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Critical Review

Neurormonal and inflammatory responses during weaning trials from mechanical ventilation

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Abstract

Introduction

Weaning from mechanical ventilation is usually accomplished with spontaneous breathing trials. The discontinuation of mechanical ventilation and the resumption of spontaneous breathing may increase oxygen demands, and patients, mainly those with limited cardiorespiratory reserve, are subjected to pulmonary and cardiovascular stress. In addition, emotional distress due to agitation after interruption of sedative drugs, anxiety and other sources of discomfort potentially contributes to pulmonary and cardiovascular stress. There is evidence of metabolic and endocrine stress response expressed as an increase in oxygen consumption and plasma concentration of catecholamines and other hormones involved in the stress system activation, in patients during the weaning process from mechanical ventilation, especially during failing weaning attempts. Furthermore, extrapolating from both physical exercise and inspiratory resistive breathing data, there is evidence of immune response expressed as an increase of proinflammatory cytokine blood levels. The purpose of this review is to summarise the published information about neurormonal and inflammatory stress response during weaning from mechanical ventilation.

Conclusion

The stress response during weaning trials from mechanical ventilation has not been studied enough. Nevertheless, there is evidence that the process of weaning from mechanical ventilation incorporates hormonal, inflammatory and neuroendocrine responses, indicating that weaning might prove physically and psychologically stressful. Further studies should evaluate this stress response more thoroughly for better management of these patients.

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Introduction

The goal of weaning from mechanical ventilation is to withdraw the respiratory support and ultimately a successful removal of the endotracheal tube. Weaning should be considered at the earliest possible time because undue prolongation of mechanical ventilation is directly associated with complications, including ventilator-associated pneumonia, airway trauma, increased ICU length of stay, cost and mortality[1]. A focused, simple daily screening has been recommended as a diagnostic test to determine the likelihood of successful extubation in patients who fulfil the weaning readiness criteria. For this purpose, two strategies of spontaneous breathing trial (SBT) have been recommended as equally effective techniques. The first one comprise the use of spontaneous breathing via a T-piece circuit, and the second one the use of a low-level pressure support ventilation (PSV) as a weaning mode[1,2].

Unless simple according to the new classification[1], weaning is time-consuming, comprising nearly 40% of the duration of mechanical ventilation[3]. Although the majority of mechanically ventilated patients finally can be successfully weaned, weaning attempts present a high rate of failure estimated to be 26%–42% and even higher (upto 60%) in patients with limited respiratory reserve such as those with chronic respiratory disorders[4]. Increasing attention has been given to the consequences of the transition from mechanical ventilation to spontaneous breathing. This is a complex and multifactorial process involving diverse pathophysiology mechanisms; the most common include an excessive load to the respiratory and cardiovascular systems, metabolic/endocrine disorders as well as neuromuscular and neuropsychological causes[1,2]. Previous studies have focused on the respiratory and cardiovascular difficulties the patients face during the weaning process; weaning from mechanical ventilation has been described as performing a sudden exercise and it has been compared to a cardiopulmonary exercise stress test[5,6]. As such, weaning involves changes and interactions in different organ systems. More specifically, unsuccessful weaning attempts, even transient, represent an acute stressful situation that can trigger a cascade of stress hormones. Potential consequences of this stress may have implications for the patients, including the safety of the SBT, and influence the weaning and the ICU outcome.

The effect of weaning from mechanical ventilation on stress response has received little attention in critical care. Extrapolating from the evidence in exercise and sports physiology, as well as from resistive breathing effects on endocrinic and

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immune system, one could suggest a similar response during an unsuccessful weaning attempt. Herein, we summarise the few available data provided by previously published studies on this topic. To this target, a short report on the stress response to exercise and resistive breathing literature is initially presented.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Stress response to exercise

Whole body exercise represents a physical stress and, if intense enough, induces an immune response in healthy subjects mediated by metabolic, endocrine and immunological factors[7]. The magnitude of this response depends on many factors including type, duration and intensity of exercise[8]. More specifically, as a response to an acute stress, the hypothalamic–pituitary–adrenal (HPA) system is activated, which in turn, triggers the production and release of steroid hormones including cortisole, which is the primary mediator of the stress system, release of catecholamines, which are neuroendocrinic hormones, particularly epinephrine and norepinephrine and β-endorphin and growth hormones. Furthermore, exercise stress and the resultant catecholamine release stimulate cytokine production, mainly IL-6, at an extent that is correlated with catecholamine levels, leading to post-strenuous exercise immune function depression[9–11]. Therefore, exercise stress response is considered as an important factor in the modulation of immune function. Moreover, data from patients with chronic obstructive pulmonary disease (COPD) show that physical exercise induces a systemic inflammatory and oxidative response[12]. Notably, compared with healthy subjects, COPD patients presented a marked accentuation of exercise-induced increase in the IL-6 level[13].

Stress response to resistive breathing

Resistive breathing refers to breathing through an increased resistance added to respiration[14,15]. Similarly to the above-mentioned hormonal and inflammatory response to intense physical exercise[9–11], recent experimental and human studies indicate that strenuous resistive breathing, as a form of respiratory muscles exercise, induces proinflammatory cytokines and stimulates the HPA axis in healthy humans[14–16]. Shortly, a significant increase in the plasma levels of IL-6, IL-1β, ACTH and β-endorphin was observed in healthy volunteers after strenuous breathing with an additional inspiratory load at 75% of their maximum inspiratory pressure for 45 min. Particularly, IL-6 was found to be responsible for the activation of the HPA system, leading to the increase in plasma β-endorphin and ACTH[15,16]. The possible participation of cytokines in the mechanisms of respiratory muscle fatigue and in the ventilatory control has been suggested. To note, as in moderate whole body exercise, the moderate inspiratory resistive breathing does not lead to such a response, indicating that the phenomenon is restricted to intense conditions.

The origin of plasma cytokines increase during resistive breathing is questionable. Although circulating monocytes are a major source of immune-inflammatory mediators, strenuous resistive breathing-induced plasma cytokines in healthy humans do not originate from circulating monocytes[16]. As shown experimentally, resistive breathing induces cytokines within the diaphragm. IL-6 and, to a lesser extent, IL-1β, TNF-α, IL-10, IFN-γ and IL-4, were significantly increased in the diaphragm of animals subjected to inspiratory resistive loading in a time-dependent manner[17].

Stress response to weaning from mechanical ventilation

Stress hormones

A usual SBT trial is a short testing period, lasting either 30 or 120 min[1,2]. The stress of spontaneous breathing with an increase in catecholamine release had been initially assumed by Annat and colleagues in an earlier study performed in patients with cardiopulmonary diseases, mainly COPD, who increased their oxygen cost of breathing when changed from controlled mechanical ventilation to spontaneous breathing with continuous positive airway pressure (CPAP)[18]. This assumption was based on the enhanced systolic blood pressure usually observed when changing from CMV to spontaneous breathing.

The sympathoadrenal response during weaning from mechanical ventilation has been first demonstrated by Kennendy et al.[19]. A significant increase of urinary norepinephrine excretion was shown in weaning success and weaning failure patients, suggesting sympathoadrenal stimulation. However, the amounts of norepinephrine and epinephrine excretion were smaller in weaning failure compared with weaning success, attributable by the authors to an inadequate stimulus or response of the sympathoadrenal system in the former group.

Catecholamines, having a short half life of only a few minutes when circulating in the blood, provide an immediate measure of stress. Increased sympathetic activity reflected by tachycardia, increased arterial blood pressure and augmented blood levels of epineph-

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rine and norepinephrine has been documented in mechanically ventilated COPD patients at 10 min after the start of a failed SBT, by Lemaire and colleagues in their landmark study on the haemodynamic effects of weaning[20]. The mean plasma norepinephrine levels significantly increased from 1.13 ± 0.55 ng/ml on CMV to 1.85 ± 0.96 ng/ml during spontaneous breathing, and epinephrine levels significantly increased from 0.10 ± 0.05 to 0.20 ± 0.13 ng/ml, respectively. Similarly, in another study by Oh and coworkers[21], increases in plasma catecholamine levels during weaning trials were found. Mean plasma epinephrine levels significantly increased from 136 pg/ml on CMV to 508 pg/ml during weaning, and norepinephrine levels increased from 483 to 1143 pg/ml, respectively. The greater increases occurred in patients failing to wean. It is necessary to note that normal plasma concentrations of epinephrine and norepinephrine range, respectively, from about 30 to 200 pg/ml at rest and increase when metabolic rate increases. This stress hormone secretion was thought to contribute to the increase of oxygen consumption the patients had during weaning. The results of the above studies support the hypothesis that, during weaning metabolic stress from a combination of increased respiratory work and sympathetic activation leads to increased oxygen demand. This may have detrimental effects, through tachycardia and increased heart afterload and preload, on myocardial oxygen demand, that may promote myocardial ischaemia, resulting in more anxiety and dyspnoea, thus leading to weaning failure if cardiorespiratory reserve is insufficient.

Endocrine stress response during weaning was investigated by Koksal et al.[22]. They demonstrated changes in blood concentrations of insulin, cortisol and glycose, and in urine vanilmandelic acid during weaning from mechanical ventilation using three different modes, i.e. PSV, CPAP and T-piece. They found that weaning increases the endocrine stress response and that the magnitude of increase was influenced by the mode used, being significantly greater at the end of a SBT using a T-piece than using either PSV or CPAP modes. Such an increase in endocrine stress response has not been confirmed by other authors. Calzia et al.[23] compared the effects of weaning, using synchronised intermitted mandatory ventilation, on the stress hormone response, oxygen uptake and work of breathing in 10 patients after uncomplicated cardiac surgery. Although plasma concentrations of epinephrine, norepinephrine, ACTH, cortisole, vasopressin and prolactin were greater than normal during the weaning process, they did not change significantly at the end of weaning compared with baseline values. Obviously, the absence of a pre-existing pulmonary or other disease in these patients and the uncomplicated surgery made the weaning successful and "simple", according to the current classification[1]. Quinn et al.[24] also reported changes in stress hormone concentrations on different modes of ventilation. Mechanically ventilated preterm babies with respiratory distress syndrome significantly reduced adrenaline concentration when changed from conventional mandatory ventilation, which did not take into account of the baby's efforts leading to asynchrony, to patient triggering ventilation which provides synchrony between the baby and the ventilation. The reduction in adrenaline concentration was thought to reflect a genuine reduction in stress. Nevertheless, all the above studies have been performed in a small patient population and their results are not absolutely dependable; more rigorous research data are not available as yet.

Emotional distress during weaning

Patients with total or partial dependence from a ventilator are at risk for emotional distress and mental discomfort, especially in prolonged ventilatory support[25,26]. The transfer from mechanical ventilation to spontaneous breathing also has an emotive component. The withdrawal of ventilator support, the lowering or interruption of sedation and the resultant arousal required for the weaning process can lead to the patients' agitation and/or delirium, sometimes enhanced by benzodiazepine and/or opioid withdrawal syndrome. The inability to talk because of the presence of an endotracheal tube, along with total or partial dependence on the ventilator, makes it difficult for patients to communicate their needs. Additionally, psychological disturbances increase due to fear of death and abandonment by staff. Thus, beyond the respiratory distress experienced by some patients, weaning can induce agitation and diffuse anxiety, potentially contributing to weaning difficulty. Indeed, agitation and anxiety are included among the weaning failure criteria[1] indicating that the patient is not ready to be discontinued from mechanical ventilator support. To date, however, only a limited number of studies have investigated this issue. Jubran and colleagues described depressive disorders in 42% of patients who were being weaned from prolonged ventilation[26]. Importantly, the patients with depressive disorders were more likely to experience weaning failure and death. On the other hand, the beneficial effects of alpha-2 adrenergic agonists, such as clonidine[27] or dexmedetomidine[28], as well as of loxapine[29] on resolution of agitation during weaning from mechanical ventilation of patients who failed conventional therapy, provide an indirect evidence of the neurological and emotional stress the patients face during this critical period.

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A growing body of research indicates that exposure to psychological stress activates multiple biological systems, including the HPA axis, which as mentioned above, regulates the inflammatory response. A transient rise in peripheral cytokines in healthy adult humans after acute psychological stress has been shown[30,31]. Also, recent data are indicative of anxiety-specific effects on inflammatory activity. Clinically anxious individuals had higher levels of the pro-inflammatory cytokine IL-6 and lower levels of the stress hormone cortisol, compared with non-anxious individuals, whereas both groups had equivalent levels of the systemic inflammatory marker C-reactive protein (CRP)[32].

Inflammatory indices during weaning

Sometimes, the process of weaning may impose high inspiratory load on the respiratory muscles, either from a small artificial airway size, accumulation of secretions or bronchoconstriction during an SBT or from increased respiratory resistance after extubation because of mucosal swelling and oedema that develops in the upper airways or increased airway secretions and sputum retention, resulting in postextubation distress. Therefore, an SBT could be considered a stress phenomenon, similar to resistive breathing. Therefore, just like in previous experiments in humans mentioned above[14–17], pro-inflammatory cytokine production could be expected during SBT contributing to the development of stress response.

Indeed, there is recent evidence for weaning-induced cytokine release. Sellares et al.[33] have examined the levels of IL-6, other cytokines (tumour necrosis factor-α, IL-1β, IL-8, 1L-10) and CRP before and at the end of an SBT, conducted on T-piece, in 49 mechanically ventilated patients. They found an increase in IL-6, which is a major modulator of stress response, in SBT failure. Importantly, when the patients were divided into COPD and non-COPD subgroups, only the subset of patients with COPD increased IL-6 during the SBT, possibly indicating the increased cardiopulmonary stress these patients face during the SBT. No changes were observed in the other inflammatory mediators assessed.

The mechanism of IL-6 induction remains unknown. Given the complex physiologic nature of weaning failure, it is not clear whether the increase in IL-6 was triggered by a hard working cardiorespiratory system and the resultant dyspnoea or by non-respiratory factors such as pain, anxiety and other psychological such factors, although one could speculate that all these determinants contribute to the IL-6 increase. Increase in blood levels of inflammatory markers during failed weaning attempts has not been reported elsewhere, so these findings should be confirmed in future studies. Nevertheless, the existing data indicate that a failed SBT might cause systemic adverse reactions by inducing release of mediators into the circulation.

Conclusion

In summary, there is available evidence that the process of weaning from mechanical ventilation incorporates hormonal, inflammatory and neuroendocrine responses, indicating that weaning might prove physically and psychologically stressful. Future research should elucidate the mechanisms of such responses and evaluate the role of diverse indices as surrogate biomarkers indicating potential patient discomfort during the weaning process, especially during failing weaning attempts.

References

1. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melote C, et al. Weaning from mechanical ventilation. Statement of the Sixth International Consensus Conference on Intensive Care Medicine organized jointly by the European Respiratory Society (ERS), the American Thoracic Society (ATS), the European Society of Intensive Care Medicine (ESICM), the Society of Critical Care Medicine (SCCM) and the Société de Réanimation de Langue Francaise (SRLF). Eur Respir J. 2007;29(5):1033–56.
2. Perren A, Brochard L. Managing the apparent and hidden difficulties of weaning from mechanical ventilation. Intensive Care Med. 2013;39(11):1885–95.
3. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation. A 28-day international study. J Am Med Assoc. 2002;287(3):345–55.
4. 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.
5. Pinsky MR. The hemodynamic consequences from mechanical ventilation: an evolving story. Intensive Care Med. 1997;23(5):493–503.
6. Pinsky MR. Breathing as exercise: the cardiovascular response to weaning from mechanical ventilation. Intensive Care Med. 2000;26(9):1164–6.
7. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. Physiol Rev. 2000;80(3):1055–81.
8. Nieman DC. Exercise immunology: practical applications. Intern J Sports Med. 1997;18:S91–100.
9. Papanicolaou DA. Exercise stimulates interleukin-6 secretion: inhibition by glucocorticoids and correlation with catecholamines. Am J Physiol. 1996;271(3 pt 1):E601–5.
10. Mastorakos G, Ilias I. Interleukin-6, a cytokine and /or a major modulator of the response to somatic stress. Ann N Y Acad Sci. 2006;1088:373–81.
11. Chroussos GP. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. N Engl J Med. 1995;332(20):1351–62.
12. Van Helvoort HA, van de Pol MH, Heijidra YF, Dekhuijzn PN. Systemic inflammatory response to exhaustive exercise in patients with chronic obstructive pulmonary disease. Respir Med. 2005;99(12):1555–67.

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All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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13. Jammes Y, Steinberg JG, Ba A, Delliaux S, Bregeon F. Enhanced exercise-induced plasma cytokine response and oxidative stress in COPD patients depend on blood oxygenation. Clin Physiol Funct Imaging. 2008;28(3):182–8.
14. Aleksandrova NP. Cytokines and resistive breathing. Fiziol Cheloveka. 2012;38(2):119–29.
15. Vassilakopoulos T, Roussos C, Zakynthinos S. The immune response to resistive breathing. Eur Respir J. 2004;24(6):1033–43.
16. Vassilakopoulos T, Zakynthinos S, Roussos C. Strenuous resistive breathing induces proinflammatory cytokines and stimulates the HPA axis in humans. Am J Physiol. 1999;277(4 pt 2):R1013–9.
17. Vassilakopoulos T, Divangahi M, Rallis G, Kishta O, Petrof V, Comtois A, et al. Differential cytokine gene expression in the diaphragm in response to strenuous resistive breathing. Am J Respir Crit Care Med. 2004;170(2):154–61.
18. Annat GJ, Viale JP, Dereymez CP, Bouffard YM, Delafosse BX, Motin JP. Oxygen cost of breathing and diaphragmatic pressure-time index. Measurement in patients with COPD during weaning with pressure support ventilation. Chest. 1990;98(2):411–4.
19. Kennedy SK, Weintraub RM, Skillman JJ. Cardiorespiratory and sympathoadrenal responses during controlled ventilation. Surgery. 1977;82(2):233–40.
20. 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.
21. Oh TE, Bhatt S, Lin ES, Hutchinson RC, Low JM. Plasma catecholamines and oxygen consumption during weaning from mechanical ventilation. Intensive Care Med. 1991;17(4):199–203.
22. Konsal GM, Sayilgan C, Sen O, Oz H. The effects of different weaning modes on the endocrine stress response. Crit Care. 2004;8(1):R31–4.
23. Calzia E, Koch M, Stahl W, Radermacher P, Brinkmann A. Stress response during weaning after cardiac surgery. Br J Anaesth. 2001;87(3):490–3.
24. Quinn MW, de Boer RC, Ansari N, Baumer JH. Stress response and mode of ventilation in preterm infants. Arch Dis Child Fetal Neonatal Ed. 1998;78(3):F195–8.
25. Schmidt M, Banzett RB, Raux M, Morelot-Panzini C, Dangers L, Similowski T, et al. Unrecognized suffering in the ICU: addressing dyspnea in mechanically ventilated patients. Intensive Care Med. 2014;40(1)1–10.
26. Jubran A, Lawm G, Kelly J, Duffner LA, Gungor G, Collins EG, et al. Depressive disorders during weaning from prolonged mechanical ventilation. Intensive Care Med. 2010;36(5):828–35.
27. Liatsi D, Tsapas D, Pampori S, Tsagourias M, Pneumatikos I, Matamis D. Respiratory, metabolic and hemodynamic effects of clonidine in ventilated patients presenting with withdrawal syndrome. Intensive Care Med. 2009;35(2):275–81.
28. Shehabi Y, Nakae H, Hammond N, Bass F, Nicholson L, Chen J. The effect of dexmedetomidine on agitation during weaning of mechanical ventilation in critically ill patients. Anaesth Intensive Care. 2010;38(1):82–90.
29. Sztrymf B, Chevrel G, Bertrand F, Margetis D, Hurel D, Ricard JD, et al. Beneficial effects of loxapine on agitation and breathing patterns during weaning from mechanical ventilation. Crit Care. 2010;14(3):R86.
30. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav Immun. 2007; 21:901–12.
31. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009;65(9):732–41.
32. Carroll JE, Low CA, Prather AA, Cohen S, Fury JM, Ross DC, et al. Negative affective responses to a speech task predict changes in interleukin-6. Brain Behav Immun. 2011;25(2):232–8.
33. Sellares J, Loureiro H, Ferrer M, Amaro R, Farre R, Torres A. The effect of spontaneous breathing on systemic interleukin-6 during ventilator weaning. Eur Respir J. 2012;39(3):654–60.

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