What Are the Implications of Blunted Load Compensation Responses in Prolonged-Weaning Patients?

Removal of patients from mechanical ventilation can be classified into 3 categories: simple-weaning, comprising the majority of patients, who can be extubated without difficulty on the first spontaneous breathing trial (SBT); difficult-weaning, defined as requiring up to 3 SBTs or as many as 7 days from the first SBT to achieve successful weaning; and prolonged-weaning, defined as requiring more than 3 SBTs or more than 7 days of weaning subsequent to the first SBT.[1] In a prospective study, the prevalence of difficult weaning was 26%,[2] whereas that of prolonged-weaning varied from 14% to 33%.[2,3] Patients with difficult weaning, compared with the simple-weaning group, had fewer ventilator-free and ICU-free days, and longer hospital stay, although mortality was similar.[2] On the other hand, the prolonged-weaning group had a significantly higher ICU mortality (22%) and hospital mortality (32%).[2] Prolonged-weaning patients who required transfer to a long-term acute care hospital had an overall mortality of 54% and 63% at 6 months and 12 months, respectively.[4] The prolonged-weaning group has a poor prognosis, and intervention to improve outcome is complex, since the etiology of prolonged weaning is multifactorial.[5]

Among the causes of prolonged weaning is an imbalance between inspiratory muscle work load and inspiratory muscle capacity, with inspiratory muscle weakness or dysfunction a major determinant of prolonged weaning.[6] A recent study reported the frequency of diaphragm muscle weakness in 85 ICU patients receiving mechanical ventilation after the first and third day of intubation.[7] The ability of the diaphragm muscle to generate force was estimated from the occluded twitch tracheal pressure, measured at the proximal end of the endotracheal tube, during twitch stimulation of bilateral phrenic nerves. Twitch tracheal pressure was used as surrogate of twitch transdiaphragmatic pressure, to reflect diaphragm muscle strength independent of the patient's voluntary effort and cooperation. Phrenic nerves stimulation was performed noninvasively, using bilateral anterior magnetic stimulation. On day 1 the patients' median twitch tracheal pressure was 8.2 cm H_2O; 64% of patients had a twitch tracheal pressure of < 11 cm H_2O (the value considered as indicating diaphragm muscle weakness). On day 3 the median twitch tracheal pressure was virtually unchanged, at 8.7 cm H_2O. The ICU mortality of patients with diaphragm muscle weakness (48%) was nearly 3-fold that of those without diaphragm muscle weakness (16%). In the controls (17 patients, anesthetized, intubated, and on mechanical ventilation for < 2 hours for gastrointestinal endoscopic procedures) the average twitch tracheal pressure was 23.2 cm H_2O, and 95% of the controls had twitch tracheal pressure > 11 cm H_2O. This study suggests a high prevalence of diaphragm muscle weakness in ICU patients at the initiation of mechanical ventilation. Diaphragm muscle weakness may have contributed to the requirement for ventilatory support, and is associated with high mortality. Furthermore, sepsis and severity of illness were independent predictors of diaphragm muscle weakness. The lack of deterioration in twitch tracheal pressure following 3 days of mechanical ventilation may be either the result of severe diaphragm muscle weakness (ie, pressure generation had already reached its lower limit), or the fact that the application of patient-triggered mechanical ventilation helps maintain diaphragmatic force production, a phenomenon demonstrated in animal studies.[8,9] Unfortunately, the study did not specify the mode(s) of mechanical ventilation.

In another study of ICU patients, diaphragm muscle weakness occurred progressively, with a 30% decline in twitch tracheal pressure over 5–6 days of controlled mechanical ventilation.[10] The investigators postulated that the mechanical ventilation itself might have contributed to the development of diaphragm muscle weakness, as has been observed in experimental animals[11] and brain dead organ-donors.[10,12,13] Inspiratory muscle weakness is unquestionably a major contributor to prolonged weaning.[6]

Intervention to strengthen the inspiratory muscles seems a logical step to facilitate weaning from mechanical ventilation. Several methods of inspiratory muscle training have been employed; these include isocapnic hyperpnea to improve respiratory muscle endurance,[14] inspiratory resistive-flow training,[15,16] inspiratory threshold-pressure training,[17,18] and adjustments of ventilator pressure sensitivity.[19] While the first method focuses on endurance, the latter 3 are to improve inspiratory muscle strength. Comparison among training methods based on efficacy to facilitate weaning is unavailable. The method employing the inspiratory threshold-pressure training device, which maintains a given constant pressure, independent of flow,[20]

and is commercially available, has therefore been commonly employed.[17,18] Most studies on inspiratory muscle strength training (IMST) for facilitating weaning from mechanical ventilation are case series without controls,[21] making IMST efficacy difficult to interpret. However, IMST appears safe.

Only 3 prospective, randomized-controlled studies of IMST efficacy with an inspiratory threshold-pressure training device have been reported.[17,22,23] Cader and co-workers[22] randomized 41 patients of 70 years or older into a group receiving IMST ($n = 21$) or a control group ($n = 20$). Duration of mechanical ventilation prior to IMST was 7 days. IMST began when the patients were on spontaneous ventilation (ie, pressure support). The load was set at 30% of maximum inspiratory pressure (P_{Imax}), increasing daily by 10% with training for 5 min, twice a day, 7 days a week. Compared with the control group, the training group increased P_{Imax} from an average of 15 cm H_2O to 25 cm H_2O, and weaning time was shorter (3.6 d vs 5.3 d). The successful weaning rate at 15 days was similar.

Martin and co-workers[17] randomized 69 patients into groups receiving IMST ($n = 35$) or sham control ($n = 34$). In the training group the load was set at the highest pressure at which the subject could consistently open the valve. IMST was performed via tracheostomy, 5 days a week, in 4 sets of 6–10 breaths per day, with 2 min of rest with ventilatory support between each set. The duration of mechanical ventilation in the IMST group versus controls prior to IMST was 42 days and 47 days, respectively. P_{Imax} improved in the IMST group from 44 cm H_2O to 54 cm H_2O. Among the 35 patients in the IMST group, 25 patients (71%) were weaned, versus 16 of 34 (47%) patients in the controls.

In the third study, Condessa and co-workers[23] randomized 92 patients to IMST ($n = 45$) or control ($n = 47$). Average duration of mechanical ventilation prior to IMST was 16 days. IMST began when patients had been on pressure support ventilation of 12–15 cm H_2O. IMST load was set at 40% of P_{Imax}. The IMST sessions consisted of 5 sets of 10 breaths, twice a day, 7 days a week. In the IMST group, P_{Imax} increased from 34 cm H_2O to 41 cm H_2O, and was unchanged in controls. Tidal volume (V_T) increased, but weaning time did not change, 2.2 days versus 2.5 days. The rate of successful extubation was similar between groups.

There are similarities and substantial differences among the 3 controlled studies. The similarities include small sample size and study setting at a single center. Differences include:

- In both the Cader et al[22] and the Condessa et al[23] studies, the patients were intubated, and the need for tracheostomy was considered failed IMST, while in the Martin et al study all the patients had tracheostomy.[17]
- The duration of mechanical ventilation prior to IMST ranged between 7 and 42 days.
- The duration of IMST varied considerably, and the protocols for IMST were not uniform among the studies.

Clearly, there is a need for standardization of IMST protocol, to allow comparison among studies.

Since inspiratory muscle weakness in a large proportion of patients is apparent at onset of mechanical ventilation, it seems prudent to begin inspiratory muscle conditioning as early as possible, to prevent prolonged weaning, which consumes substantial healthcare resources.[24] In a pilot study of healthy diaphragm of pig, unilateral phrenic nerve pacing (synchronized with mechanical breaths for 72 h of controlled mechanical ventilation) mitigated diaphragmatic atrophy of type II (fast twitch) fibers and myofiber damage, as compared with the contralateral inactive hemidiaphragm.[25] Although in that study diaphragm muscle function was not tested, the study suggests that active conditioning of diaphragm muscle from day 1 of mechanical ventilation application may prevent atrophy.

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The study by Martin and colleagues[17] on IMST in patients with prolonged weaning is encouraging. In this issue of the Journal, Smith and co-workers,[18] of the same group, analyzed 16 patients who underwent IMST from the same data set: those with inspiratory load compensation (ILC) responses to a pressure threshold load of 10 cm H_2O. Ten patients weaned successfully, and 6 patients failed weaning. The applied loads represented 25% and 27%, respectively, of the average P_{Imax} in the successful-weaning versus failed-weaning groups. Baseline P_{Imax} was similar in both groups (52 cm H_2O vs 42 cm H_2O), and increased by 18% and 11% after training in the successful and failed weaning groups, respectively. ILC responses were estimated as peak inspiratory flow (PIF) and V_T. Independent of IMST, patients who weaned successfully significantly increased their average PIF (47 L/min pre-IMST vs 55 L/min post-IMST) and V_T (5 mL/kg pre-IMST vs 6 mL/kg post-IMST), compared with the failed-weaning group (PIF 29 L/min pre-IMST vs 26 L/min post-IMST, V_T 3 mL/kg pre-IMST vs 4 mL/kg post-IMST). Only in the successfully weaned patients, IMST improved ILC response over a range of threshold loads from 5 to 15 cm H_2O. After training the average PIF and V_T increased significantly: PIF range 16–18%, V_T range 14–42%. However, there was a large overlap between before and after IMST (see figure 6 in Smith et al[18]).

ILC can be described as the ability of the respiratory system, when challenged with increased load, to increase neuromuscular output and to translate that output into

ventilation (neuroventilatory efficiency) to maintain CO_2 homeostasis.[26] Smith and co-workers[18] found that prolonged-weaning patients who continued to fail SBTs had blunted ILC responses, similar to those who failed weaning for the first time.[27] Blunted ILC response may be due to depressed neuromuscular output and/or neuroventilatory inefficiency. Neuroventilatory inefficiency results from inspiratory muscle weakness and/or increased inspiratory muscle work load. Evaluating factors separately is important to assess the pathophysiology of blunted ILC responses in failed weaning patients. Patients who failed weaning retained the ability to enhance neuromuscular output, as estimated by diaphragm muscle electrical activity.[27] In fact, during SBTs the diaphragm muscle electrical activity of patients who failed weaning was nearly 2-fold that of patients who weaned successfully.

With regard to inspiratory muscle weakness as a determinant of neuroventilatory efficiency, Smith and co-workers[18] did not distinguish significant weakness in failed versus successfully weaned patients. Baseline P_{Imax} was similar, but the failed-weaning patients tended to have lower P_{Imax} and smaller improvement after training than did the successful-weaning patients. The small sample size precludes statistical significance. However, in a prospective study of 30 patients in a weaning center, Carlucci et al[28] measured P_{Imax} at enrollment, then either at the time of successful weaning ($n = 16$) or after 5 weeks in those who consistently failed weaning ($n = 14$). All the patients underwent a supervised and standardized rehabilitation program. In the successful weaned group, P_{Imax} improved from an average of 45 cm H_2O to 57 cm H_2O, and V_T increased from 337 mL to 386 mL, whereas among those who failed weaning, P_{Imax} changed minimally, from 33 cm H_2O to 39 cm H_2O, and V_T was virtually unchanged, from 300 mL to 289 mL at the end of the study. This suggests that recovery of inspiratory muscle generating capacity improves neuroventilatory efficiency: a precursor to successful weaning.

With regard to inspiratory muscle work load as a determinant of neuroventilatory efficiency, Smith and co-workers[18] showed that the failed weaning patients had similar respiratory mechanics or inspiratory muscle work load, as did successfully weaned patients. However, measurements were made during mechanical ventilation. Studies have demonstrated that, at the time of SBT, the major determinants of weaning failure are the increased inspiratory muscle work load (as estimated by the inspiratory muscle tension-time index) and the rapid-shallow breathing pattern.[29,30] Tension-time index is calculated as the product of the ratio of mean inspiratory pressure per breath to P_{Imax} and the ratio of inspiratory time to total breath cycle. In order to determine the tension-time index of the diaphragm muscle, transdiaphragmatic pressures replace inspiratory muscle pressures. Interestingly, Carlucci et al[28] measured diaphragm tension-time index and found that it decreased significantly from its baseline value in both the successful and failed weaning groups. Among the successfully weaned, average diaphragm tension-time index decreased from 0.13 to 0.08; in the failed group, diaphragm tension-time index decreased from 0.21 to 0.14. Both inspiratory muscle weakness and high inspiratory muscle work load are determinants for neuroventilatory inefficiency; however, recovery from inspiratory muscle weakness in tandem with decreased work load is of paramount importance. In the study by Smith and co-workers[18] the blunted ILC response in the failed-weaning patients was most likely due to both factors.

Why does IMST have no impact on ILC responses in patients who fail weaning despite improvement in P_{Imax}? From the above discussion, P_{Imax} is only one determinant of ILC response. Neuromuscular output, and the balance between inspiratory muscle force-generating capacity and work loads, are important determinants and should be systematically and independently evaluated.

In summary, in prolonged-weaning patients IMST has the potential to accelerate weaning; however, a large randomized controlled study with defined, standardized protocol is needed. The rapid development of inspiratory muscle weakness in critically ill patients receiving mechanical ventilation[7,10] suggests that it is essential for IMST to begin early: on the first day of mechanical ventilation. ILC response is linked to the success of IMST in improving neuroventilatory efficiency.

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