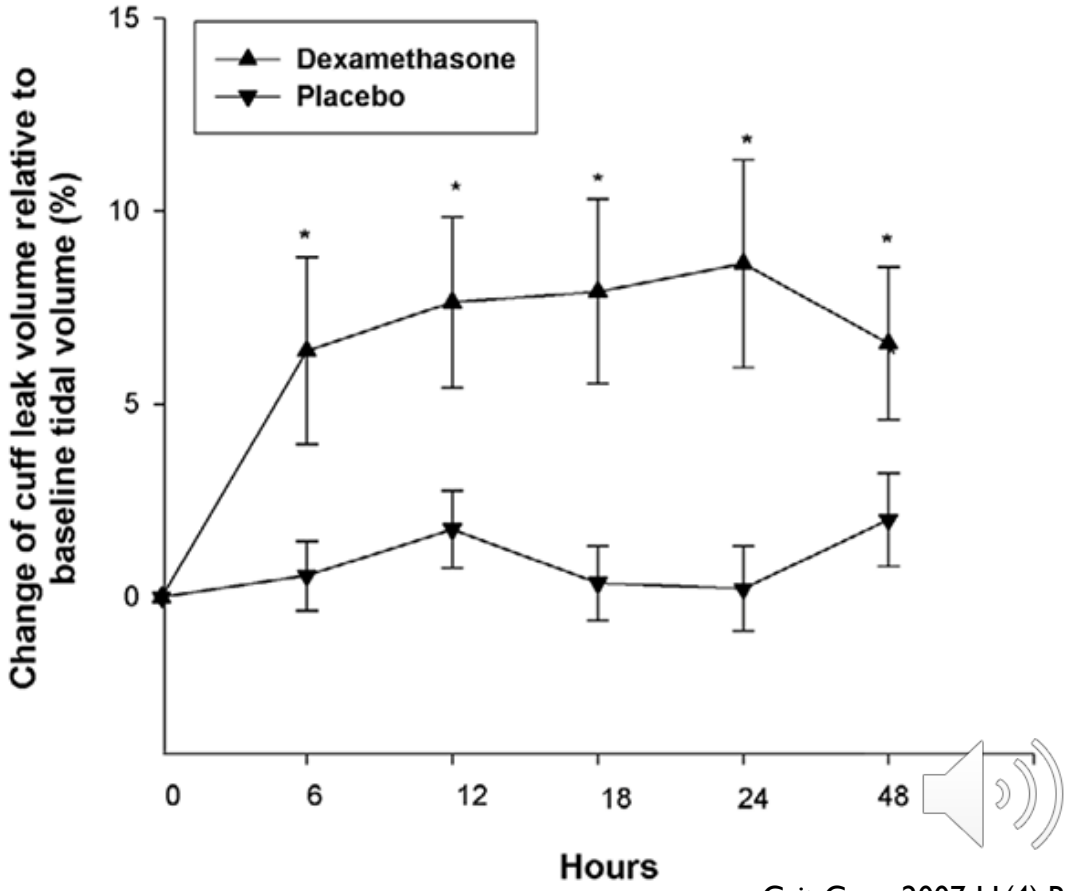
- Prophylactic CS before elective extubation: 57% reduction in incidence of post extubation airway events and reintubation (Chest 2017, systematic review)
- Subgroup analysis showed beneficial effects only in subgroup at **high risk**
  - Defined by absence of leak when cuff leak test is performed
- In high risk patients
  - NNT to prevent one episode of post extubation airway events: 5
  - NNT to prevent reintubation: 16
- Routine administration of steroids not recommended
- Should only be given to high risk patients
  - Side effects rare: hyperglycemia, GI bleeding, infections

Chest. 2017 May;151(5):1002-1010


Trial (Year)
Favors Corticosteroids
Favors Control
RR (95% CI)
Corticosteroids event/total
Control event/total
Weight
Participants selected with cuff-leak test
Cheng (2006) 0.31 (0.14-0.69) 8/85 13/43 9.61
Lee (2007) 0.36 (0.13-1.05) 4/40 11/40 7.60
Baloch (2010) 0.40 (0.17-0.94) 6/46 15/46 9.16
Cheng (2011) 0.40 (0.17-0.94) 6/38 20/33 9.22
Yu (2014) 0.33 (0.17-0.67) 11/109 16/53 10.55
Lin (2016) 0.28 (0.12-0.65) 7/83 13/43 9.27
Subtotal (I^2 = 0.0%, P = .99) 0.34 (0.24-0.48)
Unselected participants
Gaussorgues (1987) 2.00 (0.37-10.74) 4/138 2/138 4.35
Darmon (1992) 0.67 (0.32-1.40) 11/327 17/337 10.11
Ho (1996) 0.68 (0.29-1.61) 7/39 10/38 9.14
Shih (2007) 1.22 (0.56-2.69) 9/49 11/49 9.73
François (2007) 0.14 (0.08-0.26) 11/355 76/343 11.26
Subtotal (I^2 = 84.0%, P < .001) 0.62 (0.24-1.61)
Total (I^2 = 63.2%, P = .002) 0.43 (0.29-0.66) 86/1,309 195/1,163 100.00
0.01
1
10
Note: Box size is proportional to study weight

HOW TO GIVE STEROIDS?

- Common steroid regimens based on prior studies
  1. Single dose IV Methylpred 40mg 4 hours prior to extubation
  2. IV Methylpred 20mg 4H over 12H for 4 doses, last dose just before extubation
  3. IV Dexa 4mg 6H for 24H
- No evidence to support one over the other
- Guidelines recommend **extubating 4-6h after steroids** based on pharmacokinetics



Crit Care. 2007;11(4):R72.

DO WE REPEAT THE CUFF LEAK TEST AFTER GIVING STEROIDS?

- No need to repeat the cuff leak test
- Cuff leak test only validated as an upfront test, prior to use of steroids
- Performance of the test is lower after giving steroids
  - False absences of leak may still exist: adherent secretions around the tube, ETT that is large compared to the size of the glottis
- Patients treated with steroids who lack a cuff leak can stil be extubated safely (Cheng 2006, Cheng 2011, Crit Care Med)

- Prepare for the worst, standby adjuncts if difficult airway was encountered initially
- Even if post-extubation stridor is present, published re-intubation rates average 50%

LAST WORDS ABOUT CUFF LEAK

- Absent cuff leak: increased incidence of post-extubation stridor and unsuccessful extubation
- Cuff leak test: decreases reintubation rate and post-extubation stridor rate
- Delays extubation 24-48h with no effect on duration of IMV
- Extubation can still be successful in patients without a positive leak
  - Low pre-test probability of re-intubation
- Corticosteroids reduce rate of re-intubation and post-extubation stridor
  - Administered at least 4 hours before extubation in high risk populations
  - High risk = identified by the leak test

LAST CONSIDERATIONS BEFORE EXTUBATING

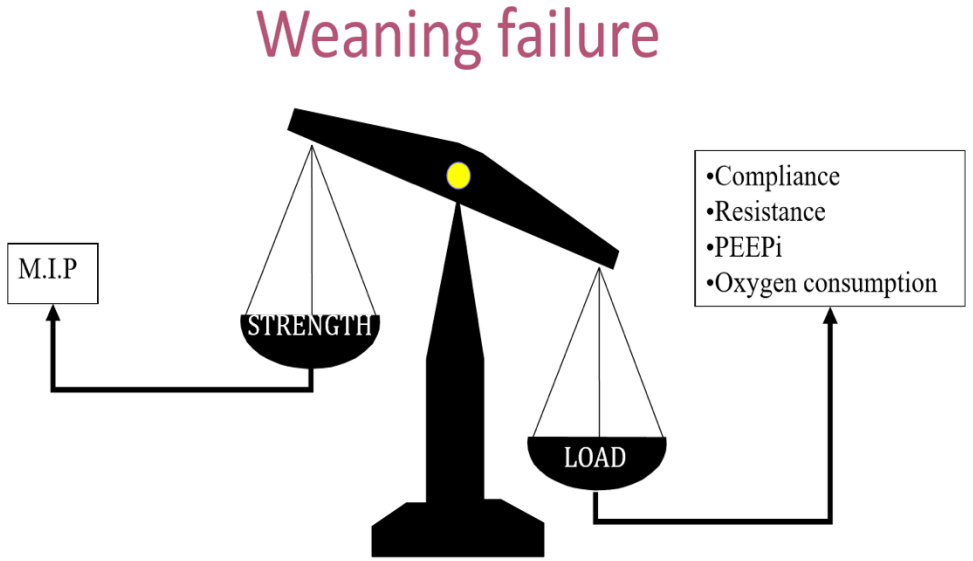
- Positive fluid balance the day before is unfavourable (Frutos-Vivar, Chest 2006)
- Consider the ability to clear secretions
  - Gag and cough reflex, frequency of suctioning
- Mental status
  - Especially if there are plans to extubate to HFNC and NIV – patient cooperation is key
- Upper airway structural abnormalities
- Intubation difficulty

WEANING FAILURE

- Success = absence of vent support during the first 48 hours after planned extubation
- Extubation failure = reintubation and reinstitution of ventilatory assistance within 48h of extubation (~15%)
  - Increased risk of death, prolonged hospital stay, decreased likelihood of returning home
- Weaning failure = (1) failed SBT (2) reintubation or resumption of ventilatory support within 48h following extubation

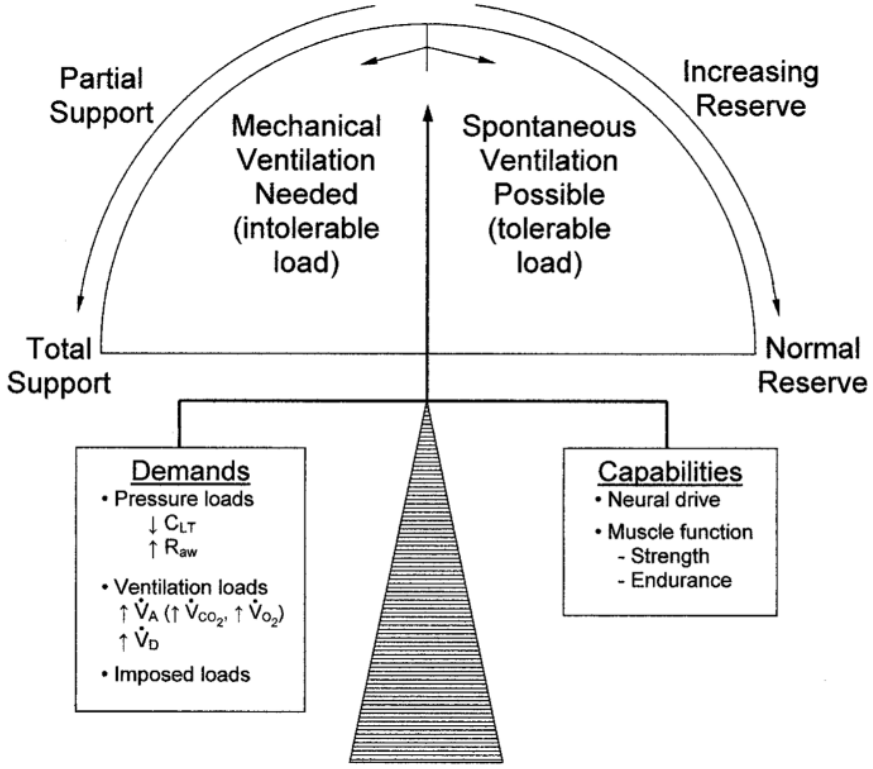
GENERAL APPROACH

- **Once-daily SBT**
  - Extubation 3x more quickly than intermittent mandatory ventilation and 2x more quickly than PSV weaning (Esteban, NEJM 1995)
- **PSV as weaning mode after failed SBT**
  - PSV had lower number of weaning failure compared to SIMV, T-piece (Brochard, AJRCCM 1994)
- Newer weaning modes
  - Proportionate assist ventilation
  - Adaptive servo-ventilation
    - Shorter time to extubation but mainly in cardiac surgery patients



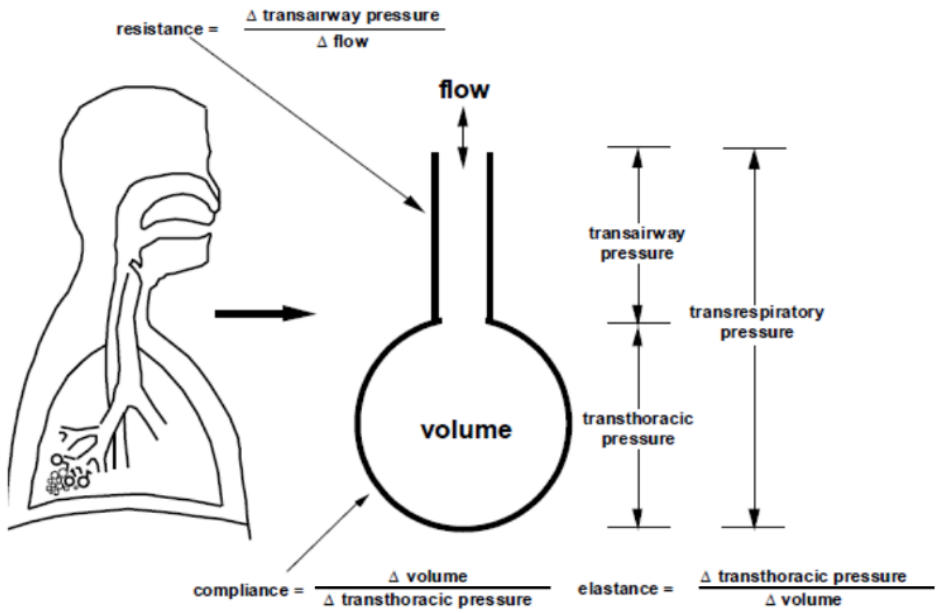
Imbalance between drive, respiratory workload and muscle efficency

DETERMINE THE CAUSE



Macintryre NR. Respir Care 1995; 40: 244 – 248

Equation of Motion



ventilator pressure + muscle pressure = elastic load + resistive load

$$P_{vent} + P_{Muscle} = \frac{Volume}{Compliance} + Flow \times Resistance$$

FAILURE TO WEAN

- Respiratory
  - Muscle power
  - Decrease WOB/ respiratory demand
  - Optimize drive: too much or too little?
  - Increase oxygenation and carrying capacity
  - Sputum clearance
- Brain
- CVS
- Metabolic/ electrolytes

Table 1. Factors affecting respiratory mechanics

Increased airway resistance	Reduced compliance
Tube (small diameter, sputum retention)	Chest wall
Central airways	Edema
Tracheostomy malposition	Elevated abdominal pressure
Sputum plug	Pleural fluid and ascites
Corpus alienum (after trauma)	Obesity
Tracheomalacia or tracheal stenosis	Lung
Small airways	Intrinsic positive end-expiratory pressure
Asthma and chronic obstructive pulmonary disease	Alveolar filling (edema, pus, and collapse)
Acute respiratory distress syndrome	Pneumonia
	Interstitial lung disease and fibrosis

ABCDE TO DIFFICULT TO WEAN PATIENTS

	Airway / lung			Brain		Cardiac	Diaphragm		Endocrine	
	Resistance	Complance	Gas exchange	Delirium	Other cognitive dysfunction				Endocrine	Metabolic
Assessment	Flow-time loops, inspiratory occlusion	inspiratory /expiratory occlusion	$(A\text{-}a)D_{O_2}$	CAM-ICU	Screening: depression, anxiety, sleep pattern	12 lead ECG before at end SBT Sv_{O_2} before / at end SBT	Pi, max	Serial physical examination (other neuromusc disorders)		Electrolytes Blood gas Indirect calorimetry
Intervention	albuterol, steroids Repeat loops, inspiratory occlusion PEEPi:Modify EIC in PSV bronchodilators	Radiology: Pleural fluid Atelectasis Ascites Diuretics Physiotherapy		Reorientation Mobilization Haloperidol	Anxiolytics Behavioral therapy Reduce noise / light during sleep	Echocardiography before & after SBT Afterload reduction Inotropes If ischemia: betablocker optimize hemoglobin	Early mobilization	Early mobilization		Provide adequate energy intake
Advanced assessment	Diagnostic bronchoscopy during SBT				Neuropsychologist: depression, anxiety,	Pulmonary artery catheter	Diaphragm fluoroscopy / echography $P_{0.1}$	Examination by neurologist EMG, nerve conduction velocity	Plasma cortisol before / after 250 umol ACTH Plasma thyroid hormone	
Advanced intervention		Thoracosentesis				Afterload reduction Inotropes	Reduce analgetics/ hypnotics		Cortisol iv Thyroid hormone	
Rescue assessment		Contrast echocardiography: intracardial shunt				BNP	Phrenic nerve conduction velocity Transdiaphragmatic pressure using gastric and esophageal balloon Diaphragm EMG	Muscle biopsy		
Rescue intervention				Dexmedetomidine		Levosimendan Bosentan	Antioxidants (vitamin C and E) Inspiratory muscle training			

Crit Care. 2010;14(6):245.

ABCDEF BUNDLE

TABLE 1. Definitions of the ABCDEF Bundle Components and Compliance Measurements[a]

Awakening	Complete interruption of sedative infusions and analgesic infusions as long as the patient was not having active pain
Breathing	Patients receiving mechanical ventilation were placed on continuous positive airway pressure or pressure-support ventilation 5/5 or blow-by for a minimum of 30 min
Choice of sedative/analgesics	Statement by the pharmacist that pain, agitation, delirium guidelines were being followed, including light sedation target, avoidance of benzodiazepines, and use of a pain-first sedation approach
Delirium monitoring and management	Confusion assessment method for the ICU was used to assess the patient on both the current shift and prior shift
Early mobilization	Patient was mobilized to maximum potential
Family engagement	The patient or family participated in rounds or a family conference had been held
Total compliance	Proportion of days during the patient's ICU stay that he or she received all elements of the ABCDEF bundle that the patient was eligible for on a given day
Partial compliance	Proportion of the number of components the patient received on a given day divided by the number of components the patient was eligible for on a given day, averaged over the ICU stay

[a]Components were considered compliant if they were accomplished during the previous 24 hr (rounds from prior day to rounds on present day).

1. Better patient survival
2. More days alive
3. More days free of delirium and coma

Crit Care Med. 2017 Feb;45(2):321-330

IF FIRST YOU FAIL… TRY AND TRY AGAIN

- Search for and correct causes for failure
- Gradual reduction in ventilatory support
- If patient meets SBT criteria, SBT should be performed every 24 hours
- In between, deliver stable, non-fatiguing form of ventilator support
  - Consider pressure targeted modes (PSV, PAV) for better synchrony
  - Avoid VILI and p-SILI
  - But need to balance over-supporting to avoid atrophy

NIV POST-EXTUBATION

- **Post-extubation to prevent re-intubation**
  - High risk patients (varies between studies)
    - **COPD**
    - **Heart failure**
    - **Age >65**
    - Previous extubation failure
    - Hypercapnia ($PaCO_2$ >45mmHg before or after SBT)
    - Obesity, OHS
- Rescue NIV used **after** resp distress within 48 hour, **does not prevent reintubation**
  - May increase mortality

3. For patients at high risk for extubation failure who have been receiving mechanical ventilation for more than 24 h, and who have passed an SBT, we recommend extubation to preventative NIV (Strong Recommendation, Moderate Quality of Evidence).

HFNC POST-EXTUBATION

- Reduces re-intubation rates post-extubation in respiratory failure
  - Compared to conventional O2
- Both high and low risk patients
- Non-inferior to NIV
- Alternating between NIV and HFNC may better than HFNC alone

Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients
A Randomized Clinical Trial

Gonzalo Hernández, MD, PhD; Concepción Vaquero, MD; Paloma González, MD; Carles Subira, MD; Fernando Frutos-Vivar, MD; Gemma Rialp, MD; Cesar Laborda, MD; Laura Colinas, MD; Rafael Cuena, MD; Rafael Fernández, MD, PhD

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients
A Randomized Clinical Trial

Gonzalo Hernández, MD, PhD; Concepción Vaquero, MD; Laura Colinas, MD; Rafael Cuena, MD; Paloma González, MD; Alfonso Canabal, MD, PhD; Susana Sanchez, MD; Maria Luisa Rodriguez, MD; Ana Villasclaras, MD; Rafael Fernández, MD, PhD

WHEN TO TRACH?

- Controversial
  - No benefit of early tracheostomy (4 vs 10 days, TracMAN JAMA 2013; 6-8 days vs 13-15 days, JAMA 2010)
  - In both studies, half of the patients in the late group never required tracheostomy
  - Subsequent systematic review (Hosokawa, Critical Care Medicine 2015): early tracheostomy associated with larger number of ventilator free days, shorter duration of sedation and potentially reduced long-term mortality
- Individualize
  - Global trajectory of the patient
  - Underlying reason for which the patient was intubated
  - Risks of the procedure

REFERENCES AND FURTHER READING

- ATS/CHEST Ad Hoc Committee on Liberation from Mechanical Ventilation in Adults. An Official American Thoracic Society/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 Jan 1;195(1):120-133.
- McConville JF, Kress JP. Weaning patients from the ventilator. N Engl J Med. 2012 Dec 6;367(23):2233-9.
- 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 May;151(5):1002-1010
- Frutos-Vivar F, Ferguson ND, Esteban A, Epstein SK, Arabi Y, Apezteguía C, González M, Hill NS, Nava S, D'Empaire G, Anzueto A. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. Chest. 2006 Dec;130(6):1664-71.
- Heunks LM, van der Hoeven JG. Clinical review: the ABC of weaning failure--a structured approach. Crit Care. 2010;14(6):245
- Hosokawa K, Nishimura M, Egi M, Vincent JL. Timing of tracheotomy in ICU patients: a systematic review of randomized controlled trials. Crit Care. 2015 Dec 4;19:424
- Barnes-Daly MA, Phillips G, Ely EW. Improving Hospital Survival and Reducing Brain Dysfunction at Seven California Community Hospitals: Implementing PAD Guidelines Via the ABCDEF Bundle in 6,064 Patients. Crit Care Med. 2017 Feb;45(2):171-178.