Weaning from mechanical ventilation: approach for the internist

Desmame da ventilação mecânica: abordagem para o clínico

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ABSTRACT

Weaning from mechanical ventilation is a challenge. Its prolongation is related to increased mortality. Studies have demonstrated that traditional objective criteria used are not able to shorten this time for discontinuation of mechanical ventilation. The aim of this study is to review the strategies that have been proposed and that can be used by the internist to shorten the weaning process. The judicious and systematized clinical judgment in the weaning process seems to be critical to decrease the time of weaning from mechanical ventilation. A cause of failure in weaning process should be systematically reviewed by the internist (airway and respiratory tract dysfunction, cardiac, neurological, endocrine and metabolic dysfunction). A protocol for weaning and sedation also seems crucial to shorten weaning. For the weaning process, bedside clinical follow-up by a multidisciplinary team is essential, taking various aspects into account, not only traditional objective criteria. With this approach strategy it is possible to reduce the duration of mechanical ventilation.

Keywords: Weaning; Respiration, artificial

RESUMO

O desmame da ventilação mecânica é um desafio. O seu prolongamento está relacionado ao aumento da mortalidade. Estudos têm demonstrado que os critérios objectivos tradicionais utilizados não são capazes de reduzir este tempo para interrupção da ventilação mecânica. O objetivo deste estudo é analisar as estratégias que têm sido propostas e que podem ser usadas pelo clínico para encurtar o processo de desmame. O julgamento clínico criterioso e sistematizado no processo de desmame parece ser fundamental para diminuir o tempo de desmame da ventila-

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ção mecânica. A causa da falha no processo de desmame deve ser sistematicamente revista pelo clínico (disfunções do trato respiratório, da via aérea, cardiológicas, neurológicas, endócrinológicas e disfunções metabólicas). Um protocolo para o desmame e sedação também parece crucial para reduzir o desmame. Para o processo de desmame, um acompanhamento clínico a beira do leito por uma equipe multidisciplinar é essencial, levando em consideração vários aspectos, não apenas critérios objetivos tradicionais. Com esta estratégia de abordagem é possível reduzir a duração da ventilação mecânica.

Descritores: Desmame; Respiração artificial

INTRODUCTION

Invasive mechanical ventilation is still associated with risks and complications that extend its duration⁽¹⁾ and this increase is associated with increased mortality⁽²⁾. Therefore, weaning from ventilaton safely and as early as possible is paramount.

Weaning is a process that starts with orotracheal intubation and ends with hospital discharge⁽³⁾ (Figure 1) or can be still considered a process of transition from mechanical to spontaneous ventilation in patients who remain on mechanical ventilation for more than 24 hours⁽⁴⁾.

The staff, when noting improvement in respiratory muscle function, and possible patient capacity to resume spontaneous ventilation, submits the patient to a "spontaneous breath trial" and, if the patient does not present any criteria of test intolerance, and does not have any other contraindication, mechanical ventilation is interrupted⁽⁵⁻⁷⁾.

A few fail weaning process after tolerating spontaneous breathing test, and may require a more gradual process, and an approach that is aimed at identifying the causes of intolerance.

A recent classification was proposed for weaning⁽³⁾:

- a) easy weaning: patient tolerates the first spontaneous breathing trial (SBT) and is successfully extubated (70% of patients);
- b) difficult weaning: The patient does not tolerate the first (SBT) and requires three tests, or up to 7 days from the first (SBT) for successful extubation;
- c) prolonged weaning The patient fails more than three (SBT), or takes more than 7 days, from the first (SBT) to extubation.

Patients in items "b" and "c" have higher mortality rate (25%) than other ICU patients (5%)

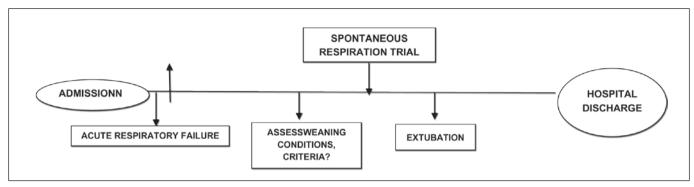


Figure 1. Weaning process

Eligible criteria for spontaneous breathing test

Patient's ability to breathe spontaneously is often underestimated. Over 50% of patients with spontaneous extubation do not return to mechanical ventilation. There are more than 50 objective physiological criteria to test the eligibility of successful weaning. Only 5 of these criteria were associated with significant changes in the probabilities of weaning success or failure, yet with low predictive value: tidal volume, minute volume, maximal inspiratory pressure, respiratory rate, and respiratory rate/tidal volume ratio (RR/TV, breaths per minute/ tidal volume in liters <105). The ratio (RR/TV) measured for 1-3 minutes was more accurate, although associated with only moderate changes in the probability of weaning success or failure⁽⁸⁾.

The subjective clinical judgment appears to have no good predictive value for possible eligibility for spontaneous breathing, with objective criteria being associated. However, approximately 30% of patients do not meet objective criteria, and yet could be successfully extubated. A randomized clinical trial⁽⁹⁾ used liberal oxygenation criteria as eligibility criteria for spontaneous breathing trial(Sat > 88%, PEEP ≤8, FiO2 ≤0.5) with a good success rate using no traditional criteria. Based on these concepts some consensus on mechanical ventilation weaning no longer recommend the use of criteria to help decide on (SBT). The most considered parameters would be hemodynamic stability, oxygenation criteria, evidence of clinical improvement, presence of spontaneous respiratory efforts.However, the eligible physiological criteria may still be useful in patients in whom the risks of weaning failure are extremely high.

There are more than 50 physiological criteria goals to test the eligibility of successful weaning. Only 5 of these criteria were associated with significant changes in the probabilities of weaning success or failure, yet with low predictive value: tidal volume, minute volume, maximal inspiratory pressure, respiratory rate, and respiratory rate/tidal volume ratio (RR/TV).

(RR/TV) ratio, measured for 1-3 minutes, was more accurate, though associated with only moderate changes in the probability of weaning success or failure.

The spontaneous breathing trial (SBT) is defined by patient disconnection from the ventilator and by respiration with or without continuous positive airway pressure (CPAP)<5cmH₂O,

pressure support <7mmHg,T-Tube. Randomized clinical trials comparing the three forms of the test were equivalent in their goals of weaning from mechanical ventilation⁽¹⁰⁾. The optimal duration of spontaneous breathing was studied in two clinical trials and suggested equivalence between 30 and 120 minutes for"T-tube" or "PS"⁽¹¹⁾.

One problem is related to the way the test is performed, for example, if performed on pressure support, continuous positive airway pressure (CPAP) or T-tube, values are different; moreover, there was a difference in the reproducibility of the test with different examiners, which also jeopardizesits goals.

Featuring some criteria of intolerance, such as tachycardia or bradycardia (increase or decrease of 20% of the baseline rate), tachypnea (more than 35 breaths per minute), hypoxemia (SpO₂<90%), hypertension (systolic blood pressure >180mmHg) or hypotension (systolic blood pressure <90mmHg), and/ or subjective criteria that can change the RR, such as anxiety and agitation. If the patient fails SBT or breathing index, the patient needs to return toMV, and what can be done to correct the problem should be discussed. The relevant clinical question is whether there is any physiological criteria that really makes the decision to perform weaning easier. In a randomized clinical trial with 304 patients who were organized with different daily criteria (PaO₂/FiO₂, PEEP, hemodynamic stability, efficient cough, level of consciousness, RR/TV), the ones who had good values in this assessment were submitted to (SBT) for 2 hours, and if they tolerated, they were extubated. The use of RR/TV ratio>105 as a criterion for continuing weaning in one group slowed the process in relation to the other groups, demonstrating no advantage⁽¹²⁾. In another study using phrenic nerve stimulation, the researcher concluded that there was no injury to the respiratory muscles associated with failure to wean in T-tube if the patient was rapidly returned to the respirator for signs of intolerance⁽¹³⁾.

A randomized clinical trial used, as eligibility criteria for spontaneous breathing trial, liberal oxygenation criteria (Sat >88%, PEEP ≤8, FiO₂ ≤0.5) with good success rate using no traditional criterion⁽¹⁴⁾. With these concepts, some consensus on mechanical ventilation weaning no longer recommend the use of criteria to help decide on the (SBT)^(3,15). The most considered parameters would be hemodynamic stability,

oxygenation criteria, evidence of clinical improvement, presence of spontaneous respiratory efforts. However, the eligible physiological criteria may still be useful in patients in whom the risks of weaning failure are extremely high.

Spontaneous breath tests

Undertaking direct extubation after establishing eligibility criteria for weaning progresses with 40% of patients reintubation⁽¹⁶⁾. Thus a prior spontaneous breathing trialis indicated involving pressure support (PS)(<7mmHg), CPAP or T-tube.

Randomized clinical trials comparing the three forms of the test were equivalent in their goals of weaning from mechanical ventilation^(5,17-19).

The optimal duration of spontaneous breathing trialwas studied in two clinical trials and it is suggested to be equally effective in 30 or 120 minutes using T-Tube or "PS"^(6,20).

This time may depend on the underlying disease. In a study involving patients with COPD and time exceeding 15 days on mechanical ventilation, the patients had a median time oftest failure of 120 minutes⁽²¹⁾.

Causes of weaning failure

Several reasons have been assigned to failures in the process of weaning: imbalances between the load imposed on the inspiratory muscles (diaphragm) and its capacity (endurance), the circuit itself, the endotracheal tube, heat and humidification devices, and respirator valves themselves; intrinsic factors, such as airway and pulmonary tract dysfunctions, neurological dysfunction, cardiac dysfunction, diaphragmatic dysfunction, and endocrine dysfunction^(22,23).

Respiratory system dysfunction

Increased airway resistance and, or decreased respiratory system compliance, as well as losses in gas exchange increase the work of breathing and hinder the weaning process. The clinician should search for factors that contribute to the worsening of respiratory mechanics and propose, if possible, reversal of the underlying clinical cause (Table 1).

Table 1. Factors affecting respiratory mechanics

Increased strength of airway	Decreased compliance
Endotracheal tube (diameter, retained secretions)	Chest wall (edema, increased abdominal pressure, ascites, pleural effusion, obesity)
Central airway (plug, foreign body, tracheomalacia, tracheal stenosis, tracheostomy malposition)	Lung (auto-PEEP, swelling, pus, alveolar collapse, pneumonia, interstitial lung disease and fibrosis)
Small airways (acute respiratory distress syndrome, chronic obstructive pulmonary disease, asthma)	

Losses in gas exchange may limit weaning progression in many patients. Many patients are unable to increase the minute volume in response to increases in carbon dioxide partial pressure. Some patients benefit from acts that restrict the dead space in mechanical ventilation (exchange filters, for example) when possible.

It is known that an important component of the imbalance between the load/respiratory muscle capacity is the geometric change of the diaphragm, for example,by lung hyperinflation, phrenic nerve injury after cardiac surgery. This change decreases the efficiency of contraction and increases breathing work. Other causes for this imbalance are neuromyopathy of critically ill^(24,25), ventilator-induced diaphragmatic dysfunction, endocrine dysfunction and malnutrition^(26,27).

Brain dysfunction

Delirium may incur in four-fold risk of extubation failure. Other psychological disorders such as anxiety and depression may also influence in weaning success^(28,29).

Cardiac dysfunction

Cardiac dysfunction may also be related to weaning failure in patients with heart failure and coronary artery disease⁽²⁸⁾. Spontaneous breathing may be associated with increased preload and afterload of the left ventricle with risk of pulmonary edema; in addition, the increased respiratory effort in spontaneous breathing is related to increased discharge of catecholamines, and may cause myocardial ischemia. These patients may not be able to increase cardiac output during spontaneous breathing and may have decreased central venous oxygen saturation⁽³⁰⁻³²⁾.

Levels of brain natriuretic peptide (BNP) in a study >275pg/ dL were a predictor for increased weaning time⁽³³⁾; positive water balance has also been associated with weaning failure by some authors.

Endocrine dysfunction

There are few studies that relate endocrine dysfunction and progression of weaning. And a study where they analyzed 93 patients with difficult weaning found diagnostic criteria for adrenal insufficiency⁽³⁴⁾. Supplemental corticosteroids in these patients reduced the time of weaning relative to placebo (3.4 ± 2.3 days *versus* 6.5 ± 4.7 days, respectively, with p<0.05). The pathophysiological mechanism has not been clarified. A retrospective study showed that hypothyroidism⁽³⁵⁾ could delay the time to weaning of patients. Mechanisms would be: decreased respiratory drive and influencein muscle dysfunction.

Weaning progression

If there is failure in the spontaneous breathing trial and the cause is identified as muscle fatigue, then the patient should receive mechanical ventilation for 24 hours⁽³⁶⁾ before another attempt; in case the cause of failure is not identified as muscle fatigue, and the cause can be corrected, other attempts are accepted.

The team must decide whether to opt for a daily trial of (SBT), or a gradual weaning process. Whether this process rebuilds the muscles or simply offers more time to recovery is not known. Two randomized clinical trials compared the progressive weaning techniques in patients with eligible criteria but who failed 2-hour(SBT). The use of T-tube was superior in one study and both showed that the use of individual SIMV delayed the time of weaning^(37,38).

Several studies have been conducted using non-invasive ventilation (NIV) as an alternative to difficult or prolonged weaning. A randomized clinical trial involved patients with failures in (SBT), most with chronic obstructive pulmonary disease (COPD). This study was terminated before being finished as it found a significant difference of decreasing time of weaning, days of ICU stay, duration of mechanical ventilation, mortality, incidence of nosocomial pneumonia and septic shock in patients undergoing noninvasive ventilation for weaning progression⁽³⁹⁾. Therefore, it is likely that it may be a valid alternative of weaning for subgroups of patients.

A recent alternative is the possibility of automated weaning. A randomized multicenter study⁽⁴⁰⁾ compared 144 patients on conventional versus automated weaning. The ventilator monitors physiological parameters and progressively decreases the pressure support of the device keeping the patient theoretically "comfortable". In the study, when minimal levels of PS have been achieved, the patient was taken to a standardized test of spontaneous breathing. The automated weaning demonstrated a shorter weaning time and ICU stay without major adverse effects such as reintubation.A later study did not confirm this superiority⁽⁴¹⁾.

Weaning protocols

The process of weaning from mechanical ventilation follows with great difficulty for the multidisciplinary team in the ICU. In a recent systematic review to analyze the effect of standardized protocols for weaning in the ICU, it is concluded that, although there is great heterogeneity among the studies, there was evidence of decreased duration of mechanical ventilation, weaning, and ICU stay using standardized protocols⁽⁴²⁻⁴⁵⁾.

However, it is believed that the protocols should be specific for different ICUs (neurosurgical, pediatric, etc.). Some studies using protocols that probably did not take into account the particularities of the studied population showed no advantages in the use of weaning protocols^(46,47).

Several randomized and observational studies have demonstrated that the minimization of the use of sedation is associated with decreased weaning time. The use of sedation scales and of scheduled daily interruption seems to reduce the time of weaning from mechanical ventilation. An observational study suggested that the use of intermittent rather than continuous sedation decreases the time of weaning⁽⁴⁸⁾.

Recently, a randomized clinical trial⁽⁴⁹⁾ compared the consecrated technique of the daily awakening with no sedation (using only intermittent morphine in the intervention group). The group of patients without sedation had a greater number

of days free of mechanical ventilation at 28 days (13.8 ± 9.6 *versus* 11 ± 10 , p=0.01)compared to the group of daily awaking. There was no difference between accidental extubation,need for reintubation, nosocomial pneumonia, hospital or ICU mortality between the groups.

Despite the very high ratio of nurses/patients in the study (1/1), and inaccuracies in the description of the level of awareness among patients, and high rates of exclusion of 288 patients, it is possible that, for selected patients, it is an alternative.Further studies are being conducted to answer this question.

Extubation

After successful completion of (SBT), extubation follows. Between 25-40 % of patients have a respiratory distress after extubation, and extubation failure (reintubation within 24 to 72) occurs in 5-20% of cases^(50,51).

The need for reintubation increases the length of ICU stay, need for tracheostomy and mortality of patients; on the other hand, slowing the process is also associated with increased mortality^(52,53).

There are not effective and reliable methods to serve as predictors of extubation failure.

A frequent extubation failure is related to the patient's inability to effectively protect the airway and manipulate secretions.

Some maneuvers may be attempted with the deflation of the cuff (leak test) previous to extubation to try to predict postextubation stridor, but there is a significant number of false positives. A randomized trial found reduced risk of reintubation using metilpredinisone for 24 hours before extubation⁽⁵⁴⁾. The III Brazilian Consensus on Mechanical Ventilation does not recommend the use of prophylactic steroids to prevent postextubation stridor in adults.

The ability to cough (peak cough flow >60L/min) and the amount of airway secretion (need for suction <2h) and level of consciousness (ability to respond to 4 simple commands) were highly predictive parameters for successful extubation in a study⁽⁵⁵⁾.

The use of noninvasive ventilation after extubation was studied in two randomized clinical trials and seems to be useful in subgroups of patients at high risk of extubation failure. (inefficient cough, heart failure, APACHE II >12, more than one comorbidity, patients >65 years old, failed SBT)^(56,57).

Weaning in patients with prolonged mechanical ventilation (PMV)

Approximately 10-30% of patients require mechanical ventilation for more than three weeks. The change in medical care (eg transfer of critically ill to ICU) makes about 50% not to progress to weaning that would have a high probability of success⁽⁵⁸⁻⁶⁰⁾.

For some of these patients, the imbalance between imposed respiratory load and neuromuscular capacity forms the substrate for dependence on the respirator and remains the major challenge related to weaning from mechanical ventilation⁽⁶¹⁾.

The computerized system of weaning has been studied by several randomized clinical trials with conflicting results. The reduction in the mean duration of mechanical ventilation was found in one study, 5 days to 3 days⁽⁶²⁾, and another found decreased time duration of weaning (29 *versus* 45h) compared to non-automated methods⁽⁶³⁾ but this outcome was not present in the other two^(64,65). The main reason for the divergence of results is attributed to the difference among the population of patients studied and among the protocols. There is insufficient evidence to recommend the method in comparison with the non-automated one.

There are a number of studies to be currently conducted, with a good level of evidence, and many aspects of the weaning process. Patients would be ready for weaning before the clinical perception of the specialist. The conduct of the process can be guided by a more liberal strategy of oxygenation without the need, and real usefulness, of predictors for weaning. The attempt of spontaneous breathing should be performed for at least 30 minutes in T-tube, CPAP or minimal pressure support. The team must systematically take into account all possible causes of unsuccessful weaning. The process conducted by noninvasive ventilation and "automatically"(66,67) seemsto be a promising strategy, as well as assessments with use of echocardiography and BNP (brain natriuretic peptide)⁽⁶⁸⁾. Identification of patients at high risk of extubation failure should be performed by the team. Integrity of cough capacity, amount of secretion, level of consciousness and leak cuff test of the endotracheal tube seem to be implicated. In these patients the use of noninvasive ventilation seems a good alternative in the weaning process.

REFERENCES

- 1. Pierson DJ. Patient-ventilator interaction. Respir Care. 2011; 56(2):214-228.
- Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation:a 28-day international study. J Am Med Assoc 2002;287(3):345-355.
- Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C,et al. Weaning from mechanical ventilation. Eur Respir J. 2007;29(5):1033-1056.
- Goldwasser R, Farias A, Freitas EE, Sady F, Amado V, Okamoto NV. Desmame e interrupção da ventilação mecânica. Rev Bras Ter Intensiva. 2007;19(3):384-92.
- Esteban A, Alia I, Gordo F, Fernández R, Solsona JF, Vallverdú 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(2PT1):459-65.
- Esteban A, Alia I, Tobin MJ, Gil A, Gordo F, Vallverdú I, et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med. 1999; 159(2):512-8.
- Vallverdu I, Calaf N, Subirana M, Net A, Benito S, Mancebo J. Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. Am J Respir Crit Care Med. 1998; 158(6):1855-62.

- Mion LC, Minnick AF, Leipzig R, Catrambone CD, Johnson ME. Patient-initiated device removal in intensive care units:a national prevalence study. Crit Care Med. 2007;35(12):2714-20.
- Ely EW, Baker AM, Evans GW, Haponik EF. The prognostic significance of passing a daily screen of weaning parameters. Intensive Care Med. 1999;25(6):581-7.
- El-Khatib MF, Zeineldine SM, Jamaleddine GW. Effect of pressure support ventilation and positive end expiratory pressure on the rapid shallow breathing index in intensive care unit patients. Intensive Care Med. 2008;34(3):505-10.
- 11. Tobin MJ, Jubran A. Variable performance of weaning-predictor tests:role of Bayes' theorem and spectrum and test-referral bias. Intensive Care Med. 2006;32(12):2002-12.
- Tanios MA, Nevins ML, Hendra KP, Cardinal P, Allan JE, Naumova EN, et al. A randomized, controlled trial of the role of weaning predictors in clinical decision making. Crit Care Med. 2006;34(10):2530-5.
- Laghi F, Cattapan SE, Jubran A, Parthasarathy S, Warshawsky P, Choi YS, et al. Is weaning failure caused by low frequency fatigue of the diaphragm? Am J Respir Crit Care Med. 2003;167(2):120-7.
- 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 randomized controlled trial. Lancet. 2008;371(9607):126-34.
- 15. MacIntyre NR, Cook DJ, Ely EW Jr, Epstein SK, Fink JB, Heffner JE, Hess D, Hubmayer RD, Scheinh DJ;American College of ChestPhysicians;American Association for Respiratory Care; American College of Critical Care Medicine. Evidence-based guidelines for weaning and discontinuing ventilatory support:a collective task force facilitated by the American College of Chest Physicians;the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest. 2001; 120(6 Suppl):375S-395S.
- Zeggwagh AA, Abouqal R, Madani N, Zekraoui A, Kerkeb O.Weaning from mechanical ventilation:a model for extubation. Intensive Care Med. 1999;25(10):1077-83.
- Farias JA, Retta A, Alia I, Olazarri F, Esteban A, Golubicki A. A comparison of two methods to perform a breathing trial before extubation in pediatric intensive care patients. Intensive Care Med. 2001;27(10):1649-54.
- Jones DP, Byrne P, Morgan C, Fraser I, Hyland R. Positive end-expiratory pressure vs. Tpiece.Extubation after mechanical ventilation. Chest. 1991;100(6):1655-9.
- Haberthur C, Mols G, Elsasser S, Bingisser R, Stocker R, Guttmann J. Extubation after breathing trials with automatic tube compensation, T-tube, or pressure support ventilation. Acta Anaesthesiol Scand. 2002;46(8):973-9.
- Perren A, Domenighetti G, Mauri S, Genini F, Vizzardi N. Protocol-directed weaning frommechanical ventilation:clinical outcome in patients randomized for a 30-min or 120-min trial with pressure support ventilation. Intensive Care Med. 2002; 28(8):1058-63.
- Vitacca M, Vianello A, Colombo D, Clini E, Porta R, Bianchi L,et al. Comparison of two methods for weaning patients with chronic obstructive pulmonary disease requiring mechanical ventilation for more than 15 days. Am J Respir Crit Care. Med 2001;164(8):225-30.
- 22. Vassilakopoulos T, Routsi C, Sotiropoulou C, Bitsakou C, Stanopoulos I, Roussos C, et al. The combination of the load/ force balance and the frequency/tidal volume can predict weaning outcome. Intensive Care Med. 2006;32(5):684-91.

- 23. Girault C, Breton L, Richard JC, Tamion F, Vandelet P, Aboab J, et al. Mechanical effects of airway humidification devices in difficult to wean patients. Crit Care Med. 2003;31(5):1306-11.
- 24. Jubran A, Grant BJ, Laghi F, Parthasarathy S, Tobin MJ. Weaning prediction:esophageal pressure monitoring complements readiness testing. Am J Respir Crit Care Med. 2005;171(11):1252-9.
- 25. De Jonghe B, Bastuji-Garin S, Sharshar T, Outin H, Brochard L. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? Intensive Care Med. 2004;30(6):1117-21.
- 26. Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med. 2004;169(3):336-41.
- 27. Datta D, Scalise P. Hypothyroidism and failure to wean in patients receiving prolonged mechanical ventilation at a regional weaning center. Chest. 2004;126(4):1307-12.
- Salam A, Tilluckdharry L, Moateng-Adjepong Y, Manthous CA. Neurologic status cough secretions and extubation outcomes. Intensive Care Med. 2004;30(7):1334-9.
- 29. Rothenhausler HB, Enhentraut S, von Degenfeld G, Weis M, Tichy M, Kilger E, Stoll C, Schelling G,Kapfhammer HP. Treatmentof depression with methylphenidate in patients difficult to wean from mechanical ventilation in the intensive care unit. J Clin Psychiatric. 2000;61(10):750-5.
- Chatila W, Ani S, Guaglianone D, Jacob B, Amoateng-Adijepong Y, Manthous CA. Cardiac ischemia during weaning from mechanical ventilation. Chest 1996;109(6):1577-83.
- 31. Frazier SK, Brom H, Widener J, Pender L, Stone KS, Moser DK. Prevalence of myocardial ischemia during mechanical ventilation and weaning and its effects on weaning success. Heart Lung. 2006;35(6):363-73.
- 32. Hurford WE, Lynch KE, Strauss HW, Lowenstein E, Zapol WM. Myocardial perfusion as assessed by thallium-201 scintigraphy during the discontinuation of mechanical ventilation in ventilatordependent patients. Anesthesiology. 1991;74(6):1007-16.
- 33. Lemaire F, Teboul JL, Cinotti L, Giotto G, Abrouk F, Steg G, et al. Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. Anesthesiology. 1988;69(2):171-9.
- Huang CG, Lin HC.Association between adrenal insufficiency and ventilator weaning. Am J Respir Crit Care Med. 2006,173(3): 276-80.
- 35. Martinez FJ, Bermudez-Gomes M, Celli BR. Hipothyreoidism. A reversible cause of diaphragmatic disfunction. Chest. 1989; 96(5):1059-63.
- 36. Mekontso-Dessap A, de Prost N,Girou E, Braconnier F, Lemaire F, Brun-Buisson C, et al. B-type natriuretic peptide and weaning from mechanical ventilation. Intensive Care Med. 2006;32(10):1529-36.
- Laghi F, D'Alfonso N, Tobin MJ. Pattern of recovery from diaphragmatic fatigue over 24 h. J Appl Physiol. 1995;79(2):539-46.
- 38. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med.1994;150(4):896-903.
- Esteban A, Frutos F, Tobin MJ, Alía I, Solsona JF, Valverdú 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(6):345-50. Comment in: N Engl J Med. 1995;332(6):388-9.
- 40. Ferrer M, Esquinas A, Arancibia F, Bauer TT, Gonzalez G, Carrillo A, et al. Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. Am J Respir Crit Care Med. 2003; 168(1):70-6.
- 41. Lellouche F, Mancebo J, Jolliet P, Roeseler J, Schortgen F, Dojat

M,et al. A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. Am J Respir Crit Care Med. 2006;174(8):894-900.

- 42. Chan PK, Fisher S, Stewart TE, Hallett DC, Haynes-Gay P, Lapinsky SE, et al. Practicing evidence- based medicine:the design and implementation of a multidisciplinary team-driven extubation protocol. Crit Care. 2001;5(6):349-54.
- 43. Henneman E, Dracup K, Ganz T, Molayeme O, Cooper CB. Using a collaborative weaning plan to decrease duration of mechanical ventilation and length of stay in the intensive care unit for patients receiving long-term ventilation. Am J Crit Care. 2002;11(2):132-40.
- 44. 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(5):943-51;discussion 951-2.
- Alderdice F, Burns KE, Cardwell CR, Cardwell CR, Lavery GG, O'Halloran P. Protocolized vs. non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients:Cochrane review protocol. J Adv Nurs. 2009; 65(5):957-64.
- 46. Blackwood B, Alderdice F, Burns K, Cardwell C, Lavery G, O'Halloran P. Use of weaning protocols for reducing duration of mechanical ventilation in critically ill adult patients:Cochrane systematic review and meta-analysis. BMJ.2011;342:c7237.
- 47. Namen AM, Ely EW, Tatter SB, Case LD, Lucia MA, Smith A, et al. Predictors of successful extubation in neurosurgical patients. Am J Respir Crit Care Med. 2001;163(3 Pt 1):658-64.
- 48. Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. J Am Med Assoc. 2002;288(20): 2561-8.
- 49. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. Chest. 1998;114(2):541-8.
- 50. Strom T, Martinussem T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation:a randomized trial. Lancet. 2010;375(9713):475-80.
- Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguía C, González M, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004; 350(24):2452-60. Comment in: N Engl J Med. 2004;350(24): 2452-60.
- 52. Epstein SK. Decision to extubate. Intensive Care Med. 2002; 28(5):535-46.
- 53. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. Chest. 1997;112(1):186-92.
- 54. 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(5):1530-6.
- 55. 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(5):1345-50.
- Salam A, Tilluckdharry L, Amoateng-Adjepong Y, Manthous CA.. Neurologic status, cough, secretions and extubation outcomes. Intensive Care Med. 2004;30(7):1334-9.
- Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early non-invasive ventilation averts extubation failure in patients at risk. a randomized trial. Am J Respir Crit Care Med. 2006;173(2):164-70.

- Nava SG, Gregoretti 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(11):2465-70.
- Scheinhorn DJ, Hassenpflug MS, Votto JJ,Chao DC, Epstein SK, Doig GS,et al. Post-ICU mechanical ventilation at 23 long-term care hospitals:a multicenter outcomes study. Chest. 2007;131(1):85-93.
- 60. Jouvet P, Farges C, Hatzakis J, Monir A, Lesage F, Dupic L, et al. Weaning children for mechanical ventilation with a computer driven system (closed loop protocol);a pilot study. Pediatr Crit Care Med. 2007;10(4):218-22.
- Scheinhorn DJ, Hassenpflug MS, Votto JJ, Chao DC, Epstein SK, Doig GS, et al. Ventilator-dependent survivors of catastrophic illness transferred to 23 long-term care hospitals for weaning from prolonged mechanical ventilation. Chest. 2007;131(1):76-84.
- Lellouche F, Mancebo J, Jolliet P, Roeseler J, Schortgen F, Dojat M, et al. A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. Am J Respir Crit Care Med. 2006;174(8):894-900.
- 63. Liu L, Su ST, Yang Y, Huang YZ, Liu SQ, Qiu HB. Computer-

driven automated weaning reduces weaning duration in difficultto-wean patients. Chin Med J. 2013;126(10):1814-8.

- 64. Rose L, Presneill JJ, Johnston L, Cade JF. A randomised, controlled trial of conventional versus automated weaning from mechanical ventilation using SmartCareTM/PS. Intensive Care Med. 2008;34(10):1788-95.
- 65. Schadler D, Elke G, Pulletz S, Haake N, Frerichs I, Scholz J, et al. The effect of automatic weaning with SmartCare/PS on ventilation time in postsurgical patients - A randomized controlled trial. Am J Respir Crit Care Med. 2009;179:A3646.
- Schadler D, Engel C, Elke G, Pulletz S, Haake N, Freichs I, et al. Automatic control of pressure support for ventilator weaning in surgical intensive care patients. Am J Respir Crit Care Med. 2012;185(6):637-44.
- 67. Burns KE, Adhikari NKJ, Meade MO. A meta-analysis of noninvasive weaning to facilitate liberation from mechanical ventilation. Can J Anesth. 2006;53(3):305-15.
- Zapata L, Vera P, Roglan A, Gich I, Ordonez-LlanosJ, Betbesé AJ. B-type natriretic peptides for prediction and diagnosis for weaning failure for cardiac origin. Intensive Care Med. 2011;37(3): 477-85.